ORIGINAL ARTICLE

Diarrhoea Risk Factors in Critically Ill Patients Receiving Enteral Nutrition

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ABSTRACT

Introduction: Diarrhoea affects up to 95% of critically ill patients receiving enteral nutrition (EN). EN is commonly misjudged as the factor causing diarrhoea. This study aimed to investigate factors contributing to diarrhoea among critically ill patients receiving EN. **Methods:** A prospective observational study was conducted in general intensive care unit (ICU) of a teaching hospital. Newly admitted critically ill adult patients receiving exclusive enteral nutrition were included in this study. Data were collected up to 14 days or until discharge, whichever comes earlier. Faecal output was measured using King's Stool Chart. Multivariate logistic regression was employed to identify aetiologies of diarrhoea during EN. **Results**:A total of 102 patients were analysed. Diarrhoea incidence was 48%. Daily faecal score was higher 10.2 (7) among critically ill patients with diarrhoea compared to non-diarrhoea patients 2.9 (15), p<0.001. Median diarrhoea onset day was at day four post-admission. Length of ICU stay and use of diuretic were factors contributing to occurrence of diarrhoea during EN (odds ratio [OR] 0.173, 95% confidence interval [CI] 1.05-1.336, p=0.004 and OR 2.381, CI 2.092 -5.927, p=0.004). **Conclusion**: Diarrhoea is common among critically ill patients receiving EN. Diarrhoea during critical illness was not attributed to enteral nutrition. Length of stay and use of diuretics were factors contributing to diarrhoea in critically ill patients receiving EN. These findings may assist for continuity and abstinence from unnecessary cessation of feeding when critically ill patients develop diarrhoea.

Keywords: : Diarrhoea, Enteral nutrition, Critical illness, Critical care

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INTRODUCTION

Enteral nutrition (EN) is routinely administered as part of critically ill patients' care. The provision of nutrition through EN aids in maintaining gut function by preventing mucosal atrophy (1), reducing endotoxin translocation (2) and preserving gut immunity (3). Despite the importance of EN, diarrhoea is a commonly reported complication. There is a considerable variation in the reported incidence of diarrhoea during EN in previous studies, ranging from 2% to 95% (4). Variations in reporting diarrhoea incidence may leads to difficulty in interpreting the results and any associations made in studies on diarrhoea. Diarrhoea not only causes discomfort to patients, but it is also associated with poor clinical outcomes (5). A local study reported diarrhoea was associated with sepsis, prolonged ICU and hospital stay (6). Previous studies reported inconsistent varying factors causing diarrhoea during EN, namely enteral feeding, medications, infections and the patients' underlying conditions and illnesses (7). Therefore, this article aimed to investigate the incidence of diarrhoea in critically ill patients receiving EN using a validated stool chart for critically ill patients on EN and to investigate risk factors of diarrhoea in critically ill patients receiving enteral nutrition in our local setting.

MATERIALS AND METHODS

Study design

This single centre prospective observational study was conducted in a 25 beds general intensive care unit (ICU) in a teaching hospital in Malaysia, University Malaya Medical Centre. Written approvals of the study was obtained from University of Malaya Medical Centre (UMMC) Ethics Committee, reference number 2017-47-5130 and Universiti Technology Mara Research Ethics Committee UiTM, reference number 600-IRMI(5/1/6) prior to the commencement of the study.

Participants

This study employed convenience sampling where all newly admitted critically ill patients to the unit were screened. Patients who met the criteria parts were observed for 2 weeks post ICU admission. Patients were eligible for inclusion if they were:1) adult patients >18 years old and above, 2) expected to stay in the unit for at least three days ICU for more than 3 days, 3) on exclusive enteral nutrition. Participants were excluded from this study if they were: 1) immunocompromised, 2) burns patients 3) suffered hepatic failure, 4) underwent gastrointestinal surgery, 5) gastrointestinal bleeding patients 6) were already receiving EN before admission. Sample size required was 69 subjects as per calculated using Sampsize calculator with two considerations such are the prevalence of diarrhoea total population of critically ill patients of the general ICU, UMMC per year.

