

Diarrhea and constipation in hospitalized patients treated with fiber-exclusive enteral therapy: longitudinal study

Short Title:

Diarrhea and constipation in fiber nutritional therapy

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Conflict of interest

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ABSTRACT

Background and objectives: Studies analyzing the frequency of diarrhea and constipation with exclusive enteral nutrition therapy (ENT) enriched with fibers assessing the time effect in clinical outcomes are scarce. So, this was the aim of the present study. **Methods:** This is a prospective study carried out in hospitalized patients who were fed exclusively on ENT for at least seven days. Those patients were followed daily until reaching 14 days of exclusive ENT diet. The frequency of diarrhea and constipation, the data related to the ENT, the liquids and the medicines received were logged daily. Generalized Estimated Equation was used for statistical analysis ($p < 0.05$). **Results:** The sample was of 28 patients (64.21 ± 17.70 years and 75% men), 15 patients remained until the end of the study. The percentage of diarrhea was 3.6% to 14.3%, and constipation was 32.1% to 0% ($p = 0.035$). Normal intestine function was more frequent and increased during the study ($p = 0.001$). Patients with diarrhea and constipation presented lower infusion speed, dietary volume and adequacy of total fibers ($p < 0.05$). The daily medication was the only variable that remained associated to diarrhea ($\beta = 0.125$; $p = 0.04$) after multivariate analyses. Age ($\beta = -0.021$; $p < 0.001$) and liquids ($\beta = -0.001$; $p < 0.001$) were inversely associated to constipation. The use medicines that reduced intestine motility was also associated with constipation ($p < 0.001$). The prevalence of patients without gastrointestinal dysfunction using fiber-enriched diet was more expressive during the study. **Conclusion:** Age, medication and liquids were associated to both diarrhea and constipation.

Keywords: Fibers in the diet; Enteral nutrition; Diarrhea; Constipation.

1. Introduction

Many patients who are undernourished or at risk of malnutrition and are hospitalized, need enteral nutrition therapy (ENT) to replace or supplement oral feeding (1, 2). However, several complications are associated to the use of enteral nutrition in these patients, especially when enteral diet is used exclusively (3). Patients hospitalized under exclusively enteral nutrition may have compromised intestine motility, including diarrhea and constipation (4-6), with frequency ranging from 11% to 63% (7) and 15% to 83% respectively, depending on the definition used (8). It is important to report that both diarrhea and constipation are associated to the increase of morbidity and extended hospitalization of patients (3, 9).

Nowadays, fibers are modified to be introduced and be available in several formulas used in enteral diets (10), and could bring benefits to the intestine function of hospitalized patients treated with ENT (11). Although this topic has been discussed for many years in literature (12), while some studies reveal its benefits (13), it is still considered a controversial matter (14, 15).

Studies assessing gastrointestinal complications in patients under ENT should consider whether it was used exclusively, especially in the long-term. Furthermore, determine such conditions longitudinally by assessing the effect of time in clinical outcomes are still rare. Thus, this study aimed to longitudinally analyze the incidence of diarrhea and constipation and the associated factors to their occurrence in hospitalized patients receiving exclusively fiber-enriched enteral nutritional therapy.

2. Methods

2.1 Study Design

This is an analytical, observational and prospective study in patients under fiber-enriched ENT in a Hospital Foundation in Minas Gerais, Brazil. Patients over the age of 18 who were hospitalized in general, surgery and oncology infirmaries or in intensive care units (ICUs) under ENT in continuous infusion pump (CIP) as exclusive feeding source for at least seven days, were included. patients under mixed ENT (enteral nutrition combined with parenteral or oral nutrition), patients who interrupted the ENT during the minimum stipulated period (seven days) or those who received fiber-free ENT, were excluded.

After seven days under exclusive ENT, the patients were followed daily until the completion of 14 days exclusively under ENT. The data for the study was annotated until the patient had their diet interrupted to start oral or parenteral diet, for medical discharge, death or when the period for data collection was finished.

