ORIGINAL ARTICLE

Role of Peripheral Parenteral Nutrition Composition on Clinical Outcomes in Patients Undergoing Gastrectomy or Colectomy: A Phase III Indian Clinical Trial

Amit Goyal[1], Anand Pathak[2], Madhu BS[3], Harshad Soni[4], Keyur Bhatt[5], KVVN Raju[6], Murali K Voonna[7], Rakshit Shah[8], Chetna Shah[9], Dignesh Patel[10]

Received on: 29 June 2024; *Accepted on:* 13 August 2024; *Published on:* 31 August 2024

Abstract

Aims and background: Various types of parenteral nutritional products exist, each with specific formulations designed to meet the diverse nutritional needs of patient's post-abdominal surgery. Here, two different parenteral nutrition (PN) solutions BFLUID and NUTRIFLEX PERI are compared in terms of therapeutic efficacy and safety profile.

Materials and methods: A prospective, multi-center, randomized, parallel-group, non-inferiority Phase III clinical trial compared two PN solutions namely BFLUID (*N* = 78) and NUTRIFLEX PERI (*N* = 72) in 150 patients undergoing gastrectomy or colectomy. Primary endpoints included length of hospital stay while secondary endpoints included assessment and comparison of length of ICU/HDU stay, assessment of incidents of infections and mortality, change in blood levels of vitamin B1, change in nutritional parameters, thrombophlebitis, pain at the injection site, and recording of adverse events (AEs).

Results: There was no significant difference in terms of length of hospital stay, length of ICU/HDU stay as well as changes in nutritional parameters from baseline and change in blood levels of vitamin B1 from baseline. Both study groups exhibited comparability in terms of AEs, pain at the injection site, and the incidence of phlebitis. There was no significant difference in the number and severity of adverse events reported in both groups. Additionally, no signs of infection were observed in patients from either group.

Conclusion: The trial successfully demonstrated the non-inferiority of BFLUID to NUTRIFLEX PERI. Moreover, the results indicated that PN enriched with high levels of branched-chain amino acids (BCAAs), essential amino acids (EAAs), and thiamine is both safe and efficacious for adult patients undergoing gastrectomy or colectomy.

Keywords: Amino acids, Gastrectomy, Parenteral nutrition, Thiamine.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24800

Highlights

Nutritional deficiencies following gastrointestinal surgery can have significant consequences for a patient's recovery and overall health. In order to mitigate the nutritional needs, parenteral nutrition (PN) support is often considered post gastrointestinal surgery. In this randomized multi-center phase III trial, we compared the efficacy and safety profiles of BFLUID [product containing glucose, electrolytes, supplemented with thiamine and with higher proportion of branched-chain amino acids (BCAAs)], vs NUTRIFLEX PERI (product with glucose, electrolytes and lower proportion of BCAAs). The results of our efficacy assessments unequivocally demonstrate that BFLUID is non-inferior to NUTRIFLEX PERI in terms of therapeutic efficacy. Furthermore, safety assessments revealed that the incidence of adverse events (AEs) remained consistent across both treatment groups. These findings underscore the potential viability of BFLUID as a clinically effective and safe option for addressing nutritional deficiency and maintaining nutritional status post gastrectomy or colectomy.

Introduction

Malnutrition is a common concern after major surgeries like gastrectomy or colectomy due to the potential impact of the surgery on digestion, nutrient absorption, and dietary intake. Malnutrition after major abdominal surgery has been linked to delayed wound healing, hospital-acquired infection, prolonged length of hospital

[1]Department of General Surgery, SMS Medical College, Jaipur, Rajasthan, India

[2]Department of Clinical Research Secretariate, National Cancer Institute, Nagpur, Maharashtra, India

[3]Department of General Surgery, Mysore Medical College and Research Institute, Mysuru, Karnataka, India

[4]Department of Surgical Gastroenterologist, Kaizen Hospital, Ahmedabad, Gujarat, India

[5]Department of GI and HPB Surgery, Surat Institute of Digestive Sciences, Surat, Gujarat, India

[6]Department of Surgical Oncology, Smt. BIACH and RI, Hyderabad, Telangana, India

[7]Department of Surgical Oncology, Mahatma Gandhi Cancer Hospital and Research Institute, Vizag, Andhra Pradesh, India

[8]Department of Surgical Oncology, Care Super Speciality Hospital, Vadodara, Gujarat, India

[9,10]Department of Medical Affairs, Otsuka Pharmaceutical India Pvt. Ltd., Ahmedabad, Gujarat, India

Corresponding Author: Chetna Shah, Department of Medical Affairs, Otsuka Pharmaceutical India Pvt. Ltd, Ahmedabad, Gujarat, India, Phone: +91 8758825195, e-mail: chetna.shah@Otsukapharma.in

How to cite this article: Goyal A, Pathak A, BS Madhu, Soni H, Bhatt K, Raju KVVN, *et al*. Role of Peripheral Parenteral Nutrition Composition on Clinical Outcomes in Patients Undergoing Gastrectomy or Colectomy: A Phase III Indian Clinical Trial. Indian J Crit Care Med 2024;28(9):871–878.

stay, and increased risk of morbidity and mortality.[1–3] Hence, when a patient's gastrointestinal system is partially functional or when enteral nutrition is contraindicated, healthcare providers turn to alternative methods, such as PN and/or enteral nutrition (EN). These nutritional therapies typically provide supplementation with amino acids (AA), glucose and electrolytes in varying amounts, thereby improving the functional recovery including individual's overall quality of life.[4,5]

The surgical stress response (characterized by a hypermetabolic and hypercatabolic state) often leads to a loss of lean body mass, particularly skeletal muscle mass, resulting in potential postoperative complications and prolonged recovery. As a results, it becomes critically important to supplement the patient with BCAAs, which act as essential substrates for the regulation of protein metabolism. These BCAAs act as a precursor in the restoration of depleted alanine and glutamine levels during prolonged surgical stress.[6]