Data collection

Data collections was conducted for up to 14 days or discharge, whichever comes earlier. Data were collected based on the objectives of the study and were recorded in case report forms. Data collected were subjects' demographic data: age, gender, co-morbidity, type of admission, admission and discharge dates; medical data: ventilator settings, Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment (SOFA) scores; biochemical data: albumin, white blood cell, C-reactive protein, random blood glucose; microbiological data; nutrition data: Nutrition Risk in Critically ill (NUTRIC) score, commencement and cessation of EN, types of formula, volume and rate of administration, gastric residual volume; faecal output data: frequency, volume and consistency of daily stool output; and medications data.

Patients' care was undertaken by a multidisciplinary team consisting of intensivist, registrars, pharmacist, therapists, registered nurses, and dietitians. The volume of enteral formula prescribed was based on each patient's total energy requirement, which was calculated by the attending dietitian. Estimation of energy and nutrient requirements was based on the Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill (8). Enteral formula was prepared and delivered through a Ryles tube by the ICU staff nurses according to dietitian's order and the institution's enteral feeding protocol.

Definition of diarrhoea

Faecal output was measured using King's Stool Chart. This faecal chart validated to use in critically ill patients receiving EN (9). The pictorial chart assists in faecal output identification by observation based on the consistency and amount of the stool. Each picture represents a specific score and the cumulative score of 15 or more using the King's Stool Chart was used in defining diarrhoea. Patient was considered experiencing diarrhoea if the subject experience diarrhoea for at least one day.

Statistical Analysis

All data were analysed by using SPSS for Windows (Version 21.0, Chicago, IL, US). The normality of the distribution was tested using Kolmogorov-Smirnoff for baseline data and Shapiro-Wilk. Data was presented as mean s ± standard deviation or medians (Interquartile range) as indicated based on its normality. A p-value of <0.05 was taken to be considered statistically significant. All continuous variables are presented as mean and standard deviation for normally distributed data and median and interquartile range (IQR) for data that was not normally distributed. Univariate and multivariate analyses using logistic regression was also conducted to elucidate relationship.

RESULT

A total of 182 critically ill admissions were prospectively screened, 102 patients were included in this study. Eighty patients excluded due to patients were younger than 18 years old, on oral or parenteral nutrition, readmitted to ICU, suffered GI bleeding and predicted short ICU stay.

Patients characteristic

Table I presents characteristics of critically ill patients receiving EN included in the study. The mean age of patients recruited was 53.06 ±17.34 years old. The median weight and body mass index (BMI) were 67.2 (19) kg and 25 (6.1) kg/m^2. Most of the recruited patients were admitted to ICU due to medical reasons (71.6%) and the least of them were trauma patients (2.9%). The patients recruited in this study were severely ill patients with the mean SOFA score of 12.5 ± 2.8. The mean NUTRIC score of the critically ill patients were 5.8 indicating most of the patients were at high nutritional risk of malnutrition. Median length of ICU stay of the critically ill patients were 6 (7) days. Forty-nine, critically ill patients receiving EN experienced at least one day of diarrhoea during their ICU stay while receiving enteral nutrition. Diarrhoea incidence of the population studied was 48%. The characteristics of critically ill patients who experienced diarrhoea and no diarrhoea were comparable, except for the white blood cell, C-reactive proteins and length of stay. White blood cell and C-reactive proteins counts were higher in the diarrhoea group, p=0.006 and 0.032. Patients who develop diarrhoea had longer median of ICU stay compared with non-diarrhoea patients, 9(12) vs 4(3), p = 0.010.

Nutrition and medications administration.