2.2 Collected data

The patients were classified according to the gastrointestinal complications analyzed (diarrhea and constipation) and with patients' daily evacuation. Diarrhea was considered as three or more liquid or pasty evacuations within 24 hours (16) and intestine constipation was considered as no evacuation within three days (2). In the absence of diarrhea and/or intestine constipation, patients were considered as having a normal gastrointestinal function.

The patients received diets with 15g/L of fibers, but with different compositions between soluble and insoluble fibers. Table 01 demonstrates dietary information. The

percentage of total fiber adequacy was also calculated. Intake above 14g for every 1000 kcal was considered adequate according to recommendation by *Dietary Reference Intakes* - DRI (17).

Personal (sex and age), clinical (reason and place of hospitalization) nutritional therapy, administration of liquids, and medication data were noted. Total water was calculated by adding the water administered via ENT and the prescribed amount of serum. All medications administered daily up to the last day of study were collected from the patient's record, considering the total number of medications and also adding the medications according to the type of treatment that could influence the patients' intestine motility. Antibiotics, catecholamines, antidopaminergics, laxatives, H2 antagonists, diuretics and non-steroid anti-inflammatory drugs were classified as medications that cause diarrhea. Among the therapeutic classes that reduce intestine motility were included anticholinergics, tri-cyclic antidepressants, antiparkinsonians and antipsychotics, benzodiazepines and opioids (6, 9, 18, 19).

2.3 Ethical aspects

This study was approved by the Research Ethics Committee under Approval number: 1.341.526 and by the Ethics Committee of the Hospital Foundation in which the study was conducted.

2.4 Statistical analysis

The software Statistical Package for the Social Sciences (SPSS), version 20.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. Cochran Q and Friedman's test were used to verify alterations occurred in the presence or absence of gastrointestinal complications

and in alterations of numerical variables, respectively, in the different days of study. The data regarding the first, seventh and fourteenth days was presented and McNemar's and Wilcoxon's tests were used to verify the differences in pair analysis.

The predicting factor of frequency for diarrhea and constipation was assessed by generalized linear models to accommodate longitudinal data - Generalized Estimated Equation (GEE) in binary logistic model in univariate and multivariate analyses. The structure of the work correlation matrix was AR (1) (First Order Autoregressive). The Quasi-likelihood Information Criterion (QIC) was used to define the final model with the best adjustment for multivariate analysis. The value $p < 0.05$ was considered as significant for all statistical analyses.

3. Results

During the study, 28 patients satisfied all inclusion criteria and were followed by a minimum of seven days. A total of 53.6% (n=15) remained until the end of data collection. Among the patients who did not remain in the study, 10.7% (n=3) died and 89.3% (n=25) received medical discharge or were introduced to oral feeding. The patients were fed via enteral with fibers by 11.75 ± 2.67 days. The average age of the patients was of 64.21 ± 17.70 years, 75% (n=21) men. Clinical (39.3%; n=11), surgical (32.1%, n=9) and oncology treatment (21.4%; n=6), were the main reasons for hospitalization and, 21.4% (n=6) remained in ICU since the beginning of the study.

The percentage of diarrhea ranged from 3.6% (n=1) to 14.3% (n=7) and constipation ranged from 0% (n=0) to 32.1% (n=9). There was no statistically significant difference between the frequency of diarrhea over time ($p=0.111$); However, there was a significant

reduction of the frequency of intestine constipation ($p=0.035$) and after the 11th day, no patient had presented constipation. Thus, the frequency of patients without gastrointestinal dysfunction was more prevalent and increased significantly ($p=0.001$). The association between the fiber adequacy percentage and the presence or absence of gastrointestinal dysfunctions ($p<0.001$) (Figure 1), was statistically significant.

