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Original article

The effect of a natural food based tube feeding in minimizing diarrhea in critically ill neurological patients

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SUMMARY

Background & aims: Diarrhea has negative consequences for patients, health care staff and health care costs when neurological patients are fed enterally over long periods. We examined the effect of tube feeding with natural foods in reducing the number of fluid stool evacuations and diarrhea in critically ill neurological patients.

Methods: A multicenter, prospective, open-label and randomized controlled trial (RCT) was conducted at facilities in Germany specializing in early rehabilitation after neurological damage. Patients of the INTERVENTION group were fed by tube using a commercially available product based on real foods such as milk, meat, carrots, whereas CONTROL patients received a standard tube-feed made of powdered raw materials. All received enteral nutrition over a maximum of 30 days. The number of defecations and the consistency of each stool according to the Bristol Stool Chart (BSC) were monitored. In addition, daily calories, liquids and antibiotic-use were recorded.

Results: 118 Patients who had suffered ischemic stroke, intracerebral hemorrhage, traumatic brain injury or hypoxic brain damage and requiring enteral nutrition were enrolled; 59 were randomized to receive the intervention and 59 control feed. There were no significant differences in clinical screening data, age, sex, observation period or days under enteral nutrition between the groups. Patients in both groups received equivalent amount of calories and fluids. In both groups antibiotics were frequently prescribed (69.5% in the INTERVENTION group and 75.7% in the CONTROL group) for 10–11 days on average. In comparison to the CONTROL group, patients in the INTERVENTION group had a significant reduction of the number of watery stool evacuations (type 7 BSC) (minus 61%, IRR = 0.39, $p < 0.001$). Further statistical evaluations using the following corrections: major diarrhea-associated confounders (number and duration of antibiotics); shorter observation period of 15 days; excluding patients with *Clostridium difficile* associated diarrhea (CDAD) and the Per Protocol Population, confirmed the primary hypothesis. The number of days with diarrhea was significantly lower in the INTERVENTION group (0.8 ± 1.60 days versus 2.0 ± 3.46 days).

Conclusions: Tube feeding with natural based food was effective in reducing the number of watery defecations and diarrhea in long term tube-fed critically ill neurological patients, compared to those fed with standard tube feeding.

Abbreviations: AE, Adverse event; AN(C)OVA, Analysis of (co-)variance; BMI, Body mass index; BSC, Bristol Stool Chart; CDAD, *C. difficile* associated diarrhea; CIP, Critical illness neuropathy; (E)TF, (Enteral) tube feeding; ERBI, Early Rehabilitation Barthel Index; FAS, Full Analysis Set; FAS-Clost, Full Analysis Set without patient who suffered a *C. difficile* infection; ICU, Intensive care unit; IR, incidence rate; IRR, incidence rate ratio; LOCF, Last value carried forward; NFTF, Natural food based tube feeding; NG, Nasogastric tube; PEG, Percutaneous endoscopic gastrostomy; PPS, Per Protocol Set; RCT, Randomized controlled trial; SA, Safety Analysis Set; SCFA, Short chain fatty acids.

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1. Introduction

The most frequent complication during enteral tube feeding (ETF) is diarrhea. The incidence reported in the literature is highly variable, ranging from 2% to 95% depending on morbidity and different diarrhea definitions [1]. Diarrhea during ETF is a multifactorial challenge leading to dehydration, electrolyte imbalance, malnutrition, bacterial translocation and perianal wound infection [1,2]. Although the leading cause of diarrhea during ETF is unclear, medicines probably underlie most cases of nosocomial diarrhea due to gut toxicity and/or disruption of normal enteric bacterial flora [3]. Antibiotics and, in particular, combinations of two or more antibiotics [4] are associated with diarrhea [5,6]. In addition, several other factors such as gut colonization with enteropathogens, e.g. *Clostridium difficile*, may promote diarrhea [1,7].