In this study, most feedings commenced within 24 hours of ICU admission. The mean energy and protein intake were 1171.9 ± 448.3 kcal/day and 48.2 ±19.8 g/day as shown in table II. Energy, protein, and fibre intake of patients with diarrhoea were significantly higher

Table I: Patients' characteristic

Characteristic	Total (N=102)	Diarrhoea (n=49)	Non-diarrhoea (n=53)	P-value
Age [a]	53.1 ±17.3	52.4±16.1	53.6±18.5	0.726
Sex[b]				
Male	65 (63.7)	30 (46.2)	35 (53.8)	0.613
Female	37 (36.3)	19 (51.4)	18 (48.6)	
Weight, kg[c]	67.2 (19)	67.9 (20)	65 (19)	1.000
Body Mass Index (kg/m²)[c]	25 (6.1)	25.0 (6.7)	25.0 (5.9)	0.988
Type of admission[b]				
Surgical	26 (25.5)	9 (34.6)	17 (65.4)	0.225
Medical	73 (71.6)	39 (53.4)	34 (46.6)	
Trauma	3 (2.9)	1 (33.3)	2 (66.7)	
Total of co-morbid disease[b]				
0	38 (37.3)	17 (44.7)	21 (55.3)	0.525
1	27 (26.5)	16 (59.3)	11 (40.7)	
2	29 (28.4)	12 (41.4)	17 (58.6)	
3	7 (6.9)	3 (42.9)	4 (57.1)	
4	1 (1)	1 (100)	0 (0)	
Albumin (g/L)[a]	22.5 ±5.1	22.1 ±4.3	22.8 ±5.7	0.440
White blood cell (g/L)[c]	15.4 (8.1)	17.4 (7.3)	13.3 (9.7)	**0.006**
C Reactive Protein (mg/L)[c]	7.3 (13.4)	10.2 (12.8)	1(11.48)	**0.032**
Random blood sugar (mmol/L)[c]	10.1 (3.2)	10.3 (3.8)	10.1 (2.8)	1.000
APACHE II score[a]	23.4 ±6.7	24.5 ±5.8	22.4 ±7.4	0.112
SAPS score[a]	55.4 ±14.9	57.5 ±13.7	53.47 ±15.9	0.173
SOFA score[a]	12.5 ± 2.8	12 ±3	13 ±3	0.346
NUTRIC score[a]	5.8 ± 1.6	5.8 ±1.5	5.8 ±1.7	0.914
Length of ICU stay[c]	6 (7)	9 (12)	4 (3)	**0.010**

[a] Data between the two groups were analysed using Student's t-test and reported as mean SD.
[b] Data between the two groups were analysed using Chi square test and reported as n (%).
[c] Data between the two groups were analysed using Mann-Whitney Test and reported in median (IQR).

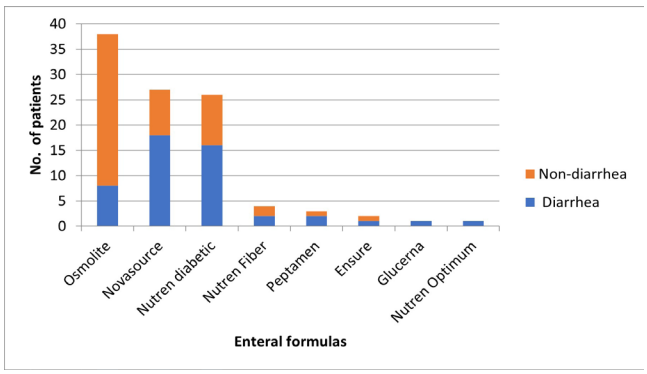

Figure 1: Types of enteral formulas received by critically ill patients receiving enteral nutrition.