Available in several Asian countries, BFLUID (marketed by Otsuka Pharmaceutical Factory, Inc, Japan) is one such PN product that contains glucose, electrolytes, water, vitamin B1, and 3% AAs (out of which 30% are BCAAs); intended to provide energy through supplemental nutrition. NUTRIFLEX PERI (marketed by B BRAUN Medical India Pvt. Ltd., India) is another such PN product that is available in India with a composition similar to that of BFLUID except that it contains 4% AAs (out of which 20% are BCAAs) and is devoid of thiamine. This prospective, multi-center, randomized, parallel-group, non-inferiority, and active-controlled Phase III trial was conducted in order to assess the efficacy and safety of BFLUID as compared with NUTRIFLEX PERI in patients that had undergone gastrectomy or colectomy.

Materials and Methods

This study was a prospective, multi-center, randomized, parallel-group, non-inferiority, and active-controlled Phase III clinical trial. The study enrolled 150 patients from 13 distinguished medical institutions across India, from April 2021 to January 2022. This comprehensive and nationwide dispersed approach aimed to ensure a robust and representative dataset for our evaluation. Following provision of informed consent and completion of all screening assessments, adult patients [aged between 18 and 70 years; body mass index (BMI) ≥18–30 kg/m^2] undergoing gastrectomy or colectomy and patients deemed fit for peripheral parenteral nutrition (PPN) therapy (based on the subjective global assessment) as per the physician's discretion were included in this study. Patients were excluded from the study if they were infused with vitamin B1 as a standard multivitamin in the previous 3 days from pre-op visit; with known sensitivity to thiamine hydrochloride and with serum albumin levels <30 gm/L. Patients classified as severely malnourished were excluded from the study. Also, patients with a history of congenital abnormal AA metabolism were also deemed as screen failure and were not part of the study. Additional inclusion and exclusion criteria are described in the Supplementary Materials. Participants who met the eligibility criteria were randomized in 1:1 ratio to either receive the BFLUID or NUTRIFLEX PERI.

Treatments Administered

The BFLUID, available in 500/1000 mL bag is a double chambered infusion solution. The 1000 mL of BFLUID contains an AA solution with electrolytes (300 mL) in the upper chamber while the lower chamber contains a glucose solution with electrolytes and vitamin B1 (700 mL). A 1000 mL of BFLUID contains 30 gm AA, 60% EAAs, 30% BCAAs, 75 gm glucose, 300 kcal non protein energy and provides 420 kcal of total energy. The maximum dosage of BFLUID was 2500 mL/day. The AA composition of BFLUID is stricter than World Health Organization (WHO) standard and is compliant with Tanabe, Eisai, Otsuka (TEO) standard. The detailed composition of BFLUID and NUTRIFLEX PERI has been depicted in Supplementary Material Table S1. NUTRIFLEX PERI, available in 1000/2000 mL bag is also a double chambered infusion bag that houses the AA solution in the upper compartment and glucose in the lower compartment. A 1000 mL of NUTRIFLEX PERI solution provides 480 kcal and contains 40 gm AA, 47.5% EAAs, 20% BCAAs, 80 g glucose, and 320 kcal non protein energy. The recommended daily dose for adults of NUTRIFLEX PERI is up to 40 mL solution for infusion per kg body weight corresponding to up to 1.6 g amino acids/kg BW/day, up to 3.2 g glucose/kg BW/day. The precise infusion rate and dosage for individual participants of both the study arm were subject to discretionary adjustments made by the Investigator, taking into consideration factors such as the patient's clinical condition, body weight, and age. All the patients were started on intravenous infusion within 24 hours of surgery. Total energy intake, comprising enteral (including other polymeric formula feeds) and parenteral (including PPN) therapy, was maintained within the range of 25–30 kcal/kg of body weight. In cases of obese patients (BMI > 25 kg/m^2), dosing was adjusted based on estimated ideal body weight. The minimum duration for infusion was 3 days for both the study products and was continued as per Investigators discretion. The ratio of enteral to PPN therapy for each participant was decided by the investigator based on the clinical condition of the participant. All concomitant nutritional and fluid therapy were permitted separately through enteral route. No concomitant medication was mixed with the study product. Administration of any other nutritional products through peripheral or central vein other than the study products were prohibited. Multivitamins containing vitamin B1 or preparations related with vitamin B1 were also prohibited. Details of study visits and procedures for each visits are described in Figure 1.

Sample Size

Sample size was estimated based on the hypothesis that primary endpoint which is length of hospital stay will be non-inferior in the treatment arm to the comparator. Considering the mean length of hospital stay as 7.25 days with standard deviation of 3.5 days, a sample size of 67 in each arm gave 80% power to detect an absolute non-inferiority margin of 1.5 days at 5% level of significance.[7,8] Considering a 10% drop out in the follow-up, the final sample size was 150 in both the study arms. Of 150 patients, 78 were included in BFLUID group and rest 72 were included in NUTRIFLEX PERI group. Detailed breakdown of patient enrolment has been depicted in Figure 2.

Randomization and Blinding

Patients were randomly assigned to one of the study treatments based on the randomization schedule generated using permuted

Source of support: The clinical trial was sponsored by Otsuka Pharmaceutical India Pvt. Ltd., which also provided the study drug. All investigators received research funding, although Otsuka Pharmaceutical India Pvt. Ltd. was not directly involved in the disbursement process.

Conflict of interest: Chetna Shah and Dignesh Patel are currently an employee of Otsuka Pharmaceutical India Pvt. Ltd.

