JOURNAL OF NUTRITION RESEARCH

JNR

ORIGINAL ARTICLE

An Exploratory Cum Prospective Study to Assess the Impact of Nutritionally Balanced Enteral Formula Feed in Critical Care Patients

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OPEN ACCESS

Received: 23.12.2024
Accepted: 30.12.2024
Published: 31.12.2024

Citation: Reddy BR, Sahu S, Reddy CVKK, Bhoite RM, Immadisetti P, Unnisa R, Sanghavi A, Satyavrat V. (2024). An Exploratory Cum Prospective Study to Assess the Impact of Nutritionally Balanced Enteral Formula Feed in Critical Care Patients . Journal of Nutrition Research. 12(2): 110-122. https://doi.org/10.55289/jnutres/v12i2.47

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Funding: This work was supported by Dr Reddy's Laboratories Limited, Ameerpet, Hyderabad, Telangana, India.

Competing Interests: None

Published By India Association for Parenteral and Enteral Nutrition (IAPEN)

ISSN
Electronic: 2348-1064

Abstract

Enteral Nutrition (EN) prevents malnutrition and promotes recovery in critically ill patients. Despite the benefits, current EN formulations are associated with concerns like gastrointestinal intolerance, electrolyte imbalances, and hyperglycemia. Balanced EN formulations improve recovery, reduce hospital stays, and enhance patient outcomes. This study evaluated efficacy and tolerability of a novel balanced EN formula in supporting patient recovery and reducing length of hospital stay in critically ill patients. The study included 19 hospitalized critically ill patients aged ≥18 years, with mean (SD) age of 52.4(14.98) years. EN intake was monitored for a minimum of 3-14 days or until discharge. Target calorie and protein intakes were evaluated in accordance with ASPEN/ESPEN guidelines 2019. The analysis of target macronutrient intake reported adequate levels in 17 (89.5) patients, with a mean (SD) daily caloric intake of 1737 (582.1) kcal, and 95% Class Interval (CI) ranging from 1646 to 1828 kcal. The mean (SD) of daily protein intake was 82.9 (27.78) grams. The mean (SD) hospital stay was 12.7 (9.39) days, with a Interquartile range (IQR) of 11 (7.0;18.0) days and a median of 8 days. Most patients showed improvements in micronutrient profiles and achieved electrolyte

homeostasis without hyperglycemic episodes. Notably, no gastrointestinal (GI) complications were observed, and no prokinetic agents were administered, indicating tolerability and acceptance of the formula. No serious adverse events (SAEs) were reported. These findings suggest that the novel EN formula is effective in supporting the recovery of critically ill patients, while demonstrating favourable safety and tolerability profile.

Keywords: Critical Illness; Nutritional Support; Enteral Nutrition; Macronutrients; Micronutrients; Gastrointestinal Tract; Feed Tolerance; Prokinetics; ESPEN Guidelines

1 Introduction

Nutrition is essential for overall health maintenance[1] with its importance magnified in critically ill patients due to increased energy demands, insufficient intake, impaired absorption, and heightened catabolic stress.[2,3] Malnutrition during hospitalization causes increased complications, prolonged hospital stays, and impaired immune responses, thereby elevating the risk of nosocomial infections.[4] Numerous studies have highlighted the prevalence of malnutrition among hospitalized patients. Globally, the prevalence of malnutrition among critically ill patients ranges from 38% to 78%, highlighting a significant health concern, with prevalence rates of 78.1% in developing countries and 50.8% in developed countries.[5,6] In India, evidence from Indian hospitals indicates that patients frequently experience inadequate nutritional intake upon admission.[7]

Patients with minimal or no oral intake, particularly those in the intensive care unit (ICU) for more than 48 hours,[3] are at elevated risk for malnutrition.[8] In order to mitigate the risk and promote optimal outcomes of such scenarios, artificial nutrition either enteral or parenteral nutritions is recommended.[9] Enteral Nutrition (EN) administers nutrients directly to the gastrointestinal tract,[10] and should be initiated within 48 hours in critically ill patients.[8] EN is preferred in ICU patients as it delays or halts the catabolic response, preserves intestinal integrity, reduces bacterial translocation, stimulates the immune response, promotes tissue healing, and decreases the risk of infections.[11] Specifically, EN reduces complications, shortens the length of hospital stay, and lowers mortality rates in critically ill patients.[12] EN is superior to parenteral nutrition in nutrient delivery, offering enhanced safety, greater efficacy, lower cost, and prevention of gastrointestinal atrophy.[13,14] According to the ESPEN guidelines, the daily recommended enteral nutrition for critically ill patients includes an energy intake of 20–25 kcal/kg/day and a protein intake of 1.3 g/kg/day.[15]