The median total fiber intake was of 14.4g (4.8g-26.4g) and increased significantly ($p<0.001$), ranging from 12g (7.2g-24g) to 15.5g (12g-24g). The soluble fiber intake was 6.7g (2.2g-17.2g) and the insoluble fiber was 6.4g (1.9g-3.4g). Likewise, there has been a significant increase in soluble fibers [minimum median of 5.6g (3.4g-11.2g) and maximum median of 7.5g (5.6g-19.2g), $p<0.001$], as well as in insoluble fibers [minimum median of 6.4g (1.9g-12.8g) and maximum median of 7.5g (3.8g-11.5g, $p<0.01$].

Table 2 summarizes the behavior of the other variables included in the study on the first, seventh and fourteenth day of the study. The infusion speed and the dietary volume increased and differed significantly between days 01, 07 and 14 ($p<0.05$). The caloric value and the number of medications increased significantly between the beginning and the end of the study. Among the medications that could cause diarrhea, the most common were antibiotics, laxatives and antihypertensive medications. Out of the medications associated with constipation, the most frequently used were antiparkinsonians and opioids.

Regarding longitudinal data analysis, it is noted that the presence of diarrhea and constipation was associated with younger patients. The hospitalization in ICU was not associated to the frequency of diarrhea, but to the lower incidence of constipation. The larger amount of medications in general was associated with the frequency of diarrhea and the larger number of medications with implications to the gastrointestinal tract was associated with the frequency of constipation. Patients who had diarrhea and constipation had lower infusion

speed and hence received lower dietary volume. However, the calories and total liquids were statistically lower only for patients with constipation. With regards to fibers, patients with diarrhea and constipation received lower contents of total fibers, which resulted in lower fiber adequacy by these groups. Patients with diarrhea had lower value of insoluble fibers (Table 3).

After multivariate analysis, the presence of diarrhea was positively associated to the total number of medications prescribed. Intestine constipation had an inverse association with age and the total liquid. The number of medications associated to constipation was also present in the final model for constipation ($\beta=0.236$; $p=0.013$). These results are demonstrated in Table 4.

Discussion

In this study, all patients were being exclusively fed via fiber-enriched ENT diet and, despite the high prevalence of gastrointestinal complications associated with the use of ENT described in literature, the frequency of absence of gastrointestinal dysfunctions was higher throughout the entire study.

Alterations in the frequency of diarrhea was not statistically significant, which has already been demonstrated by some authors (14)., .However, in the systematic review conducted by Elia et al., (13) fiber-enriched ENT showed to be well tolerated by hospitalized patients, reducing the incidence of diarrhea and aiding in the intestine's functioning.

In the present study, the percentage of diarrhea was below that found by other authors which uses the same definition of diarrhea in hospitalized patients under ENT (in which prevalence range from 13.0% to 32.8%) (2, 5, 16, 20). It is important to be careful when comparing the prevalence of diarrhea in hospitalized population, as was identified the use of 33 different definitions for diarrhea in studies involving ENT (7).

Luft et al. (16) found that incidence of diarrhea was associated to the use of ENT with hospitalization during summer months and to the patients' advanced age. The administration of ENT has also been described in other studies. . Shimoni et al. (21), assessed 148 patients exclusively under ENT, and the group which received fiber-supplemented continuous diet presented a reduction in the episodes of diarrhea. In the present study, all patients received ENT via continuous infusion pump. In addition, the negative alterations at the colon's microbiota produced by enteropathogenic colonization and abnormal colon responses contribute to the pathogenesis of diarrhea in patients under ENT (19). ICU hospitalizations is another factor associated with diarrhea, with frequency over 80% in patients (3). In the study by Yagmurduur and Leblebici (22), the frequency of diarrhea in ICU patients fed with fiber-enriched formulas was of 36.6% (similar to ours). On the other hand, this result was statistically lower than the frequency of diarrhea in the fiber-free ENT group, which was of 63.3%

The frequency of intestine constipation was significantly reduced with the use of fiber-enriched enteral diet throughout the study. In the study by Bittencourt et al. (5) the fiber-free ENT increased the risk of constipation by seven times. In our study, the prevalence of constipation ranged from 0% to 32.1% and, after getting an average from the percentages of constipation, a prevalence of 4.75% (data not shown) was found. Such data is inferior to that reported by other studies using the same definition of constipation; however, in these studies was used fiber-free diets, in which the percentage of constipation ranges from 29.0% to 76% (2, 5, 23).