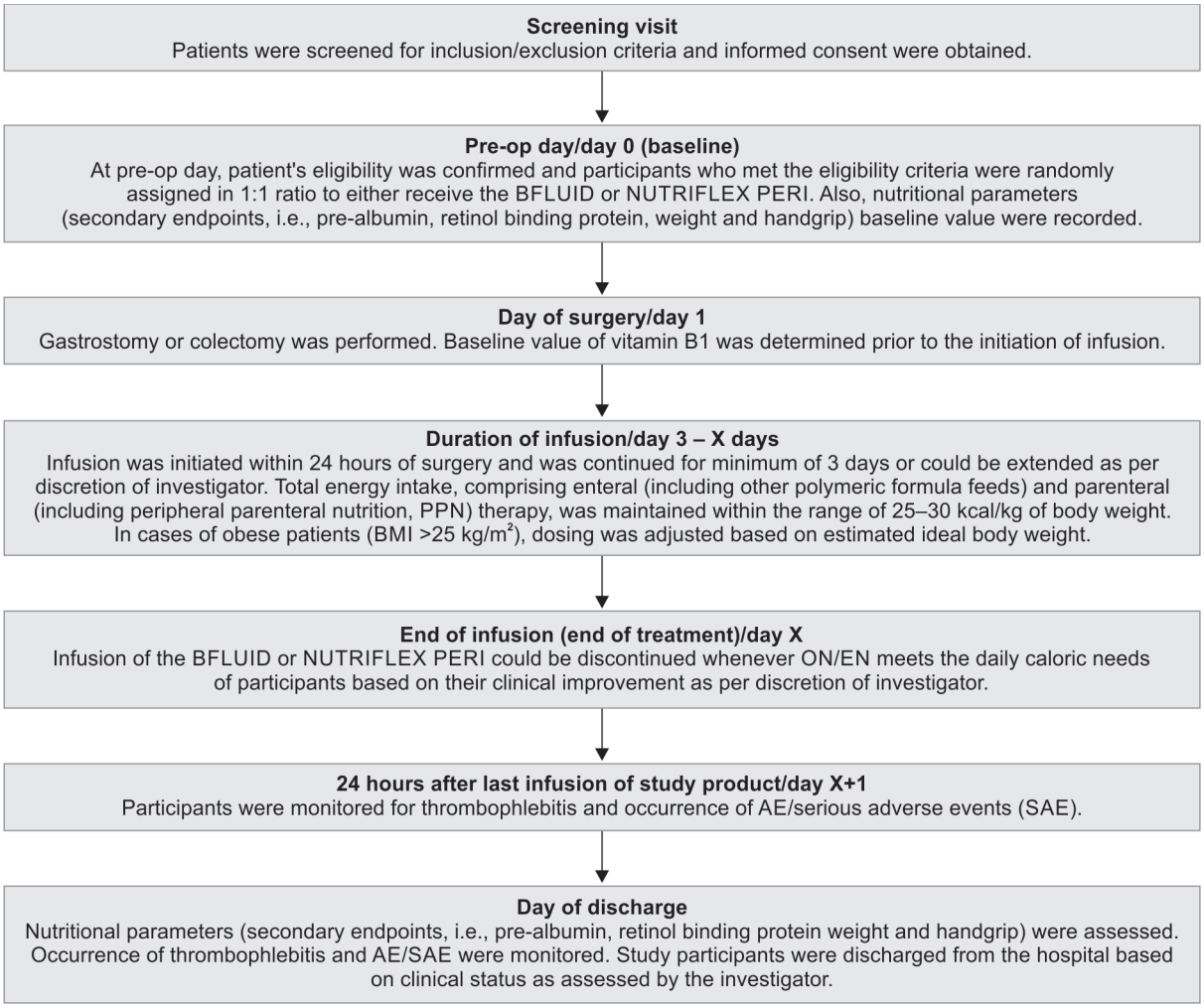

Fig. 1: Study visits and procedures

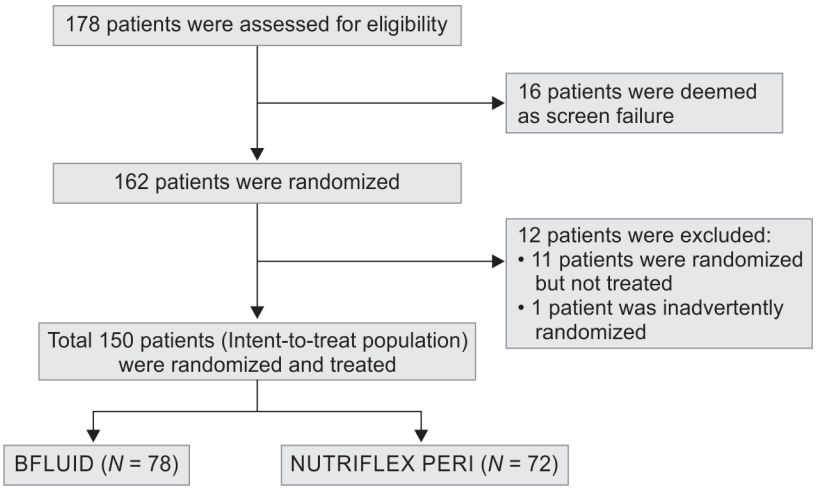

Fig. 2: Study flowchart

block randomization method with the help of a validated computer program, statistical analysis system® (SAS®) for Windows version 9.3/Proc PLAN (SAS® Institute Inc., Cary, NC, USA). Blinding was performed by members of the study staff responsible for the preparation of the infusion bags (opening the seals, mixing the contents of the chambers, assembling the infusion line). The infusion bags were enwrapped in an opaque envelope labeled appropriately for participant details. To ensure an unbiased

assessment of Thrombophlebitis and hand grip, the "assessor(s)," i.e., the physician(s) designated to assess and score local vein- and skin reactions at the sites of study product infusions and independent assessor for hand grip assessment, were blinded for the study medication allocation.