Adequate Medical Nutrition Therapy (MNT), with balanced macro and micronutrients, antioxidants, and anti-inflammatory elements, help critically ill patients in meeting their energy requirements.[16] Despite the advantages, existing enteral formulas have inadequately addressed several concerns like gastrointestinal intolerance,[17] electrolyte disturbances[18] and hyperglycemia.[19] Additionally, complications such as diarrhea, vomiting, and nausea, are persistant with the existing EN formulas.[20] Other challenges, such as ensuring the appropriate enteral formula, the effective delivery of prescribed nutritional therapy, and feed interruptions, further exacerbate the complexities associated with existing EN formulations.[21] Strategies such as employing a low-fat enteral formula, administering prokinetic agents, and reducing the infusion rate were explored.[22] Currently, there is no validated adherence rate for EN formulations that guarantees therapeutic outcomes and address the complications, related to formula tolerance, which are usually considered under non-adherence.[23]

These challenges have prompted the development of a nutritionally balanced novel EN formula. This study aimed to evaluate the effectiveness and tolerability of the novel EN formula in critically ill patients. Specifically assessing the formula's ability to achieve the prescribed nutritional targets, its impact on reducing hospital stays, and its potential to minimize gastrointestinal complications. This study focused on improving the patient outcomes, and enhancing overall nutritional care in critically ill patients.

2 Methods

2.1 Study Design and population

A prospective, open-label, single-arm, multicentred interventional study was conducted across three sites in India between December 2022 and January 2024, adhering to the principles outlined in the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. The sudy was approved by the Ethics Committee (EC), and registered with the Clinical Trials Registry of India (CTRI/2022/12/047818). The study included haemodynamically stable patients aged $\geq$18 years, admitted to ICU and requiring enteral nutrition support as per physician discretion for a minimum of 3-14 days or until discharge. Informed consent was obtained from the patients themselves or their next-of-kin. Exclusion criteria included patients contraindicated for nasogastric or naso-enteric tube placement and enteral feeding, patients who underwent Percutaneous Endoscopic Jejunostomy (PEJ), Percutaneous Endoscopic Gastrostomy (PEG) and Surgical Jejunostomy (SJ) 6 months back or any other procedure and with a risk of refeeding syndrome, pregnant or breastfeeding women, patients who were already enrolled in another trial/study within 30 days before screening and those with any other clinical conditions. were also excluded from the study.

2.2 Study Procedure

The study was conducted in collaboration with health care professionals. The participants were explained the purpose of the study and informed consent was obtained from each patient before commencing any study-related activities. A comprehensive range of data was collected including demographic information, personal history, medical history, surgical history, as well as physical and systemic examinations, vital signs and details of concomitant medications. Laboratory tests were conducted, to measure fasting blood sugar (FBS), postprandial blood sugar (PPBS), liver profile, complete blood count (CBC), renal profile, blood urea nitrogen (BUN), serum creatinine, serum pre-albumin, and levels of micronutrients such as Zn, Vitamin C, Mg, Potassium, and Phosphorus before and after the study.

2.3 Study Intervention

The intervention is an energy-dense, high-protein, low glycemic index (39 ± 3) EN formula, designed to provide comprehensive nutritional support. It contains 25 essential micronutrients, ensuring a nutritionally balanced composition. The formula was designed with a 3:1 ratio of whey protein concentrate (a fast-acting protein) to calcium caseinate (a slow-acting protein) promoting prolonged muscle protein synthesis. Additionally, the EN formula is enriched with medium-chain fatty acids (MCTs), which are rapidly metabolized to provide immediate energy. The inclusion of carnitine and taurine supports lipid and glucose metabolism, improving fat malabsorption and maldigestion, thereby enhancing gastrointestinal tolerance. This EN formula was titrated from 1 kcal to 2 kcal per milliliter, facilitating smooth tube flow and offering a flexible approach to meet varying energy needs based on patient requirements.

2.4 Method of Preparation

The study intervention provides 440 kcal of energy and 21 grams of protein per 100 g. The EN formula, when 50 g is dissolved in 200 ml of water, provides 1 kcal/ml of energy. Similarly, 50 g of the study EN formula can be dissolved in 125 ml, 110 ml, or 90 ml of water to provide 1.52 kcal/ml, 1.69 kcal/ml, and 2 kcal/ml of energy, respectively. This flexibility allows the formula to cater to both isocaloric and hypercaloric nutritional requirements based on individual patient needs.

2.5 Method of Analysis

To comprehensively assess the various parameters following enteral nutrition (EN) administration, the study employed the following analytical methodologies: Biochemical assessments were conducted using the COBAS 8000 analyzer to evaluate fasting blood glucose levels (adjusted for age and diabetic status), serum potassium, and serum phosphorus. Hematological profiles were determined using the UNICEL DXH 600 analyzer, which measured leukocyte count, erythrocyte count, hemoglobin concentration, platelet count, and hematocrit. Zinc levels were quantified through Nexlon 2000B Inductively Coupled Plasma Mass Spectrometry (ICP-MS), while Vitamin C concentrations were analyzed using High-Performance Liquid Chromatography (HPLC).