Table II: Nutritional intake of critically ill patients receiving EN

Characteristic	Total (N=102)	Diarrhea (n=49)	Non-diarrhea (n=53)	P-value
Day start EN initiation [a]	1.3 ± 0.5	1.3 ±0.47	1.2 ±0.45	0.637
Energy intake (kcal/day)a	1171.9 ± 448.3	1320 ±383	1034 ± 463	<0.001
Protein intake (g/day)[a]	48.2 ± 19.8	55.8 ±18.8	40.9 ±18.0	<0.001
Fibre intake (g/day)[b]	0 (18.4)	2.8 (21.3)	0 (14.2)	0.052
Mode of feeding[c]				<0.001
Continuous	102 (100)	49 (48)	53 (52)	
Intermittent	0 (0)	0 (0)	0 (0)	
Route of feeding[c]				1.000
Nasogastric tube	101 (99)	49 (48.5)	52 (51.5)	
Orogastric tube	1 (1)	0 (0)	1 (100)	
Fibre in EN[d]				0.032
Yes	34 (33)	21 (62)	13 (38)	
No	68 (67)	28 (41)	40 (59)	
Enteral formula concentration[d]				0.027
Isocaloric	75 (76)	31 (41.3)	44 (58.7)	
Hypercaloric	27 (24)	18 (66.7)	9 (33.3)	

[a]Data between the two groups were analysed using Student's t-test and reported as mean SD.
[b] Data between the two groups were analysed using Mann-Whitney Test and reported in median (IQR).
[c]Data between the two groups were analysed using Fisher's Exact test and reported as n (%).
[d]Data between the two groups were analysed using Chi square test and reported as n (%).

than non-diarrhoea patients, p<0.001, p<0.001 and p = 0.052. Figure 1 shows the type of enteral formulas received by the patients with most of the critically ill patients were prescribed with Osmolite 1 Cal (n=38). Fibre content in enteral formula and concentration of enteral formula were found to be associated with diarrhoea, p= 0.032 and p= 0.027. Critically Ill patients who experienced diarrhoea had significantly higher number of antibiotics 2 ±1.5 compared to non-diarrhoea patients 1.4 ± 0.9, p<0.001. Prokinetic, sedative, protein pump inhibitor (PPI), diuretic, laxative and vasopressor use were significantly associated with diarrhoea (Table III).

Faecal output

Most critically ill patients (85%) had at least one bowel activity during their ICU stay (Table IV). Median daily faecal score was 5.3 (8) with higher scores reported 10.2 (7) among critically ill patients with diarrhoea compared to non-diarrhoea patients 2.9 (15), p<0.001. Median diarrhoea onset day was at day four post admission. Figure 2 illustrates the daily prevalence of diarrhoea throughout the two weeks prospective observation. Faecal frequency, number of diarrhoea days and cumulative faecal score were significantly higher in patients with diarrhoea compared to non-

Table III: Medications received by subjects

Characteristic	Total (N=102)	Diarrhea (n=49)	Non-diarrhea (n=53)	P-value
Total number of antibiotics prescribed[a]	2 ±0.5	2 ±1.5	1.4 ± 0.9	<0.001
Antibiotic[c]				0.163
Yes	93(91.2)	47 (50.5)	46 (49.5)	
No	9 (8.8)	2 (22.2)	7 (77.8)	
Prokinetic[b]				0.050
Yes	34 (33.3)	21 (61.8)	13 (38.2)	
No	68 (66.7)	28 (41.2)	40 (58.8)	
Sedative[c]				0.027
Yes	96 (94.1)	49 (51)	47 (49)	
No	6 (5.9)	0 (0)	6 (100)	
PPI[b]				0.034
Yes	78 (76.5)	42 (53.8)	36 (46.2)	
No	24 (23.5)	7 (29.2)	17 (70.8)	
Sorbitol[b]				0.355
Yes	64 (62.7)	33 (51.6)	31 (48.4)	
No	38 (37.3)	16 (42.1)	22 (57.9)	
Diuretic[c]				0.001
Yes	70 (68.6)	42 (60)	28 (40)	
No	32 (31.4)	7 (21.9)	25 (78.1)	
Laxative [c]				0.005
Yes	7 (6.9)	7 (100)	0 (0)	
No	95 (93.1)	42 (44.2)	53 (55.8)	
Vasopressor [b]				0.028
Yes	53 (52)	31 (58.5)	22 (41.5)	
No	48 (47.1)	18 (36.7)	31 (63.3)	

[a] Data between the two groups were analysed using Student's t-test and reported as mean ±SD.
[b] Data between the two groups were analysed using Chi square test and reported as n (%).
[c] Data between the two groups were analysed using Fisher's Exact test and reported as n (%).