Assessment

Primary Endpoints

In order to compare the clinical efficacy, the length of hospital stay in post-operative patients (gastrectomy or colectomy) that were infused with either BFLUID or NUTRIFLEX PERI was assessed.

Secondary Endpoints

The secondary endpoints included assessment and comparison of length of hospital stay in Intensive care unit (ICU)/High dependency unit (HDU), change in blood levels of vitamin B1 from baseline (just before start of infusion) to post end of infusion, change in nutritional parameters (albumin, pre-albumin, retinol binding protein, weight, and hand grip) from baseline to the day of discharge, assessment of thrombophlebitis and pain at injection site, assessment of incidents of infections and mortality, and recording of adverse events (AEs) during the study period.

A comprehensive physical examination including head and neck, skin, eye, ears, nose, and throat (ENT), cardiovascular system (CVS), respiratory system (RS), gastrointestinal system (GIS), endocrine system including thyroid, genitourinary system (GUS), central nervous system (CNS), musculoskeletal system, nails, and lymph nodes was performed, and any relevant findings were recorded in the case record form. Vital signs such as heart rate (beats/min), respiration rate (breaths/min), systolic and diastolic blood pressure (mm Hg), and body temperature (°F) were recorded. Standard 12-lead ECG were recorded for all the enrolled participants. Hematology, blood chemistry lipid profile, urine pregnancy test (only for females of childbearing potential or were ≤ 1 year postmenopausal at screening) was collected. The values of all laboratory parameters at pre-op day served as the baseline values (Fig. 1). The length of hospital stay was measured from the day of surgery till the day of discharge. In order to measure muscle strength, independent-blinded assessor performed the hand-grip strength test using hand-held dynamometer. An independent-blinded assessor assessed the venipuncture PPN infusion sites for thrombophlebitis from the start of infusion till 24 hours after last infusion and till the day of discharge. Any event of thrombophlebitis was followed until resolution/end of study. Visual infusion phlebitis score was used to assess phlebitis. An AE was defined according to the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (ICH E6:1.2). Worsening of a pre-existing medical condition (e.g., diabetes, migraine headaches, and gout) was considered an AE if there was either "an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes." The intensity of the AE was described in terms of mild, moderate or severe, life threatening and fatal according to the Principal Investigator's clinical judgement. A serious AE (SAE) was defined as "an AE that was fatal, life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, caused a congenital anomaly/birth defect, or was a medically significant event." The causality was assessed as related or unrelated for the events.

Action Taken and Its Description

- Study product interrupted: Study product was temporarily discontinued.
- Study product withdrawn: Study product was permanently discontinued.
- No action taken: The AE did not result in any modification of dose or frequency of dosing.
- Not applicable: The AE occurred prior to first dose or following last scheduled dose.

Statistical Methods

To ensure data fidelity, the pertinent information from the electronic health record was extracted by the trained study members and was later entered onto REDCap (a secure web-based data management system). After appropriate data filtration, the datasheet was transferred and analyzed using statistical analysis system® (SAS®) for Windows version 9.3/Proc PLAN (SAS® Institute Inc., Cary, NC, USA). All analyses were performed on the ITT population. Continuous variables were described as mean ± SD, unless otherwise stated, while categorical variables were presented in frequencies and percentages. Comparison of continuous variables between the study groups was done using two sample *t*-test and/or analysis of variance test as and where applicable. For comparing categorical data, Chi square (χ^2) test/Fisher's exact test was performed. Results were considered statistically significant at a *p*-value ≤ 0.05. Mean length of hospital stay was compared between BFLUID and NUTRIFLEX PERI by using two sample *t*-test. Following hypothesis was defined to test if length of hospital stay is non-inferior in the treatment arm to the reference arm:

H_0: $M_T - M_R > 1.5$ days

H_1: $M_T - M_R \leq 1.5$ days

where M_T and M_R are the mean length of hospital stay in treatment and reference arms, respectively, and 1.5 days is the pre-specified non-inferiority margin. The hypothesis was tested against the alternative by constructing a two-sided 95% confidence interval (CI) of the difference in mean length of hospital stay. The non-inferiority was established if the upper limit of two-sided 95% CI (or a one sided 97.5% CI) of the difference in mean length of hospital stay was ≤1.5 days.

This study was conducted according to the US and international standards of Good Clinical Practice (CFR Title 21 part 312 and ICH guidelines), applicable government regulations and Institutional research policies and procedures. Also, the study was registered with Clinical Trial Registry of India; CTRI/2021/01/030728.

Results

A total of 150 patients who met the inclusion criteria were included in this clinical trial. Among these 150 patients, there were no significant differences in sex, age, BMI as well as total volume of study drug infused between the BFLUID and NUTRIFLEX PERI group, which implied the comparable results (Table 1). All the patients were of Asian ethnicity. Mean estimated energy intake by amount of ON/EN provided to patients was 1257.81 ± 1067.566 kcal in BFLUID group and 948.22 ± 758.916 kcal in NUTRIFLEX PERI group. The difference in Estimated Energy Intake by amount of ON/EN provided to patients was statistically non-significant between both the groups (Table 1). Mean total volume of study drug administered was 6.66 ± 1.704 L in BFLUID group and 6.13 ± 1.663 L in NUTRIFLEX PERI group.