2.6 Study Outcomes

The primary outcome was the evaluation of the achievement of targeted macronutrient levels (caloric and protein intake) within the prescribed timeframe and their impact on the duration of hospital stay. Secondary outcomes included the assessment of micronutrient levels (Vitamin C, magnesium, and minerals such as zinc, potassium, and phosphorus) and the incidence of feed-related adverse events, including

abdominal pain, distension, vomiting, and diarrhea. Hematological parameters were measured from baseline to the end of the study. Feed tolerance was evaluated by monitoring feed interruptions to assess the overall impact of the formula on patient health and recovery. Patient compliance with the intervention was monitored using a patient diary.

2.7 Statistical Analysis

All continuous data (such as age, blood tests and biochemical parameters) were summarized and presented as mean with standard deviation and 95% confidence intervals (CI). Categorical and nominal data were presented in numbers and percentages. The duration in the hospital (Survival propability) was estimated using a Kaplan-Meier (KM) plot and descriptively presented with 95% confidence intervals. Statistical analysis was performed using SAS V9.4.

3 Results

3.1 Patient Demographics

Of the 19 patients enrolled, 16 patients completed the study. The mean (SD) age was 52.4 (14.98) years, with a gender distribution of (57.9%) males and (42.1%) females. The comprehensive baseline demographics of the patients are detailed in (Table 1).

Table 1. Demographic and Baseline Characteristics

Baseline Characteristics	Full Analysis Set (N=19)
Age (in years)	
N	19
Mean (SD)	52.4(14.98)
Median	59
IQR (Q1; Q3)	19.0(43.0; 62.0)
Min; Max	19;73
Gender, n (%)	
Male	11(57.9)
Female	8(42.1)
Weight (kgs)	
N	19
Mean (SD)	63.3(11.96)
Median	59.7
IQR (Q1; Q3)	10.00(56.00;66.00)
Min; Max	48.5;100.0
Height (cms)	
N	19
Mean (SD)	160.1(5.59)
Median	158.5
IQR (Q1; Q3)	6.00(156.0;162.0)
Min; Max	151;173.7
BMI (kg/m2)	
N	19
Mean (SD)	24.6(4.30)
Median	24
IQR (Q1; Q3)	2.40(22.40;24.80)
Min; Max	19.4;39.90

N: Number of patients, SD: Standard Deviation, Q1: 1st Quartile, Q3: 3rd Quartile, IQR: Inter-quartile range, Min: Minimum, Max: Maximum, %: Percentage of patientsDenominator for percentage calculation is number of patients in full analysis set

3.2 Achievement of desired target macronutrients and No.of Days in Hospital

Among 19 enrolled patients, 17(89.5%) patients achieved the desired target macronutrient levels. The mean (SD) duration of days in hospital was 12.7 (9.39) days with a median duration of 8.0 days. Similarly, the mean (SD) duration of ICU stay was 12.6 (9.30), with a median of 8.0 days and an IQR of 11.0 (7.0 to 18.0) days. (Table 2)

The prescribed daily feeds and the volume of feeds delivered from day 1 to day 14 were administered according to the feeding schedule at the physician's discretion, as illustrated in Figure 1**.** Subsequently, starting from Day 6, most of the patients recovered and were discharged.

3.3. Achieving Target Macronutrients (Calories)

The overall mean (SD) of achieved target caloric intake was 1737 (582.1) kcal, with a median of 2200 kcal and a 95% CI ranging from 1646 to 1828 kcal, while the overall planned caloric intake mean (SD) was 1602 (314.1) kcal (Figure 2).

Table 2. Summary and Analysis of Achieved Desired Targets and No. of Days in Hospital

	Full Analysis Set (N=19)
Achieved Desired Target n(%)	
Yes	17(89.5)
No	1(5.3)
NAP	1(5.3)
Number of Days in Hospital	
N	19
Mean(SD)	12.7± 9.39
Median	8.0
IQR(Q1;Q3)	11.0(7.0;18.0)
Min;Max	3; 40
95%CI	[17.2; 8.2]
Number of Days in ICU	
N	19
Mean(SD)	12.6± 9.30
Median	8.0
IQR(Q1;Q3)	11.0(7.0;18.0)
Min;Max	3; 40
95%CI	[17.1; 8.1]

Denominator for percentage calculation was number of patients in Full Analysis set N: Number of patients, SD: Standard Deviation, Q1: 1st Quartile, Q3: 3rd Quartile, IQR: Inter-quartile range, Min: Minimum, Max: Maximum, %: Percentage of patients, 95% CI: 95% confidence interval No of days to achieve target: Day target macronutrient levels reached No of days in ICU= (date of discharge from ICU- date of ICU admission) +1 No of days in Hospital= (date of discharge from Hospital-date of hospital admission) +1