Though strongly prevalent, constipation is less researched in literature when the aim is to report complications associated with ENT (14, 24). However, intestine constipation has already been associated to withdrawal from the breathing device, an increase in hospitalization time and ICU mortality (25). The use of a fiber-enriched enteral diet reduces

or excludes the need of laxatives in hospitalized patients and, in more severe cases, the need for colon cleansing (15). Constipation in hospitalized patients could have several causes, such as the insufficient administration of liquids, medications, lack of fibers in the diet and reduction of physical activity (9). In this study, after multivariate analysis, intestine constipation was associated to age and the low total liquids, as well as to medications that reduce intestine motility. Intestine constipation is physiologically prevailing in elderly people (26), however, age was inversely proportional to the presence of constipation in the present study, which brings us the thought that, in a hospital environment, pathological, clinical, medication-related conditions, etc, exceed physiological matters. In a study investigating the use of partially hydrolyzed guar gum (PHGG) in patients with irritable bowel syndrome, 67.7% of the population was under 45 years of age. The use of PHGG increased the frequency of evacuations only in patients over 45 years of age, which demonstrates that age is a factor that influences in the results of intestine constipation in patients with the use of fibers (27).

The volume of total water (serum + water) was independently associated to constipation. Patients who had constipation received a volume 700 mL lower than patients who did not develop constipation. The amount of liquids also plays an important role in intestine function. It is important to provide the appropriate relation of water and fibers, since water is necessary in retention or leaching of the fibers to promote the physiological effects of fibers (10, 11). The low volume of water is considered one of the factors influencing intestine constipation (3, 9), a fact not always quantified in studies (5) as done in the present sample. On the other hand, the maximum value of liquids (serum + water) received by the patients was 4434.0 mL (Table 01) was worthy of further investigation. Hyperhydration, is associated to metabolic complications, and aggravates the pre-existing gastrointestinal lack of motility when taken to the TGI edema, which alters the response of gastrointestinal hormones and neurotransmitters (28).

Several studies report the interference of medication with gastrointestinal complications (9, 18). In this study, the medications was the only variable associated to the frequency of diarrhea after multivariate analysis, and those related to the decrease in intestine motility were associated to the frequency of constipation. The median of the number of medications per patient (11 to 15 medications/per person on the 1st and 14th day, respectively) demonstrates that patients were polymedicated. In the study by Hammes et al. (29) the use of more than six medications/day increased by 9.8 times the risk of potential medication interaction after multivariate logistic regression analysis. Also, the number of medications could also interact with the ENT (18). The use of fiber-enriched enteral diet was associated to the prevention of disturbances in intestine motility related to the medication (5). However, the literature lacks studies assessing medication interaction in patients under ENT (whether or not fiber-enriched), and more studies are necessary.

The association between multiple medications associated to the frequency of diarrhea in the present sample was also reported in a review study by Chang and Huang (6) which concludes that the ENT is not the basic cause of diarrhea in hospitalized patients, being more related to the medications prescribed. In the study by Borges et al. (30) each day of added antibiotics determined an increase by 16% in the risk of diarrhea, while the addition of another antibiotic to the therapy determined an increase by 65% in the frequency of diarrhea. Indeed, the prescription of antibiotics is often reported in studies assessing ENT patients, but not always the prescription of antibiotics *per se* is associated to the incidence of diarrhea, and the duration of the treatment with antibiotics, as well as its related interactions, must be considered (19).