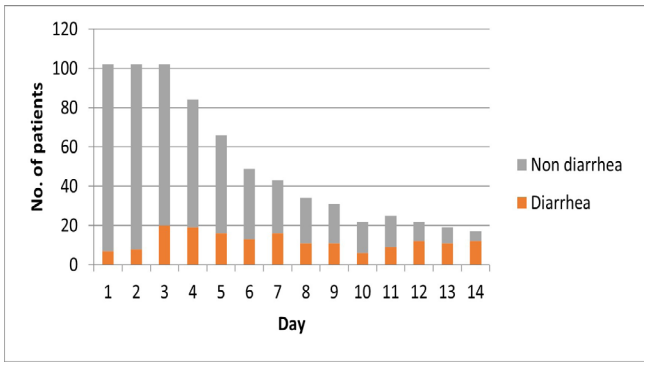

Figure 2: Prevalence of diarrhoea in critically ill patients receiving EN.

diarrhoea patients. A multivariate logistic regression analysis was employed to determine contributing factors to diarrhoea during EN. Length of ICU stay and use of diuretic were factors contributing to occurrence of diarrhoea during EN (odds ratio [OR] 0.173, 95% confidence interval [CI] 1.05-1.336, p=0.004 and OR 2.381, CI 2.092 -5.927, p=0.004) (Table V).

Table IV: Faecal output of critically ill patients receiving enteral nutrition.

Characteristic	Total (N=102)	Diarrhea (n=49)	Non-diarrhea (n=53)	P-value
Bowel activity[a]				<0.001
Yes	87 (85.3)	49 (56.3)	38 (43.7)	
No	15 (14.7)	0 (0)	15 (100)	
Faecal frequency[b]	0.8 (1)	1.2 (1)	0.43 (1)	<0.001
Diarrhea days[b]	0 (2)	3 (4)	0 (0)	<0.001
Diarrhea onset day[b]	0 (4)	4 (3)	0 (0)	<0.001
Daily faecal score[b]	5.3 (8)	10.2 (7)	2.9 (15)	<0.001
Cumulative fecal score[b]	25 (64.5)	76 (100.5)	12 (20)	<0.001

[a] Data between the two groups were analysed using Chi square test and reported as n (%).

[b] Data between the two groups were analysed using Mann-Whitney Test and reported in median (IQR).

Table V: Final model for multivariate analysis of diarrhoea in critically ill patients receiving EN.

Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Length of ICU stay	0.182 (1.086-1.325)	<0.001	0.173 (1.05-1.336)	0.004
White blood cell	0.061 (1.001-1.128)	0.045	0.044 (0.966-1.130)	0.273
Fibre	0.040 (1.411-3.342)	0.050	0.028 (0.967-1.092)	0.375
Antibiotic	0.075 (1.411-3.342)	0.000	0.265 (0.101-5.833)	0.789
Prokinetic	0.836 (0.186-1.007)	0.052	0.086 (0.311-3.824)	0.893
Diuretic	1.678 (0.071-0.490)	0.001	2.381 (2.092-5.927)	0.004

DISCUSSION

The incidence of diarrhoea in this prospective observational study was 48% when using King's stool chart, a validated diarrhoea scoring tool for critically ill patients receiving enteral nutrition. Previous study identified wide range of diarrhoea prevalence, ranging from two to 95% (10). This variation is mainly contributed by the lack of consistency in defining diarrhoea. World Health Organization recommends that it be defined as three or more defecations per day. However, this definition does not include consistency, transit time and volume. Other definitions emerge to describe diarrhoea which includes objective measures

and use of stool charts namely Bristol Stool Chart, Bliss Stool Classification system and King's Stool Chart. While standardized definition may be used in the community, there is no consensus in defining diarrhoea in clinical settings (11).