Table 1: Patient demographics and characteristics

Parameter	*BFLUID (N = 78)*	*NUTRIFLEX PERI (N = 72)*	*p-value*
Male	62.8%	59.7%	0.7389
Female	37.2%	40.3%	
Age (years)	49.2 ± 11.48	49.9 ± 12.08	0.7084
Weight (kg)	59.3 ± 11.39	59.7 ± 12.87	0.8700
Height (cm)	162.0 ± 9.86	160.0 ± 9.97	0.2101
BMI (kg/m^2)	22.5 ± 3.06	23.1 ± 3.44	0.2256
Total volume of study drug (L)	6.66 ± 1.704	6.13 ± 1.663	0.0558
ON/EN (kcal)	1257.81 ± 1067.56	948.22 ± 758.91	0.1312
Mean total energy (kcal)	4185 ± 1557.252	3905 ± 1067.344	0.4829

BMI, body mass index. Value presented as mean ± SD or %

Table 2: Comparison of clinical efficacy and safety of BFLUID vs NUTRIFLEX PERI

Parameter	*BFLUID (N = 78)*	*NUTRIFLEX PERI (N = 72)*	*95% CI*	*p-value*
Length of hospital stay (days)	9.4 ± 4.70	9.7 ± 3.34	−1.57:1.07	0.7134
Length of hospital stay in ICU/HDU (days)	2.9 ± 1.82	3.1 ± 2.12	−0.89:0.51	0.5917
Infection	0 (0%)	0 (0%)	–	–
Mortality	1 (1.28%)	0 (0%)	−3.85:6.94	>0.9999

CI, confidence interval; HDU, high dependency unit; ICU, intensive care unit. Value presented as mean ± SD or %

The mean duration of use of NUTRIFLEX PERI was 3.72 days while it was 3.66 days for BFLUID. Of the 150 patients, 134 (89.3%) had at least one medical history (Supplementary Material Table S2). Of these 134 patients, majority [113 (75.3%)] of the patients had history of neoplasms benign, malignant, and unspecified (including cysts and polyps), followed by gastrointestinal disorders in 26 (17.3%), metabolism and nutrition disorder in 26 (17.3%), vascular disorders (hypertension) in 22 (14.7%), surgical and medical procedures in 13 (8.7%), infections and infestations in 5 (3.3%) patients.

The overall mean length of hospital stay was 9.4 ± 4.70 days and 9.7 ± 3.34 days in BFLUID and NUTRIFLEX PERI group, respectively. Difference in mean length of hospital stay between two groups was only 0.3 days (95% CI = −1.57 to 1.07), which was within pre-defined non-inferiority margin of 1.5 days. This finding demonstrate that the study met its primary objective of non-inferiority of BFLUID as compared with NUTRIFLEX PERI. The mean length of hospital stay in ICU/HDU was 2.9 ± 1.82 days in BFLUID group and 3.1 ± 2.12 days in NUTRIFLEX PERI group (p = 0.5917) (Table 2). One patient in BFLUID group had a fatal outcome which was unrelated to study drug infusion. No signs of infection were observed in patients of both the group.

On infusion day 1, mean blood level of vitamin B1 was 1.74 ± 1.519 µg/dL and 1.20 ± 1.134 µg/dL in BFLUID and NUTRIFLEX PERI group, respectively (Table 3). Mean change in blood levels of vitamin B1 from baseline and end of infusion day was −0.19 ± 1.779 µg/dL in BFLUID group and 0.16 ± 1.723 µg/dL in NUTRIFLEX PERI group. The change in blood levels of vitamin B1 from baseline was not significant and was comparable between both the groups (p = 0.2537). Mean change in albumin from baseline

Table 3: Change in blood levels of vitamin B1 from baseline (before start of infusion) to post end of infusion

	Actual values		*Change from baseline*	
Parameter/ Statistics	*BFLUID (N = 78)*	*NUTRIFLEX PERI (N = 72)*	*BFLUID (N = 78)*	*NUTRIFLEX PERI (N = 72)*
Infusion day 1				
N	76	65		
Mean ± SD (µg/dL)	1.74 ± 1.519	1.20 ± 1.134		
p-value[a]	0.0177	NA	NA	NA
p-value[b]	NA	NA	NA	NA
End of infusion				
N	70	66	70	63
Mean ± SD (µg/dL)	1.63 ± 1.381	1.44 ± 1.305	−0.19 ± 1.779	0.16 ± 1.723
p-value[a]	0.4233	NA	0.2537	NA
p-value[b]	NA	NA	0.3719	0.4670

[a]*p*-value was calculated using two sample *t*-test between treatment arms; [b]*p*-value was calculated using paired *t*-test for change from baseline. Value presented as mean ± SD or *N*

Table 4: Change in nutritional parameters from baseline to the day of discharge

	Change from baseline		
Parameter	*BFLUID (N = 78)*	*NUTRIFLEX PERI (N = 72)*	*p-value*
Serum albumin (gm/L)	−3.6 ± 8.76	−3.9 ± 6.72	0.8357
Serum pre-albumin (gm/L)	−0.1 ± 1.04	0 ± 0.07	0.4007
Retinol binding protein (gm/L)	−0.01 ± 0.117	0 ± 0.049	0.6470
Body weight (kg)	−0.7 ± 1.07	−0.2 ± 1.70	0.0698
Hand grip strength (left arm) (kg)	−0.3 ± 2.37	0 ± 0.94	0.3908
Hand grip strength (right arm) (kg)	−0.5 ± 2.15	0 ± 1.16	0.1181

Value presented as mean ± SD

was −3.6 ± 8.76 gm/L in BFLUID vs −3.9 ± 6.72 gm/L in NUTRIFLEX PERI (p = 0.8357). While the mean change in pre-albumin from baseline was −0.1 ± 1.04 gm/L in BFLUID vs 0.0 ± 0.07 gm/L in NUTRIFLEX PERI (p = 0.4007). Similarly, there was no significant difference in mean change in retinol binding protein from baseline BFLUID and NUTRIFLEX PERI (−0.01 ± 0.117 gm/L vs 0.00 ± 0.049 gm/L, respectively; p = 0.6470). Moreover, we did not observe any significant difference in mean change in weight (p = 0.0698), hand grip in left hand (p = 0.3908) and right hand (p = 0.1181) between BFLUID and NUTRIFLEX PERI group (Table 4).

