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ORIGINAL ARTICLE

Comparison of Protocol-Based Continuous and Intermittent Tube Feeding in Mechanically Ventilated Critically Ill Children – An Open Label Randomized Controlled Trial

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Abstract

Objectives To compare the time taken to reach the target calories and proteins by protocol based "continuous tube feeding (CTF)" and "intermittent tube feeding (ITF)" in critically ill children.

Methods This trial was conducted in the Pediatric Intensive Care Unit (PICU) of a tertiary care institute. Eligible children were randomized to receive CTF or ITF. Target calories were defined as 70% of calorie amount as per the WHO formula and target protein was defined as 1.5 g/kg as per the American Society of Parenteral and Enteral Nutrition (ASPEN) criteria. The primary outcome was time taken to reach target calories, the secondary outcomes were time taken to reach target protein, incidence of feed intolerance, PICU mortality, duration of ventilation, and outcome on 28th day.

Results Fifty-eight children were randomized; 29 in each group. The baseline characters were comparable. The median (IQR) times for reaching target calories were 1.7 (1.4, 2.5) d and 1.8 (1.4, 4.4) d in the CTF and ITF groups, respectively [Hazards ratio (HR) 0.89 (95% CI 0.5, 1.5); $p = 0.69$]. For the target protein intake, the median times were comparable in the 2 groups [HR 0.82 (95% CI 0.4-1.5); $p = 0.55$]. The other outcomes were not significantly different between the groups.

Conclusions The authors did not observe any difference in the time taken to reach target calories and protein between the two different modes of delivery of enteral nutrition.

Keywords Critically ill children · Enteral feeding · Continuous versus intermittent feeding · Feed intolerance

Introduction

Critically ill children require comprehensive therapeutic measures to achieve favorable outcomes. One of the vital components is nutritional support, as the critical illness per se increases the metabolic demand and worsens the nutritional status of the child, thereby resulting in poor outcomes. The average incidence of malnutrition in children admitted in Pediatric Intensive Care Unit (PICU) is around 30% [1]. Energy deficit and poor nutritional achievement in critically ill children may increase risk of hospital acquired infections, poor healing, length of mechanical ventilation, hospital stay and risk for mortality [2]. In the PICU at authors' institute, the prevalence of malnutrition was reported to be 51.2%, and severely malnourished had longer duration of ventilation and PICU stay (>7 d) [3].

The benefits of enteral nutrition are well established. However, various factors delay the initiation of feeding and achieving the target calories and protein, of which a major precluding factor is feed intolerance. The guidelines recommend that the enteral route is preferred but the evidence for mode of delivery-either continuous or intermittent is insufficient [4]. Earlier studies in children, reported varying results. Intermittent method was better in a recent pilot randomized controlled trial (RCT) [5], while another reported continuous feeding was better in delivering protein and calories [6]. A recent systematic review in children concluded that the trials comparing continuous and intermittent feeding did not have similar feeding regimens, and attainment of nutrient delivery goals were not described; hence the evidence is insufficient to make any recommendation for the preferred mode of feeding [7, 8] and therefore the need for this study.

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The authors hypothesized that the time to achieve target calories and protein by continuous tube feeding (CTF) method would be lesser than the intermittent tube feeding (ITF) as the former results in constant slow delivery of nutrients to the injured gastrointestinal tract and might result in improved tolerance leading to better nutritional delivery by achieving target calories and proteins earlier. The aim was to compare the two methods of enteral nutritional support (intermittent vs. continuous) in critically ill children.

Material and Methods

It was an open label, randomized controlled trial carried out at a tertiary care institute in North India from August 2019 through July 2021. The study was approved by the Institute Ethics Committee (IECPG- 14/27.06.2019) and registered in the Clinical Trial Registry of India prospectively (CTRI/2019/06/019756).

Critically ill children, aged 1 mo to 18 y, admitted to the PICU and mechanically ventilated (invasive) with or without vasoactive support were eligible. Children with known malabsorption syndrome, chronic diarrhea, on peritoneal or hemodialysis; admitted for elective pre- and post-procedure care; and those already on enteral tube feeding before admission to PICU were excluded.

The primary outcome measure was time taken to reach the target calories (≥70% of calculated calories as per WHO age-sex specific equation after initiation of feeds) [9].