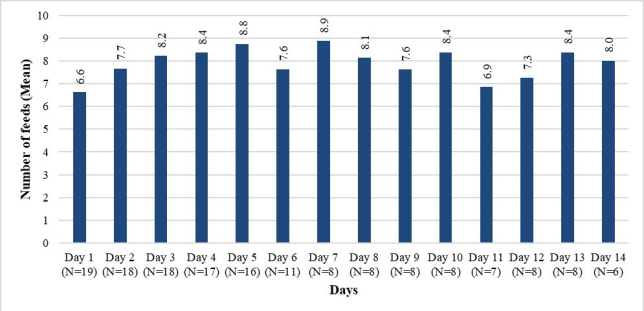

Fig 1. Number of feeds from Day 1 to Day 14.

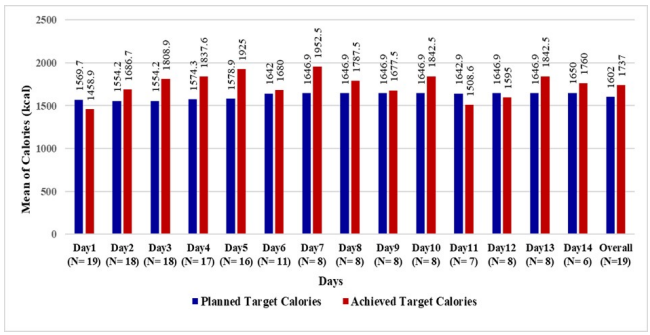

Fig 2. Planned Vs Achieved Target Calories

3.4 Achieving Target Macronutrients (Proteins)

The achieved overall mean (SD) of protein intake was 82.9 (27.78) grams, with a median of 105 grams, and a range of 0.0 to 105.0 grams, while planned mean (SD) was 72.8 (11.27) grams. (Figure 3)

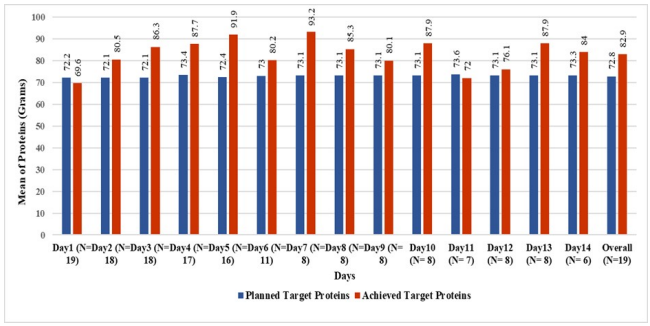

Fig 3. Planned Vs Achieved Target Protein

The Kaplan-Meier plot illustrates the survival probability and hospitalization duration in (Figure 4). The 50%-point estimate, marking the median survival time, was 10 days, indicating that, on average, half of the patients were discharged within this timeframe.

3.5 Impact of Nutritional Support on Micronutrients

Compared to Day 1, there was an increase in Vitamin C levels and the immuno-essential minerals such as zinc on Day 14, indicated by a mean (SD) of Vitamin C level was 64.1 (100.6), with a range of 0.8 to 300, while the mean (SD) level of zinc was 126.1 (44.70), with a range of 44.3 to 196. (Figure 5)

3.6 Impact of Nutritional Support on Electrolyte Balance

Levels of magnesium, phosphorus, and potassium remained relatively stable from Day 1 to Day 14. The mean (SD)