In the present study, the formula used was enriched with a dose of 14g/L of fiber, which is in accordance with other studies (24). The average consumption of fibers (14.4 grams) was below ESPEN's recommendation (31). Probability, this is the cause why fiber-

enriched ENT did not present a significant effect on the prevalence of diarrhea throughout the study. On the other hand, there was a high percentage of total fiber adequacy, and this factor may have determined the beneficial effects of fiber-enriched ENT in this study (higher frequency of patients without gastrointestinal alterations and reduction in constipation) (17). The enriched formula used contained a mixture of soluble and insoluble fibers and, by the data presented, there was a balance of soluble and insoluble fibers received by the patients. It is known that the combination of different types of fibers in small doses could result in beneficial effects to the organism and intestine health (11). The choice of the type of enteral diet to be offered to the patient was defined by the Hospital's nutritionist, and not by the researchers involved in this study. Additionally, the research did not have a fiber-free control group, since the aim of the present study was to assess the gastrointestinal alterations in patients under fiber-enriched diets throughout time. Comparisons with other studies are often complicated and inappropriate due to the difference in patient selection, location where the study was carried out, types of fibers used and differences in the definitions of gastrointestinal complications. Such factors may be considered limitations of the present study.

Patients under ENT presenting gastrointestinal complications. Determine causes of such complications, without suspending enteral nutrition, including in patients at ICU [34], is very important. The assessment of suspension/interruption of the diet for gastrointestinal complications was not the aim of the present study. However, it was observed that the patients presenting gastrointestinal complications received lower speed infusion, and consequently a lower dietary volume, which resulted in lower caloric value. The use of fiber-enriched diets is important to avoid frequent gastrointestinal complications and could avoid several interruptions in the administration of the diet, which damages the provision of energy and nutrients and, consequently, the patients' nutritional status. Consequently, the ENT not

fulfilling its true purpose, which is maintaining and/or recovering the patients' nutritional status.

4. Conclusion

The prevalence of patients without gastrointestinal dysfunction using fiber-enriched diet was more expressive. The fiber-enriched ENT reduced the frequency of intestine constipation, but not of diarrhea. The presence of diarrhea in patients exclusively under fiber-enriched ENT was associated to the number of medications prescribed, constipation was associated to age, and the total of liquids offered.

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Table 1: Composition of the enteral diets received by the participants.

CHO /PTN / LIP	49%/16%/35%	
Fibers (g/L)	7g soluble fibers + 8g insoluble fibers	12g soluble fibers + 3g insoluble fibers
Type of soluble fiber	Fructooligosaccharides, inulin and gum arabic	
Type of insoluble fiber	Soy polysaccharide, cellulose and resistant starch	
Osmolarity (mOsm/L)	250 – 290	390
CD (kcal/mL)	1.0 - 1.2	1.5
Comments	Polymeric formula Sucrose, lactose and gluten-free	
CHO: Carbohydrate, PTN: Protein, LIP: lipids; CD: caloric density		

Table 2: Variables related to nutrition therapy in patients exclusively under fiber-enriched enteral nutrition therapy at the beginning, mid and end of the study.

	Day 01 (n=28)	Day 07 (n=28)	Day 14 (n=14)	p
Infusion speed (mL/h)	50.0 (30.0-100.0)	60.0 (30.0-110.0)	65.0 (50.0-100.0)	0.010* # ¥
Dietary volume (mL)	800.0 (480.0 - 1,600.0).	960.0 (480.0 - 1,760.0).	1,040.0 (800.0 - 1,600.0).	0.010* # ¥
Caloric value (Kcal)	1,000.0 (480.0 - 1920).	1,072.0 (614.0 - 2,200).	1,120.0 (800.0 - 2,400.0).	0.036* ¥
Total liquid (mL)	1,800.0 (610.0 - 4,434.0).	1,905.0 (610.0 - 4,434.0).	1,800.0 (610.0 - 4,434.0).	0.317
Medications (No.)	11.5 (6.0 - 20.0).	13.0 (6.0 - 19.0).	15.0 (12.0 - 19.0).	0.004* ¥
Diarrhea medications (No.)	4.0 (3.0-8.0)	4.0 (1.0-10.0)	5.0 (2.0-10.0)	0.029¥
Constipation medications (No.)	4.0 (1.0-7.0)	5.0 (3.0-10.0)	5.0 (3.0-9.0)	0.001* ¥