The secondary outcomes compared were- proportion of children who received target calories for 48 h without interruption, proportion of children reaching target calories before day 7, time taken to reach target protein (1.5 g/kg as per the American Society of Parenteral and Enteral Nutrition (ASPEN) criteria) [4], incidence of feed intolerance, glucose variability (hypoglycemia <60 mg/dL, hyperglycemia >180 mg/dL) [10], and mortality rates between the 2 groups.

Feed intolerance was defined by the presence of any one of the features- vomiting, abdominal distension >10% increase from baseline girth or diarrhea (≥3 episodes of loose stools) [5, 8].

As soon as a child was admitted to the PICU, (s)he was screened for eligibility based on the inclusion and exclusion criteria by the resident-on-call. The resident-on-call informed the primary investigator who enrolled children after taking informed consent from parents/Legally Authorized Representative (LAR). Children were randomized to continuous tube feeding or intermittent tube feeding groups (1:1 ratio). Block randomization was done in varying block sizes of 2 to 8. The authors used serially numbered, opaque envelopes containing randomization codes to ensure allocation concealment. The envelopes were opened only after informed consent.

Children randomized to continuous feeding group (study group) received feeds at 1 ml/kg/h (maximum of 25 ml/h) and the rate was increased at 1 ml/kg/h (max. 25 ml/h) every 4 h till the maximum fluid volume planned for the respective day was reached (Supplementary Fig. S1).

In the intermittent feeding group (control group), children received feeds at 2 ml/kg every 2 h (max. 50 ml/feed), and the rate was increased at 2 ml/kg every 4 h (max 50 ml) till the maximum fluid volume planned for the respective day was reached (Supplementary Fig. S1).

If intolerance occurred, the feeds were restarted at 50% of the volume on which the child had developed intolerance in both the groups.

The maximum fluid volume was the amount of fluid planned for the child by the treating team based on the clinical condition of the child. The permitted feed volume was obtained after deducting the volume of medications and other fluids from the maximum fluid volume.

The type of feeds used for infants 1 mo to 1 y were either expressed breast milk (EBM) (67 kcal and 1.1 g protein/100 ml if available) or infant formula available in the unit- Dexolac (Nutricia) containing 78 kcal and 2 g of protein/100 ml. In case the quantity of EBM available was insufficient, both EBM and infant formula were used. Children 1-18 y received packaged dairy milk (containing 58 kcal and 3.3 g protein/100 ml), fortified with starch and/or edible oil to increase the calorie content to up to 0.94 kcal/ml. Calorie requirement of the child was calculated using WHO age- and gender- specific formulae [9] and target protein aimed was 1.5 g/kg/d as per the American Society of Parenteral and Enteral Nutrition (ASPEN) recommendations [4].

Baseline characteristics were recorded for all children in a predesigned proforma including demographic variables, admitting diagnosis, severity of illness score– Pediatric index of mortality-3 (PIM-3) score [11] and anthropometry. WHO charts [12] for children upto 5 y and Indian Academy of Pediatrics (IAP) growth charts for children 5 y or older [13] were used to determine the anthropometric status. Before initiation of feeds, Pediatric Logistic Organ Dysfunction (PELOD) score [14] and Pediatric Sequential Organ Failure Assessment (pSOFA) scoring [15] were noted. Thereafter, clinical variables, daily intake of calorie and protein, maximal and minimal inotropic score in 24-h and laboratory variables (serum potassium) were monitored till the child achieved the primary end point. Children were monitored for feed intolerance. The number of feed interruptions, duration, and the reasons for interruption were noted.

The medications received by the child, including antibiotics, analgesics, sedatives and paralytic agents were documented. Blood sugar was monitored by checking capillary blood glucose as per unit protocol every 6 h during the first 48 h of initiation of feeding. Child was followed up for the period of ICU stay or 10 d after initiation of feeds whichever

occurred earlier. PICU outcomes, mortality, duration of ICU stay, duration of mechanical ventilation and outcome on 28th day were noted.

Based on a previous study, intermittent feeding achieved calorie target in 4.35 (±0.98) d and continuous feed achieved calorie target in 3.17 (±1.56) d [6]. The sample size using these values for the primary outcome with power of 90% and alpha error of 5% for two-sided hypothesis was 34 children in each group (total 68 children).