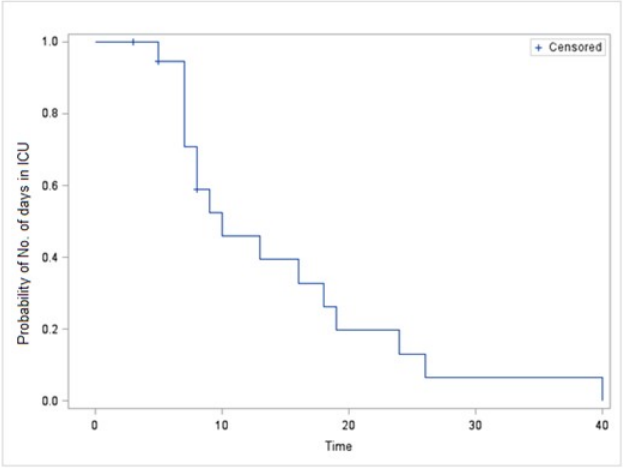

Fig 4. Kaplan-Meier Plot for Number of Days in Hospital

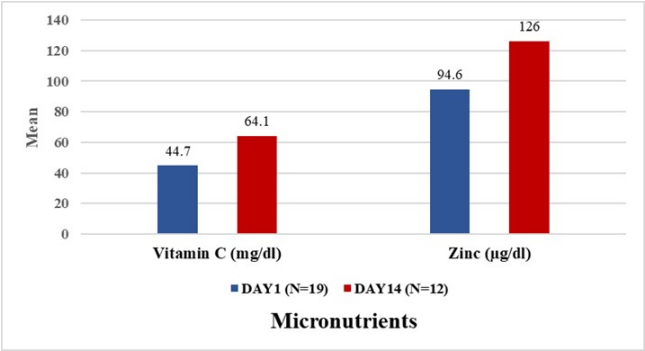

Fig 5. Analysis of Vitamin C and Zinc

magnesium level was 2.3 (0.41) on Day 1 and 2.3 (0.60) on Day 14, mean (SD) phosphorus levels were 3.7 (0.96) on Day 1 and 3.3 (0.62) on Day 14, while the mean (SD) potassium levels were 4.7 (0.74) on Day 1 and 4.4 (0.79) on Day 14. (Figure 6)

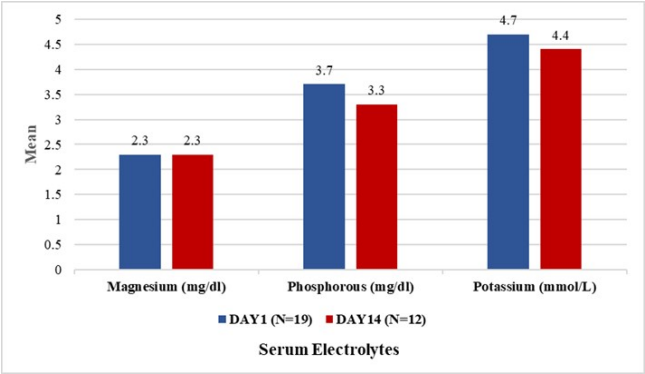

Fig 6. Analysis of Electrolytes

3.7 Impact of Nutritional Support on Glycemic Control

A reduction blood glucose concentrations with fasting blood glucose levels decreased from 137 mg/dL to 132 mg/dL, while postprandial blood glucose levels dropped from 158 mg/dL to 123 mg/dL by Day 14. (Figure 7)

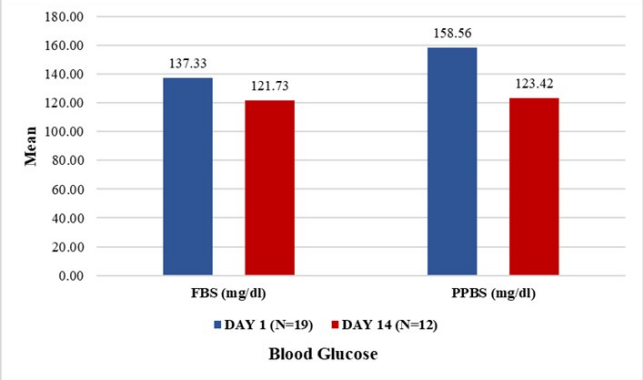

Fig 7. Analysis of Hematology (Blood Glucose)

3.8 Gastrointestinal (GI) Complications of the feed

Only 1 (5.3%) patient experienced mild gastrointestinal (GI) discomfort, particularly vomiting, which was resolved and no symptoms of diarrhoea, constipation, nausea, or abdominal distension were reported. Additionally, there were no major complaints of GI fullness and no prokinetic agents were administered. (Table 3)

3.9 Enteral Feed Interruptions

The analysis of feed interruptions showed that 12 (63.2%) patients experienced interruptions due to tracheostomy tube blockage, imaging, resurgery, and other reasons. Specifically, interruptions due to tracheostomy placement were experienced by 2 patients, interruptions due to tube blockage were experienced by 3 patients, interruptions due to imaging were experienced by 1 patient and 7 patient's feeds were interrupted due to other reasons. (Table 4)

Table 3. Summary and Analysis of GI Complications

GI Complications	Full Analysis Set (N=19) n (%)
Did Patient complain of any GI discomfort	
Yes	1(5.3)
Diarrhea	0
Constipation	0
Nausea	0
Vomiting	1(5.3)
Abdominal distension	0
No	18(94.7)
Did Patient complain about fullness	
Yes	0
No	19(100)
Prokinetic agents used	
Yes	0
No	19(100)
Was Gastric Residual Volume (GRV) measured?	
Yes	1(5.3)
No	18(94.7)
Feeding tube flushed with water after every feeds given	
Yes	2(10.5)
No	17(89.5)
Was medicines powdered and given via tube	
Yes	2(10.5)
No	17(89.5)

Denominator for percentage calculation will be number of patients in full analysis set N: Number of patients, %: Percentage of patients