Enteral feeding is commonly blamed when diarrhoea occurs during EN. This is because diarrhoea is attributable to the abnormal colonic response when EN is given (12). The provision of EN caused the secretion of fluid and electrolytes into the gut which was most notable during hyperosmolar intra-gastric feeds. It has been proposed that hypertonic feeds cause diarrhoea via an osmotic effect as the presence of a high concentration of non-absorbable carbohydrates in enteral formulas increases the osmotic load in the gut. However, the observation of 50 enterally fed patients showed that the osmolality of enteral formulas did not affect the frequency and duration of diarrhoea (13).

Result from adjusted multivariate analysis found that patients who stayed longer in ICU were prone to develop diarrhoea. Similar finding was also observed in a restrospective, large sample, 3737 critically ill patients study (14). Patients who have longer ICU stay are more likely to be a more ill group of critically ill patients and higher susceptibility to gut failure. They are subjected to receive more enteral nutrition, combination of medications especially antibiotics or other treatments in relation to their illnesses (15). Additionally, in this study, use of diuretics was found to be another aetiology of diarrhoea in critically ill patients receiving EN. Once of major adverse events with use of Furosemide is may include hypovolemia, consequently, electrolyte loss and imbalance and alteration of gut function. Excessive urination due to administration of high dosages of the drug may induce extracellular fluid volume contraction (16). Our unadjusted multivariate model found antibiotic associated diarrhoea (AAD) is a contributing factor diarrhoea in critically patients receiving EN. Gut is a host for more than 600 species of bacteria in which most of these species cannot be reproduced under laboratory conditions (17). Antibiotics therapy causes alteration of gut microbiota and reduction in production of short chain fatty acids (SCFAs), a vital source of energy for enterocytes, resulting in disruption in gut functionality and diarrhoea (18). Antibiotic therapy causes marked reduction of anaerobic intestinal bacteria which are responsible in fermenting undigested carbohydrate to SCFAs causing increase in osmotic load. Antibiotic therapy was found to be one of the aetiologies of diarrhoea during EN in previous study, but our adjusted model did not found likewise(13).

Despite being able to meet sample size calculated and the use of a validated stool chart to avoid bias by subjective interpretation by professional staff, the conclusion drawn in this study may be limited to variables studied and availability of data. *Clostridium difficile* infection is only tested when suspected and it is not a routine assessment in this ICU. Additionally, study was limited to up to 14 days of ICU stay. While mean of ICU stay of this institution was less than 7 days, data from a subgroup of critically ill patients, of longer ICU stay was systematically omitted considering limited resources to continuous data collection until discharge. Comparison with previous literature remains challenging due to the lack of consensus in defining diarrhoea. Thus, factors found in one study may not be the case for the other considering criteria used to define diarrhoea among critically ill patients receiving EN. Future studies may require more scrutinization in interpreting diarrhoea and to consider to stratify the studies based on operational definitions used in order to understand the common complication of EN in critically ill patients.

CONCLUSION

In conclusion, 48% of critically ill patients experience at least one day of diarrhoea during the first 14 days in ICU. Critically ill patients receiving EN who developed diarrhoea had longer stay in ICU, lower albumin, higher white blood cell and C-reactive protein), This study found that EN was not a contributing factor to diarrhoea in critically ill patients receiving EN. Length of stay and use of diuretics were found to be contributing to the occurrence of diarrhoea during EN. Studies with unified operational definition and gut microbiome ecology are warranted to understand the pathophysiology of diarrhoea in order to efficiently reduce burden of care and cost of diarrhoea among critically ill patients.

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