A structured proforma was filled for each patient. All the data were entered into Microsoft Excel. Analysis was performed using Stata software (Version 14.2, StataCorp, College Station, TX). Descriptive statistics were used for population baseline characteristics. Categorical data were presented as number (%) and continuous variable presented as mean ± SD. Statistical analysis was performed by using Student's t test/Wilcoxon rank-sum test and chi-square test for continuous and categorical variables, respectively. Intention to treat analysis using time to event (survival analysis) was performed for the primary outcome. Adjusted hazard ratio was derived for variables significantly different in the baseline characteristics.

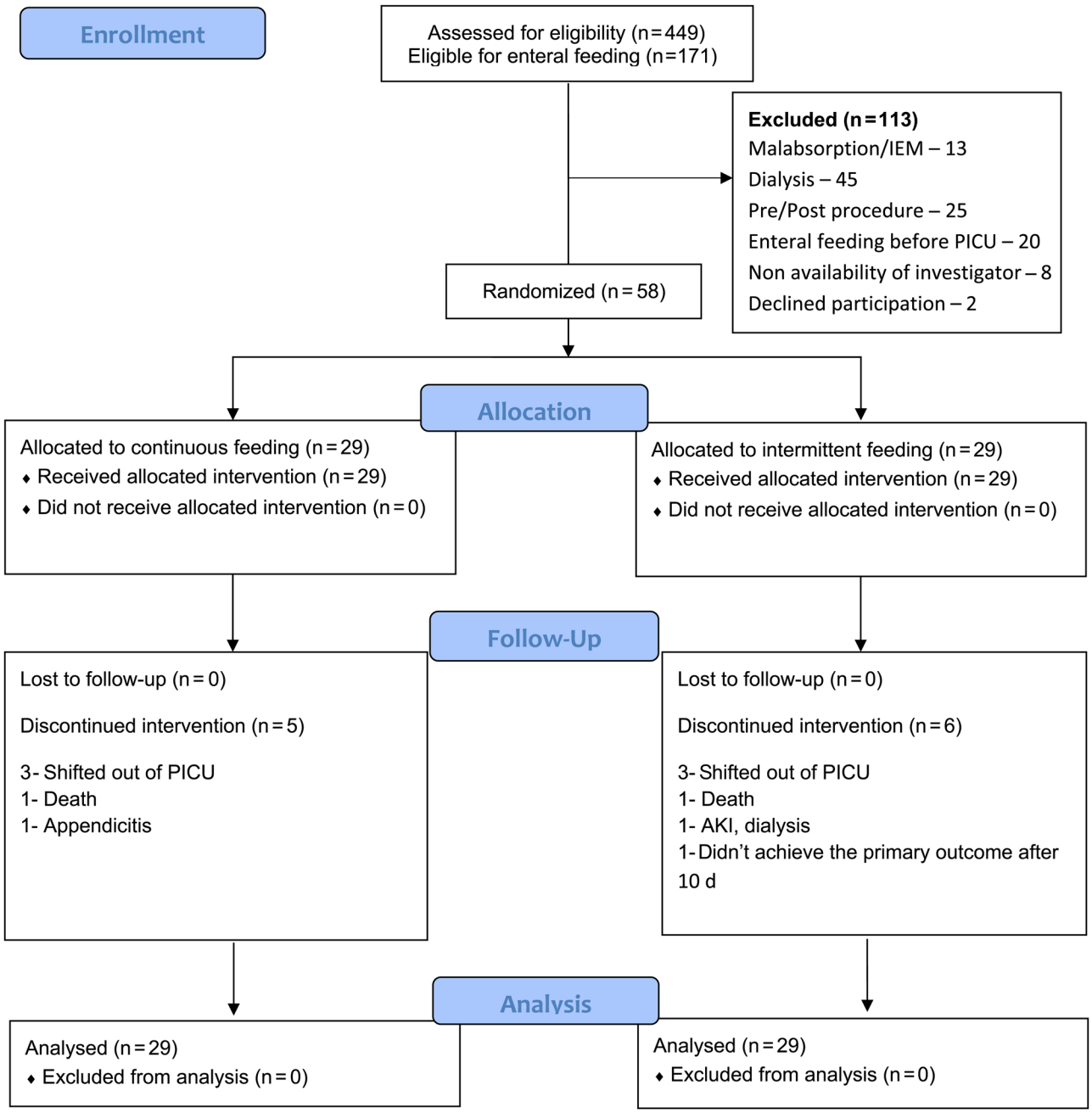

Fig. 1 CONSORT diagram – Study flow. *AKI* Acute kidney injury, *IEM* Inborn error of metabolism, *PICU* Pediatric intensive care unit