Table 4. Summary and Analysis of Interruption to Feed

Feed Interruptions	Full analysis set(N=19)
Any Feed Interruptions n(%)	
Yes	12(63.2)
No	07(36.8)
Number of hours overall feed interrupted	
N	12
Mean (SD)	13.8(11.36)
Median	10.0
IQR (Q1: Q3)	16.0(04.0:20.0)
Min ; Max	04 ; 36
95% CI	[06.6;21.1]
Number of hours feed interrupted due to placing of tracheostomy	
N	2
Mean (SD)	08.0(02.8)
Median	8.0
IQR (Q1: Q3)	04.0(06.0:10.0)
Min ; Max	06; 10
95% CI	[-17;33.4]
Number of hours feed interrupted due to Tube block	
N	3
Mean (SD)	06.7(04.6)
Median	4.0
IQR (Q1: Q3)	08.0(04.0:12.0)
Min ; Max	04; 12
95% CI	[-04.8; 18.1].
Number of hours feed interrupted due to Imaging	
N	1
Mean (SD)	08.0(.)
Median	8.0
IQR (Q1: Q3)	00.0(08.0: 08.0)
Min ; Max	08; 08
95% CI	[.;.]
Number of hours feed interrupted due to Taken to Resurgery	
N	2
Mean (SD)	09.0(04.24)
Median	9.0
IQR (Q1: Q3)	06.0(06.0:12.0)
Min ; Max	06; 12
95% CI	[-29;47.1]
Number of hours feed interrupted due to any other reason	
N	7
Mean (SD)	14.9(11.71)
Median	12.0
IQR (Q1: Q3)	20.0(04.0:24.0)
Min ; Max	04; 32
95% CI	[04.0;25.7]

*Patients who provided the informed consent was consider as screenedN: Number of patients enrolled into the study *No Values in Central Line Insertion column.

4 Discussion

The current study demonstrated that critically ill patients in ICU administered with study EN formula has exhibited enhanced recovery rates and reduced duration of hospital stay.

In this study, overall daily calorie and protein intake was found to be adequate, with the majoriy of patients meeting their nutritional targets, contributing to the achievement of the primary endpoint. The challenges in achieving optimal energy-protein levels through enteral nutrition in critically ill patients are complex and multifactorial, primarly stemming from difficulties in delivering the prescribed nutritional regimen. Notably, 17 (89.5%) patients met their nutritional targets, and over 80% of patients achieved 100% of their prescribed nutrition. This outcome is in consistent with findings by Hsu et al., 2018, who observed that patients who achieved $\geq$ 80% of the prescribed EN calories had reduced ICU and hospital mortality rates,[24] supporting the efficacy of the novel EN formula in facilitating the recovery of critically ill patients.

In the current study, the planned average daily caloric intake for the study patients was 1602 $\pm$ 314.1 kcal/day, while the achieved average caloric intake was 1737 $\pm$ 582.1 kcal/day, reflecting a 108% increase over the planned caloric intake. This indicates a positive achievement of nutritional goal, but not overfeeding. A study by Chappel et al., 2020 reported that exceeding caloric intakes of >2000 kcal/day, >25 kcal/kg/day, or >110% of the prescribed caloric requirement may be considered as overfeeding.[25] This highlights the fact that, although energy requirements are higher in critically ill patients compared to healthy individuals,[26] careful monitoring and balanced nutritional support are essential to ensure critically ill patients receive adequate calories without exceeding the recommended limits.

Achieving 100% of the target caloric intake via EN is challenging. However evidence-based studies, such as one by Lew et al., 2017, suggests that employing optimized EN delivery protocols and low glycemic index balanced EN formulations help the patients to acheive their full caloric targets, while improving clinical outcomes.[27] In a study by Ribeiro et al. (2016), it was highlighted that patients who received caloric volumes close to 100% of their prescribed targets experienced shorter hospital stays, fewer infectious complications, and lower mortality rates, according to McClave et al.[28] Zaragoza-García et al., 2023 reported that more than 110% of the target calories was administered to more than half of the patients/day in accordance with European guidelines.[15] These studies indicates that achieving excessive calories is a common occurence, but highlights the need for careful monitoring to mitigate potential adverse effects. Collectively, these findings aling with the outcomes of the present study in achieving 100% of the target calories, emphasizing the importance of balanced EN formulations in supporting the increased nutritional needs of the critically ill patients.