At the end of infusion, 4 (5.13%) patients in BFLUID group and 2 (2.78%) patients in NUTRIFLEX PERI group reported to have possible first signs of phlebitis whereas 3 (3.85%) patients in BFLUID group and 1 (1.39%) patient in NUTRIFLEX PERI group reported to have early signs of phlebitis. Also, 1 (1.39%) patient in NUTRIFLEX PERI group reported to have medium stage of phlebitis. At the day of discharge, 1 (1.28%) patient in BFLUID group reported to have possible first signs of phlebitis (Table S3). At infusion day 1, 1 (1.28%) patient in BFLUID group and 4 (5.56%) patients in NUTRIFLEX PERI

Table 5: Summary of overall AEs

Parameter	*BFLUID (N = 78)*		*NUTRIFLEX PERI (N = 72)*		
	No. of patients (Events)	*%*	*No. of patients (Events)*	*%*	*p-value*
Subjects who reported at least one AE	23 (40)	29.5	19 (26)	26.4	
Seriousness					0.2515
Yes	3 (3)	3.8	0 (0)	0.0	
No	23 (37)	29.5	19 (26)	26.4	
If yes,					
Is fatal	1 (1)	1.3	0 (0)	0.0	
Life threatening	1 (1)	1.3	0 (0)	0.0	
Requires in-patient hospitalization	1 (1)	1.3	0 (0)	0.0	
Results in persistent or significant	0 (0)	0.0	0 (0)	0.0	
Is a congenital anomaly	0 (0)	0.0	0 (0)	0.0	
Is a medically significant event	0 (0)	0.0	0 (0)	0.0	
Severity					>0.9999
Mild	18 (31)	23.1	15 (20)	20.8	
Moderate	5 (6)	6.4	4 (6)	5.6	
Severe	1 (1)	1.3	0 (0)	0.0	
Fatal	1 (1)	1.3	0 (0)	0.0	
Life-threatening	1 (1)	1.3	0 (0)	0.0	
Relationship to study medication					0.7091
Related	9 (9)	11.5	6 (6)	8.3	
Unrelated	19 (31)	24.4	16 (20)	22.2	
Action taken					0.5820
Study product interrupted	3 (3)	3.8	4 (4)	5.6	
Study product withdrawn	2 (2)	2.6	0 (0)	0.0	
No action taken	15 (22)	19.2	9 (13)	12.5	
Not applicable	9 (13)	11.5	8 (9)	11.1	
Outcome					0.8361
Recovered	20 (33)	25.6	17 (22)	23.6	
Not recovered	3 (6)	3.8	4 (4)	5.6	
Fatal	1 (1)	1.3	0 (0)	0.0	

group reported to have pain at injection site. And at the end of infusion, 4 (5.26%) patients in BFLUID group and 3 (4.17%) patients in NUTRIFLEX PERI group reported to have pain at injection site. At the day of discharge, none of the patients in BFLUID group reported pain at the injection site while 3 (4.17%) patients in NUTRIFLEX PERI group reported to have pain at injection site (Table S4). There was no significant difference between the two groups for all above AEs.

Of the 66 AEs in 42 (28.0%) patients, 40 AEs were reported in 23 (29.5%) patients in BFLUID group and rest 26 AEs in 19 (26.4%) patients in the NUTRIFLEX PERI group. In BFLUID group, 31 AEs in 18 (23.1%) patients were mild, 6 AEs in 5 (6.4%) patients were moderate, 1 AE in 1 (1.3%) patient was severe, 1 AE in 1 (1.3%) patient was life-threatening and 1 AE in 1 (1.3%) patient was fatal (Table 5). Out of 3 SAEs reported in BFLUID group, 1 (lung consolidation) was severe and required in patient hospitalization/prolongation of existing hospitalization, 1 (anastomotic leak) was life-threatening, and 1 (cardiac arrest) was fatal (case summarized in Supplementary Material). All of the 3 SAEs reported were found to be unrelated to BFLUID. The difference in severity of AEs reported in both the groups was statistically insignificant ($p > 0.9999$). In BFLUID group, study product was withdrawn for 2 AEs reported in 2 (2.6%) patients, study product was interrupted for 3 AEs reported in 3 (3.8%) patients and no action was required for 22 AEs in 15 (19.2%) patients. In NUTRIFLEX PERI group, study product was interrupted for 4 AEs reported in 4 (5.6%) patients and no action was required for 13 AEs in 9 (12.5%) patients. The difference in action taken for AEs reported in both the groups was statistically insignificant ($p = 0.5820$). All 15 AEs (9 in BFLUID and 6 in NUTRIFLEX PERI group) related to medication involved thrombosis at the infusion site. Detailed summary of AEs by system organ class (SOC) and preferred term (PT) is depicted in Supplementary Material Table S5.

Discussion

A randomized, parallel Group, Phase III trial compared two study groups BFLUID and NUTRIFLEX PERI in adult patients undergoing gastrectomy or colectomy. The trial successfully demonstrated the non-inferiority of BFLUID to NUTRIFLEX PERI. Moreover, there was no significant difference in terms of length of hospital stay, length of ICU/HDU stay as well as change in nutritional parameters from baseline and change in blood levels of vitamin B1 from baseline. Also, both the study groups were comparable in relation to AEs, pain at injection site, and incidence of phlebitis.