Results

Of 449 admissions during the study period, 60 were eligible for enrolment and 58 children were randomized to continuous (n = 29) and intermittent (n = 29) groups (Fig. 1). More than one-third had an underlying chronic condition. The most common acute illness was pneumonia followed by severe sepsis. The proportions of children with shock were more in the 'continuous feeding' group [64.5% vs. 35.5%]. Other characteristics were comparable between the groups (Table 1). The type of feed received by the enrolled children as per the age group is shown in Table 2.

A total of 47 children attained target calories after initiation of feeds in the PICU- 24 (83%) in the 'continuous' group and 23 (79%) in the 'intermittent' group. The reasons for not reaching the target calories are shown in Supplementary Table S1.

The primary outcome, the median (IQR) time to reach target calories was 1.7 (1.4, 2.5) d in the CTF group, and 1.8 (1.4, 4.4) d in the ITF group (Supplementary Fig. S2) [Hazard ratio 0.89 (95% CI 0.5, 1.5)]; the difference was not statistically significant ($p = 0.69$). As there were differences in disease severity and presence of shock between the two groups, the authors also performed adjusted analysis

Table 1 Baseline characteristics of the enrolled children

Characteristic	Continuous feeding group, N = 29	Intermittent feeding group, N = 29
Age in months, Median (IQR)	54 (16.5, 120)	8 (8, 54)
Gender		
Female, n (%)	12 (41.4)	12 (41.4)
Acute illness - diagnosis, n (%)		
Pneumonia	11 (37.9)	12 (41.4)
Severe infection/sepsis	9 (31)	5 (17.2)
Tuberculosis	4 (13.8)	2 (6.9)
Meningitis/meningoencephalitis	2 (6.9)	2 (6.9)
Refractory epilepsy	0	2 (6.9)
Snake envenomation	2 (6.9)	0
Acute liver failure	1 (3.5)	1 (3.5)
Malignancy	0	3 (10.3)
MISC	0	1 (3.5)
GBS	0	1 (3.5)
Number of children with underlying chronic disease; n (%)	18 (62.1)	16 (55.2)
Nature of chronic illness, n (%)		
Congenital heart diseases	3 (16.7)	3 (18.8)
Respiratory (airway & parenchymal)	3 (16.7)	3 (18.8)
Neurological	2 (11.1)	1 (6.3)
Gastrointestinal including CLD	2 (11.1)	2 (12.5)
Tuberculosis on treatment	0	1 (6.3)
Renal	1 (5.6)	1 (6.3)
Endocrine	0	1 (6.3)
Genetic	1 (5.6)	1 (6.3)
Post trauma	0	1 (6.3)
Weight for age Z score, Median (IQR)	-1.6 (-2.7, -0.2)	-1.2 (-3.4, -0.4)
Length for age Z score, Median (IQR)	-0.7 (-2.1, 0.5)	-1.1 (-2.3, -0.07)
BMI (± SD), kg/m^2	14.0 (12.9, 15.5)	14.2 (11.9, 15.3)
BMI Z score, Median (IQR)	-1.6 (-2.2, -0.2)	-1.4 (-3.6, -0.3)
PIM3 score (± SD); percent predicted mortality	30.6 ± 19.6	32.4 ± 19.1
PELOD score on D1, mean ± SD	6.3 ± 2.3	5.7 ± 1.6
pSOFA score on D1, mean ± SD	8.4 ± 2.3	7.6 ± 2.6
Number of children with shock at enrolment, n (%)	20 (64.5)	11 (35.5)

BMI Body mass index, *CLD* Chronic liver disease, *GBS* Guillain Barré syndrome, *IQR* Interquartile range, *MISC* Multisystem inflammatory syndrome in children, *PELOD* Pediatric logistic organ dysfunction score, *PIM3* Pediatric index of mortality score 3, *pSOFA* Pediatric sequential organ failure assessment score, *SD* Standard deviation