Adequate protein administration improves clinical outcomes in critically ill patients, as protein deficiency impairs immunity and delays recovery.[29] In many cases, protein needs exceed energy requirements needs in critically ill patients.[30] To assess the protein adequacy, a weight-based equation (Eg. 1.2–1.3 g/kg/day) is commonly used, comparing the delivered protein to the prescribed protein. In this study, the planned average daily protein intake was 72.8 $\pm$ 11.27 grams, while the achieved intake was 82.9 $\pm$ 27.78 grams, reflecting a protein adequacy of 113.9%. This higher adequacy of protein intake was attained without establishing overfeeding as per ASPEN guidelines,[31] considering the mean weight of the study patients, which was 63.3 kg. A study conducted by Song et al., 2017 reported that, achieving > 90% of the prescribed protein intake under real-world clinical conditions was associated with improved ICU outcomes in critically ill patients.[32] Similarly, Nicolo et al., 2016 reported that achieving $\geq$80% of their prescribed protein had a shorter time to discharge alive.[33] Osooli et al., reported optimal feeding as achieving 80%-120% of the target energy or protein requirements.[5] Ruijven et al., demonstrated that high protein provision ($\geq$1.2 g/kg/day) improved nutritional outcomes and reduced short-term muscle atrophy.[34] Zusman et al., 2016 also reported, improved survival rates with protein administration >1.3 g/kg/day, indicating a 1% reduction in mortality for every additional gram of protein consumed.[35] These findings support the present study, emphasizing the critical role of adequate protein intake and confirms both the effectiveness and safety of high protein intake in critically ill patients.

In addition to meeting energy and protein requirements, achieving targeted macronutrients levels may influence patient outcomes, contributing to a reduction in length of hospital stay and ICU stay duration. A study by Gabrielli et al., 2024 found that patients receiving $\geq$80% of their total energy goal experienced a reduction in both hospital length of stay (LOS) and in-hospital mortality compared to those receiving <80% of their EN requirements. This finding was further validated by Kaplan–Meier survival analysis, which demonstrated a survival benefit for patients with adequate caloric and protein intake.[36] Similarly, Lee et al., 2014 reported a survival difference in the Kaplan–Meier survival curve between patients receiving early enteral nutrition (EEN) and late enteral nutrition (LEN). The EEN group had 3% reduction in in-hospital mortality rates and lengths of hospital stay.[37]

A study by Duan et al., 2024 reported that, the length of hospital stay was significantly longer in the delayed EN group than in the early EN group.[38] Zhong et al., 2023 reported that the survival curve of patients who achieved a protein intake of 0.5 g/kg/day on Day 3 and Day 7 was superior to

those who did not reach this target. Their study suggested that the improvement is attributed to better tolerance of enteral nutrition and adequate protein intake, which enhanced survival in ICU patients.[39] These findings align with the current study, in which >80% of patients achieved 100% of their daily prescribed nutritional targets within 5 days, and more than half of the patients were discharged on or after day 6 onwards. This was further validated by Kaplan-Meier curve, which revealed a median hospital stay of 10 days, indicating that more than 50% of patients were discharged within this timeframe. These finding, highlights the role balanced EN formulas in contributing to reduced hospital stay and in-hospital mortality in critically ill patients.

In the current study, most patients showed improvements in micronutrient levels, particularly vitamin C and the immunologically essential trace element such as zinc, while maintaining relatively stable serum electrolyte concentrations. Monitoring selective micronutrients is acceptable in intensive care unit (ICU) therapy. The micronutrient status of patients reported adequate levels of essential nutrients, such as vitamin C and zinc, which are crutial for maintaining overall health and particularly important for immune system support. Deficiencies in vitamin C and zinc are commonly observed in critically ill patients[40,41] leading to adverse clinical outcomes,[42] that can potentially exacerbate the primary illness, impair immune response, delay tissue repair, and contribute to complications such as sepsis and organ dysfunction.[43,44] In the current study, most patients maintained sufficient levels of micronutrients, highlighting the efficacy of the EN formula in supporting the patients overall health.

The electrolyte imbalances in critically ill patients increase morbidity and mortality.[17] ICU patients despite the critical need for nutritional support, they often face challenges in tolerating enteral or parenteral feeding and are particularly susceptible to complications such as refeeding syndrome and electrolytic alterations.[17,45] Abnormal serum electrolyte levels disrupt the metabolic homeostasis of these patients, leading to adverse clinical outcomes.[46] This condition involves decreases in serum levels of potassium, phosphorus, and magnesium, along with deficiencies in several micronutrients.[43] In the current study, refeeding syndrome was not observed, and the majority of patients maintained balanced serum electrolyte levels throughout the study period from day 1 to day 14. This stability can likely be attributed to adequate feed tolerance, which contributed to the overall clinical stability of the patients.

Hyperglycemia is a frequent concern in critically ill patients, particularly those with glucose intolerance, who receive liquid enteral formulas high in simple sugars.[46] However, the current study reported notable improvement in both fasting and postprandial blood glucose levels with, most patients achieving normal glucose ranges. This alings with findings by Arbeloa et al., 2013 who reported that, EN formulas with improved glycemic control help reduce the incidence of infectious complications.[47] These findings suggest that the interventional enteral nutrition formula was effective, leading to improved patient outcomes in critically ill patients.