The composition of AA formulations in BFLUID and NUTRIFLEX PERI differed from each other. Primarily, NUTRIFLEX PERI has higher concentration of AAs and total energy (4% and 480 kcals/L, respectively) as compared with BFLUID (3% and 420 kcals/L, respectively). Conversely, proportion of BCAAs and EAAs are higher in BFLUID (30 and 60%, respectively) compared with NUTRIFLEX PERI (20 and 47.5%, respectively). The BCAAs (leucine, isoleucine, and valine) are clinically important since they simultaneously stimulate muscle protein synthesis and inhibit muscle protein breakdown. This dual action is particularly valuable for critically ill patients or those recovering from major abdominal surgery, as it helps in preventing muscle wasting due to factors such as immobility and increased metabolic demands. Leucine, in particular, has been shown to improve insulin sensitivity and glucose metabolism, making it important for patients with diabetes or glucose tolerance issues.[9,10] Numerous studies have consistently highlighted the significance of administering BCAAs and EAAs in PN, emphasizing their importance over the overall quantity of protein/AA. Lacone et al. conducted preliminary and retrospective clinical observations and found a significant and positive correlation between muscle mass gain in patients receiving home PN and the daily doses of total EAAs, BCAAs, as well as individual EAAs like leucine, isoleucine, valine, and methionine. The authors also emphasized a strong link between the quantities of leucine and isoleucine in the nutritional solutions and the increase in skeletal muscle mass.[11] In the present study as well, there was no decline in the muscle strength (determined by handgrip strength) and in nutritional status (determined by parameters like albumin, pre-albumin, retinol binding protein, and body weight) in patients of both the groups.

Vitamin B1, also known as thiamine, is an essential micronutrient that plays a crucial role in carbohydrate metabolism, specifically

in the conversion of pyruvate to acetyl-CoA and in the citric acid cycle. It is generally believed that patients receiving PPN therapy are not likely to develop thiamine deficiency (TD) due to low total calorie intake from carbohydrates and the shorter infusion period (1–2 weeks). However, the endogenous stores of vitamin B1 are not more than 30 mg – meaning the body's stores of vitamin B1 get rapidly depleted in surgical patients, which can lead to its deficiency, if not supplemented.[12] Similar results were observed in other clinical studies which reported a significant drop in vitamin B1 level within 5–7 days' post abdominal surgery.[13,14] This deficiency of thiamine can potentially give rise to more severe complications such as lactic acidosis and Wernicke encephalopathy.[15–18] In 1988, American Society for Parenteral and Enteral Nutrition (ASPEN) was notified regarding the death of three individuals who were administered vitamin-free TPN for several weeks. Each of these patients exhibited compelling indications of TD and died within 5 weeks of receiving TPN without thiamine.[19] Based on therapeutic challenges to correct vitamin B1 deficiency after abdominal surgery, European Society for Clinical Nutrition and Metabolism (ESPEN) recommends the administration of thiamine (2–6 mg/day) along with other essential micro- and macro-nutrients as a preventive measure for refeeding syndrome.[20] Further, ASPEN guideline also recommends thiamine (6 mg) in order to mitigate the elevated nutritional needs in a limited subset of patients who are administered high doses of glucose as part of their PN regimen.[21] In this clinical trial, 72% of adult patients that had undergone gastrectomy/colectomy already had low serum vitamin B1 level at baseline. Unlike NUTRIFLEX PERI, the BFLUID additionally contains thiamine (1.5 mg/1000 mL), which certainly provides a distinct advantage over its counterpart in maintaining vitamin B1 levels post-surgery. Also, patients in the BFLUID group exhibited blood vitamin B1 levels within the expected range. Several factors could contribute to the non-significant difference in the change in thiamine levels between the two groups. These might include a high prevalence of baseline TD (72%), the presence of thiamine in ON/EN administered to patients, and other variables affecting thiamine metabolism or absorption.

The multicentric nature of the study conferred various advantages such as increased sample size, greater diversity of participants, and enhanced generalizability of results. It is important to acknowledge that there is currently a lack of recognized procedures for effectively assessing the nutritional status during a 1–2-week timeframe following surgical stress. Also, blood protein levels following surgical insults immediately after surgery do not accurately indicate an individual's nutritional state. Instead, these levels serve as indicators of inflammation. Nevertheless, our objective was to evaluate the clinical effectiveness and safety of administering BFLUID in comparison to the well-established medication NUTRIFLEX PERI. To conclude, BFLUID achieved non-inferiority with NUTRIFLEX-PERI in primary end point (length of hospital stay) despite of presence of lower concentration of AAs and total energy. All the secondary end points (e.g., change in blood levels of vitamin B1 from baseline, change in nutritional parameters from baseline, and incidence of thrombophlebitis) were comparable between the two groups. The findings of this study shows that PPN with high BCAAs and EAAs, and thiamine is safe and effective in adult patients undergoing gastrectomy or colectomy. Moreover, the study underscores the importance of emphasizing BCAAs and EAAs in PN rather than solely focusing on the total amount of AAs and total energy provided.

Acknowledgments

This study was sponsored by Otsuka Pharmaceutical India Pvt. Ltd. The authors would like to acknowledge JSS Medical Research Asia Pacific for their help in study document preparation, study conduction, data management and preparing the preliminary report. The authors would also like to gratefully thank investigators for their active involvement throughout the conduct of this study. The authors extend their sincere and heartfelt thanks to all the patients/LAR who generously consented to participate in this research.

Author Contributions

The sponsor of the study participated in the study design, data collection, review and approval of the final clinical study report. All authors collectively contributed to the acquisition, analysis, or interpretation of the data. All authors read approved the final version of the manuscript. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Data Availability Statement

The data of the current study as well as the study protocol is available with the corresponding author of this article and will be shared on specific request.

Clinical Trial Registration Number

CTRI/2021/01/030728.

Supplementary Materials

All the supplementary materials are available online on the website of www.IJCCM.org.