Table 2 Details of feeding received by the children in both the groups

Variable	Continuous feeding group N = 29	Intermittent feeding group N = 29	*p* value
Type of feed; n (%)			0.33
Infant formula	4 (13.8)	8 (28.6)	
Institute's supply packaged milk	25 (86.2)	21 (72.4)	
Feeding route, n (%)			1
Nasogastric	28 (96.5)	27 (93.1)	
Orogastric	1 (3.5)	2 (6.9)	
Time of initiation of feeding after PICU admission			
<48 h	16 (55.2)	20 (68.9)	0.28
48 - <72 h	7 (24.1)	6 (20.7)	0.75
Time of starting feeds in hours, median (IQR)	45 (25, 67)	40 (28, 54.5)	0.69

PICU Pediatric intensive care unit

(Table 3); the adjusted hazards ratio for time to reach target calories between the continuous and intermittent group was 0.77 (95% CI 0.37, 1.5; $p = 0.48$).

Thirty-five children (19 in CTF and 16 ITF group) achieved the target for protein. The median (IQR) time taken to achieve the target protein was 2.3 (1.5, 2.3) d, in the CTF group and 3.5 (1.6, 3.5) d, in the ITF group (Supplementary Fig. S3). The hazards ratio by Cox regression analysis for achieving target protein with CTF was 0.82 (95% CI 0.4, 1.5; $p = 0.55$ by log rank test) when compared with ITF (Table 4). Children in the ITF group took longer time to achieve the target protein, however, it was not statistically significant (Table 4); the adjusted HR for time to reach target protein between the two groups was 0.62 (95% CI 0.28, 1.38, $p = 0.24$).

There were no significant differences in the other secondary outcomes such as proportion of children receiving target calories for 48 h without interruption, proportion reaching target calories before day 7 of initiation of feed and feed interruptions. Although, the overall incidence of feed intolerance was more in the ITF group in the first week after the initiation of feed, it was not statistically significant (Table 4). Other clinical outcomes such as glycemic variability, mortality, duration of ventilation, ICU stay did not differ between the two groups (Table 4).

Discussion

In this randomized controlled trial, the authors did not observe any difference in the time taken to reach target calories or proteins with continuous feeding as compared to intermittent feeding in critically ill children. The incidence of feed intolerance and other clinical outcomes except vomiting were not different between the groups.

Only a few studies have compared the continuous and intermittent feeding in critically ill children. In a pilot study in critically children (n = 25), by Brown et al., where Schofield's equation was used for calculating calorie requirement, the median time for achieving prescribed feeds was 15 h in the 'intermittent group' and 29.5 h in the 'continuous group' ($p = 1.00$) [5]. More children in the intermittent group reached target calories than the continuous group ($p < 0.001$). The volume of feed and calorie content of the feeds received by the groups were not stated. The difference in the time to reach target calories between the groups may be explained by the calorie content of the feed if the volumes were equal [5].

In another study, 'continuous' group (n = 30) achieved the target calories faster (3.17 ± 1.56 d) than the 'intermittent' group (n = 30) (4.35 ± 0.98 d) ($p = 0.001$) as the former received more volume (80 ml per 4 h) than the

Table 3 Primary outcome measure

Variable	Continuous feeding group, N = 29	Intermittent feeding group, N = 29	Hazard ratio (95% CI)	*p* value
Median (IQR) time required to reach target calorie (70% of calculated calorie), days	1.7 (1.4, 2.5)	1.8 (1.4, 4.4)	0.89 (0.5, 1.5)	0.69
Adjusted analysis			0.77 (0.37, 1.5)	0.48