In addition to the composition of EN formulas, the method of feed delivery also play crucial roles in influencing GI tolerance. Recent studies suggest that slower, continuous feeding strategies, compared to bolus feeding, may improve GI tolerance by reducing the likelihood of complications such as nausea, vomiting, and diarrhea.[17,23] These complications are frequently monitored in patients receiving EN formulations as indicators of the formula's tolerability.[48] Diarrhea occurs in 2–63% of patients, while 20% experience nausea and vomiting.[22] In the present study, diarrhea, constipation, nausea, and abdominal distension were not reported, and there were no complaints of gastrointestinal fullness, suggesting GI tolerance of the formula among patients without the need for administering prokinetic agents.

Only 1 (5.3%) patient experienced mild gastrointestinal discomfort, specifically vomiting, which was resolved spontaneously without any further medical intervention. This enhanced feeding tolerance may be attributed to the specific composition of the study EN formulation, which contains medium-chain triglycerides (MCTs), carnitine, and taurine. These components are associated with increased survival probability and are clinically proven to improve gastrointestinal tolerance.[49,50] This finding is consistent with findings of Kozeniecki et al., 2015 and Qiu et al., 2017, who found that semi-elemental or elemental formulas with a higher percentage of fat derived from MCTs, Carnitine and taurine are safe and well-tolerated. MCTs are readily digested and absorbed, while taurine and carnitine are essential nutrients that facilitate fat digestion and absorption, particularly in critically ill patients with maldigestion or malabsorption.[50–52] Another factor contributing to the superior tolerance might be hydrolyzed EN formula of the study intervention, which has been shown to offer better tolerance than peptide-based EN formulas.[53]

In critically ill patients, underfeeding is due to interruptions in enteral nutrition, difficulties in administering the prescribed nutritional regimen, and other patient-related factors.[54] In this study, approximately 63% of patients experienced multiple feeding interruptions, which is lower compared to 68-79%-83% interruptions reported in previous studies.[54–56] In another study, EN cessation occurred in over 85% of patients, with an average of 20% of the infusion time, and more than 65% of these cessations were deemed avoidable.[57] In this study, the most common interruptions were related to tracheostomy placement, tube blockage, imaging procedures, and other reasons. Studies indicate that the majority of ICU patients experience at least one interruption in enteral nutrition, with many of these interruptions under

the control of physicians, and 25% being avoidable. In the current study, the median duration of overall feed interruptions across 12 patients was 10 hours, which was much more insignificant compared to other studies. Notably, 7 patients experienced no interruptions in their feeding regimen, highlighting the feed tolerance of the intervention.

5 Limitations of the Study

Given the study population, which consisted of critically ill patients, the sample size was small. Additionally, the actual energy requirements of the patients could not be directly measured due to the unavailability of indirect calorimetry techniques in current ICU setups. Consequently, energy requirements were estimated based on recommendations from international guidelines (ESPEN/ASPEN).

6 Conclusion

The findings of this study underscore the efficacy and safety of the interventional enteral feed formula, as evidenced by improved macro and micronutrient levels critical for the well-being of critically ill patients. This formula addresses gastrointestinal intolerance and reduces the need for recalculation and dissolution due to tube blockage in a hospital setting. Notably, the study reported minimal gastrointestinal complications with no SAEs. Overall, these findings position the interventional feed formula as a valuable resource in critical care, offering enhanced patient outcomes and improved treatment efficacy.

7 Declarations

7.1 Ethics approval and consent to participate

Approval to conduct the study was received from the Institutional Ethics Committee (ECR/94/Inst/AP/2013/RR-21 approved on 08 December 2022) and the KIMS Ethics Committee (ECR/142/Inst/AP/2013/RR16 approved on 31 December 2022) in Hyderabad, India as well as from the Imperial Ethics Committee (ECR/1693/Inst/MH/2022 approved on 13 October 2023) in Pune. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and informed consent was obtained from all patients.

7.2 Consent for publication

Not applicable.

7.3 Data Availability

The datasets and analyses generated during this study are available with the corresponding author upon reasonable request.

Authors' contributions

All the authors were responsible for the conception and design of the study, data acquisition, analysis and interpretation of data, drafting of the article, and final approval of the version to be published. RMB and PI helped conceptualize and design the study. BRR, SS and RMB supervised and approved the final draft of the study. PI and KKR monitored and supervised the study. RU and AS assisted with data collection during the study. VS provided input and scientific support throughout the study period. All authors critically reviewed all manuscript drafts and provided comments. All authors approved the final version to be published. RMB is the guarantor of this work and takes full responsibility for the integrity and accuracy of the data analysis.

Acknowledgements

The authors would like to thank Mrunal Suhas Shirodkar, Consultant Clinical Nutritionist in providing technical support during protocol development and KIMS Hospitals, Hyderabad, Care Hospitals, Hyderabad and Imperial Multispeciality Hospital, Pune for conducting the study and Techsol Life Sciences Private Limited, Hyderabad for their support with statistical analysis, data interpretation, writing assistance, and paper submission.

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