Orcid

Amit Goyal https://orcid.org/0000-0002-8573-9650
Anand Pathak https://orcid.org/0009-0002-4188-5450
Madhu BS https://orcid.org/0009-0006-6857-7174
Harshad Soni https://orcid.org/0009-0002-4098-9004
Keyur Bhatt https://orcid.org/0000-0002-1734-4577
KVVN Raju https://orcid.org/0000-0002-2399-7419
Murali K Voonna https://orcid.org/0000-0002-5616-8078
Rakshit Shah https://orcid.org/0009-0002-0903-6678
Chetna Shah https://orcid.org/0009-0002-6224-6105
Dignesh Patel https://orcid.org/0009-0000-4595-8667

References

1. Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med 2009;361(11):1088–1097. DOI: 10.1056/NEJMct0806956.
2. Garth AK, Newsome CM, Simmance N, Crowe TC. Nutritional status, nutrition practices and post-operative complications in patients with gastrointestinal cancer. J Hum Nutr Diet 2010;23(4):393–401. DOI: 10.1111/j.1365-277X.2010.01058.
3. Adiamah A, Skořepa P, Weimann A, Lobo DN. The impact of preoperative immune modulating nutrition on outcomes in patients undergoing surgery for gastrointestinal cancer: A systematic review and meta-analysis. Ann Surg 2019;270(2):247–256. DOI: 10.1097/SLA.0000000000003256.
4. Thomovsky E, Reniker A, Backus R, Mann FA, Dodam JR. Parenteral nutrition: Uses, indications, and compounding. Compend Contin Educ Vet 2007;29(2):76–78. PMID: 17727158.
5. Madsen H, Frankel EH. The hitchhiker's guide to parenteral nutrition management for adult patients. Pract Gastroenterol 2006;30(7):46.

Available from: https://med.virginia.edu/ginutrition/wp-content/uploads/sites/199/2015/11/MadsenArticle-July-06.pdf.
6. Choudry HA, Pan M, Karinch AM, Souba WW. Branched-chain amino acid-enriched nutritional support in surgical and cancer patients. J Nutr 2006;136(1 Suppl):314s–318s. DOI: 10.1093/jn/136.1.314S.
7. Bellorin O, Kundel A, Ni M, Litong D. Surgical management of gastrointestinal stromal tumors of the stomach. JSLS 2014;18(1):46–49. DOI: 10.4293/108680813X13693422522150.
8. Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, et al. Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. N Engl J Med 2018;378(24):2263–2274. DOI: 10.1056/NEJMoa1801601.
9. Pennings B, Groen B, de Lange A, Gijsen A, Zorenc AH, Senden JM, et al. Amino acid absorption and subsequent muscle protein accretion following graded intakes of whey protein in elderly men. Am J Physiol Endocrinol Metab 2012;302(8):E992–E999. DOI: 10.1152/ajpendo.00517.2011.
10. Luiking YC, Deutz NE, Memelink RG, Verlaan S, Wolfe RR. Postprandial muscle protein synthesis is higher after a high whey protein, leucine-enriched supplement than after a dairy-like product in healthy older people: A randomized controlled trial. Nutr J 2014;13(1):9. DOI: 10.1186/1475-2891-13-9.
11. Iacone R, Scanzano C, Santarpia L, Alfonsi L, Marra M, Pagano MC, et al. Essential amino acid profile in parenteral nutrition mixtures: Does it meet needs? Nutrients 2018;10(12):1937. DOI: 10.3390/nu10121937.
12. Volpi E, Kobayashi H, Sheffield-Moore M, Mittendorfer B, Wolfe RR. Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. Am J Clin Nutr 2003;78(2):250–258. DOI: 10.1093/ajcn/78.2.250.
13. Fukushima R, Shiratori M, Yago H, Ogihara T, Ogawa F, Kobayashi S, et al. Should vitamin B1 be added to peripheral parenteral nutrition after major gastrointestinal surgery? Determination of perioperative vitamin B1 status. Jpn J Surg metabolism and nutrition 2003;37(1):23–31.
14. Masumoto K, Esumi G, Teshiba R, Nagata K, Nakatsuji T, Nishimoto Y, et al. Need for thiamine in peripheral parenteral nutrition after abdominal surgery in children. JPEN J Parenter Enteral Nutr 2009;33(4):417–422. DOI: 10.1177/0148607108327391.
15. Salvatori G, Mondì V, Piersigilli F, Capolupo I, Pannone V, Vici CD, et al. Thiamine deficiency in a developed country: Acute lactic acidosis in two neonates due to unsupplemented parenteral nutrition. JPEN J Parenter Enteral Nutr 2016;40(6):886–889. DOI: 10.1177/0148607114568316.
16. Teagarden AM, Leland BD, Rowan CM, Lutfi R. Thiamine deficiency leading to refractory lactic acidosis in a pediatric patient. Case Rep Crit Care 2017;2017(1):5121032. DOI: 10.1155/2017/5121032.
17. Abdalian R, Fernandes G, Duerksen D, Jeejeebhoy KN, Whittaker S, Gramlich L, et al. Prescription of trace elements in adults on home parenteral nutrition: Current practice based on the Canadian Home Parenteral Nutrition Registry. JPEN J Parenter Enteral Nutr 2013;37(3):410–415. DOI: 10.1177/0148607112463074.
18. Jin J, Mulesa L, Carrilero Rouillet M. Trace elements in parenteral nutrition: Considerations for the prescribing clinician. Nutrients 2017;9(5):440. DOI: 10.3390/nu9050440.
19. Morbidity and Mortality Weekly Report. Centers for Disease Control and Prevention 1989;38(3):43–46. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00001339.htm.
20. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clin Nutr 2017;36(3):623–650. DOI: 10.1016/j.clnu.2017.02.013.
21. Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. A.S.P.E.N. position paper: Recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. Nutr Clin Pract 2012;27(4):440–491. DOI: 10.1177/0884533614551926.