Table 4 Secondary outcome measure

Variable	Continuous feeding group, N = 29	Intermittent feeding group, N = 29	*p* value
Number of children who received target calories for 48 h without interruption, n (%)	18/24 (75)	17/23 (73.9)	0.93
Number of children who received target calorie before 7 d, n (%)	24/29 (82.8)	23/29 (79.3)	0.73
Median (IQR) time to reach target protein in days	2.3 (1.5, 2.3)[a]	3.5 (1.6, 3.5)[a]	0.55
Number of children who had glycemic variability in first 48 h			
Hypoglycemia	1 (3.4)	3 (10.3)	0.61
Hyperglycemia	9 (31)	4 (13.8)	0.21
Mortality, n (%)	8 (27.6)	4 (13.8)	0.33
Duration of invasive ventilation in days, median (IQR)	9 (4, 22)	6 (4, 12)	0.12
PICU stay			
Number of days, median (IQR)	11 (6, 26)	12 (6.5, 15.5)	0.45
Number of children who had feed intolerance, n (%)	7/29 (24.1)	12/29 (41.4)	0.16
Number of children who had vomiting, n (%)	2/29 (6.9)	9/29 (31.0)	0.04*
Number of children who had abdominal distension, n (%)	4/29 (13.8)	6/29 (20.7)	0.73
Number of children who had loose stools, n (%)	7/29 (24.1)	11/29 (37.9)	0.25
Number of children who had feed interruption, n (%)	21/29 (72.4)	25/29 (86.2)	0.33
Reason for interruption, n (%)			
Feed intolerance	6/29 (20.7)	11/29 (37.9)	0.15
Procedure related	8/29 (27.6)	12/29 (4.4)	
Tube related	2/29 (6.9)	0	
Worsening clinical condition	5/29 (17.2)	2/29 (6.9)	
No interruption	8/29 (27.6)	4/29 (13.8)	
Duration of feed interruption in hours due to feed intolerance alone, mean ± SD	43.8 ± 17.3	35.3 ± 31.8	0.55

IQR Interquartile range, *SD* Standard deviation

[a]75[th] centile could not be estimated

*p value <0.05 indicates statistical significance

latter (50 ml per 4 h). The criteria for feed intolerance and time of restarting feeds after an episode of feed interruption were not similar between the groups. Hence, the difference could be due to the volume of feed delivered [6]. The target calorie was calculated using Harris Benedict's equation which generally overestimates the requirement; this explains the longer duration in both the groups [9].

In the present study, the feed volume was standardized with bodyweight both in the continuous and intermittent feeding groups. Hence, the impact of volume and calorie content of the feeds could be minimized in the present study. As compared to previous studies showing varying results (achievement of target calories earlier in the 'intermittent feeding' group by Brown et al. [7], and earlier in the 'continuous feeding' group by Fayazi et al. [6], authors did not observe a difference in the time to reach target calories in the present study. The results in the previous studies might be influenced by factors such as volume of feed, calorie content and also number of interruptions.

In another study published in 2022, intermittent and continuous enteral nutrition strategy were compared in a propensity-score matched analyses of data of an international cohort study (n = 1375) [16]. The authors did not observe differences in energy or protein adequacy, or acquired infections, in mechanically ventilated, critically ill children.

In the present study, the volume of feed, calorie and protein contents of the feeds were similar, the feeding protocol initiation, escalation and restarting feeds after an episode of feed intolerance were standardized. Hence, the authors could avoid the influence of these baseline factors on the median time required to meet target calories in the two groups.

The authors did not observe significant difference in achieving the target protein between the groups; no other study in children had compared the time to achieve target proteins. The incidence of feed intolerance was more in the 'intermittent' group in the first week after initiation of enteral feeding, however, it was not statistically significant. The results were comparable with the earlier studies in PICU. The incidence of vomiting was significantly less in the CTF group; the effect may be due to slow and constant delivery of nutrients which might not be increasing the stress on the gastrointestinal system.

In the present study, authors ensured strict adherence to the protocol. In order to avoid the impact of volume of feed,

feed initiation and escalation was done according to the weight which ensured the children in both groups received feed volume as per protocol. The enrolled children were followed up till 28 d of initiation of feeds or discharge, whichever was earlier.

The present study has a few limitations. First, the sample size calculated was not achieved. There was an on-going SARS CoV2 pandemic during the study period. However, given the results of the study, the probability of seeing a difference even with a larger sample size appears to be low. Second, children who were not mechanically ventilated but required prolonged ICU stay, those requiring renal replacement therapy and with malabsorption/diarrhea were excluded. This population also constitutes a considerable proportion in the PICU and achieving nutritional goal is equally important.

Conclusions

The time taken to reach the target calories and target protein were comparable between the continuous feeding and intermittent feeding groups. Continuous feeding method may be considered in critically ill children in the beginning followed by change-over to intermittent method once the feeds are tolerated and children become stable.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12098-023-04941-x.

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Declarations

Conflict of Interest None.

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