*Day 01 x Day 07

#Day 07 x Day 14

¥ Day 01 x Day 14

Table 3: Associated variables with the frequency of diarrhea and constipation in patients exclusively under fiber-enriched enteral nutrition therapy.

		Diarrhea		Constipation	
		Yes (n=30)*	No (n=300)*	Yes (n=37)*	No (n=293)*
Sex (%)	men	50 (n=15)	75 (n=225)	78.4 (n=29)	72.7 (n=221)
	women	50 (n=15)	25 (n=75)	21.6 (n=8)	27.3 (n=82)
p		0.051		0.023	
Age (years)		54 (37-86)	67 (25-93)	64 (25-88)	67 (25-93)
	p	0.032		0.001	
Hospitalization (%)					
Oncological		16.7 (n=5)	20.3 (n=61)	32.4 (n=12)	18.4 (n=54)
Clinical (%)		53.3 (n=16)	38 (n=114)	54.1 (n=20)	37.5 (n=110)
Surgery (%)		10 (n=3)	35.7 (n=107)	13.5 (n=5)	35.8 (n=105)
Other (%)		20 (n=6)	6 (n=18)	0 (n=0)	8.2 (24)
p		0.003		<0.001	
ICU (%)		33.3 (n=10)	22.3 (n=67)	10.8 (n=4)	24.9 (n=73)
	p	0.903		p=0.031	
Medications (No.)		14 (8-19)	13 (6-20)	12 (6-20)	13 (6-19)
	p	0.004		0.195	
Diarrhea medications (No.)[#]		5.5 (3-8)	5 (3-10)	6 (3-9)	5 (3-10)
	p	0.389		0.003	
Constipation medications (No.)[#]		5 (1-9)	4 (1-10)	5 (3-10)	4 (1-10)
	p	0.757		0.013	
Infusion (ml/h)		50 (30-80)	60 (20-110)	50 (40-90)	60 (20-110)

p	0.021	0.001
Dietary volume (mL) #	800 (480-1280)	960 (320-1760)
p	0.021	0.001
Calorie value (Kcal) #	889.5 (614-1920)	1024 (320-2400)
p	0.652	0.014
Total liquid (mL) #	1000 (610-4434)	2010 (610-4434)
p	0.06	0.000
Fibers (g) #	12 (7.2-19.2)	14.4 (4.8-26.4)
p	0.021	0.001
Fiber adj. (%)	80 (48-128)	96 (32-176)
p	0.003	0.001
Soluble fiber (g) #	5.9 (3.4-15.4)	6.7 (2.2-19.2)
p	0.955	0.034
Insoluble fiber (g) #	5.6 (2.4-7.7)	6.4 (1.9-13.4)
p	0.000	0.001

*total number of episodes during the study period # median (minimum – maximum). Adeq. = adequacy

Table 4: Associated variables with the frequency of diarrhea and constipation after multiple logistic regression model in patients exclusively under fiber-enriched enteral nutrition therapy.

Variable	Parameter (Wald)	Beta	p	QIC
		Diarrhea		
Medications	8.07	0.125	0.004	179.28
		Constipation		
Age	15.15	-0.021	<0.001	221.58
Total liquid	14.13	-0.001	<0.001	

Figure 01: Average percentage of presence and absence of gastrointestinal complications (diarrhea and constipation) and total fiber adequacy in patients under fiber-enriched exclusively enteral nutrition therapy during the study period.

*Variable x Time (days) **Condition x Fiber adequacy (%)