However, formula related factors like high caloric density, high osmolality, large quantities, low fiber content and the mode of delivering tube feeding (bolus feeding, high flow rate, low temperature) are known as direct or indirect risk factors for diarrhea. It is an open question how ingredients (nutrient donators) of tube feeding formula might have an impact on gut physiology (digestion, absorption, gut enzymes, hormones, gut microbiota) and antibiotically disturbed gut physiology during diarrhea in tube fed patients. Almost all preparations of tube feedings available on the European market use nutrient isolates (with the exception of vegetable oils) and concentrates in powder form instead of natural foods. The nutrients and food isolates (e.g. milk protein) in these tube feedings were extracted from foods, but are provided without the natural food matrix. In this study a commercially available formula based on real foods such as milk, meat, and vegetables for ETF was used, hereinafter referred to natural food based tube feeding (NFTF). 65% of this NFTF is manufactured from natural complex foods. As human gut physiology and intestinal bacterial floras are intended to process natural food [8], a natural food matrix, as provided in NFTF, helps maintains healthy intestines and prevents gastrointestinal complications.

The aim of this randomized and controlled trial (RCT) was to investigate the effect of NFTF versus standard tube feeding on defecation frequency and stool consistency in long term tube fed patient with neurological diseases.

2. Materials and methods

2.1. Study design and trial procedures

The SOKO HiPP ("Sondenkost HiPP") study was an open-label, parallel group multicenter RCT conducted at three stroke and intensive care treatment units (early neurological rehabilitation) in Germany from December 2012 until November 2015. The primary goal was to test the hypothesis that food based enteral nutrition reduces the number of and days with watery, entirely liquid stools as compared to standard tube feeding in neurological patients, who need enteral tube feeding via percutaneous endoscopic gastrostomy (PEG) or nasogastric tube (NG). The study was performed in accordance with the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice Guidelines. Approval was granted by each local ethics committee before the trial was started. Patients eligible for randomization were enrolled, if they, or their legal representatives, had signed a written informed consent.

During the screening process, data on demographics, lifestyle factors (smoker status, alcohol consumption), laboratory parameters (albumin, total protein), neurological diagnoses and parameters of morbidity (modified Rankin Scale, rehabilitation prognosis, Charlson Comorbidity Index, Early Rehabilitation Barthel Index (ERBI) [9]) were collected. Physical condition and nutritional status, heart rate, blood pressure, weight, body mass index (BMI) and current enteral nutrition were recorded at study entry. In addition, stool microbiology and liquid/caloric requirements were determined, data on medical history and comorbidities including previous medication and adverse events were collected. Patients without violations of in- and exclusion criteria were randomly assigned to HiPP (INTERVENTION) or Fresubin (CONTROL) enteral nutrition.

Nurses and physicians were not blinded and knew to which arm of the trial the patient had been assigned. The design of an open-label study was well considered for this study, because a complete blinding could not have been achieved. During ETF with the INTERVENTION formula the coloration of the stool changes due to the amount of carrots and in particular the beta carotene. Even if is not known which tube feeding was supplied, it can be detected during nursing care and stool evaluation. Beside this, a blinding would be complicated by the fact that no black or non-transparent enteral pump giving sets for tube feeding exist. In addition, both tube feedings had to be decanting into neutral bags, because both are supplied in different forms (bottles versus bags). This would result in a higher risk of decontamination of the tube feeding.

For a maximum of 30 days, an enteral nutrition protocol (amount of nutrition and additional liquid, flow rate) as well as the monitoring of blood glucose and the number of hyper-/hypoglycemic episodes were recorded daily. Stool microbiology was examined when bacterial infections were presumed. Count and quality of stools were documented using the Bristol Stool Chart (BSC) [10]. The BSC allows stool evaluation through a 7-point scale ranging from "1" (indicating separate, hard lumps) to "7", which stands for entirely liquid, watery stool without any hard components. Diarrhea was defined as three or more liquid stools per day according to the World Health Organization [11]. ERBI reassessments and blood draw for clinical laboratory (hematology/chemistry, inflammatory parameters) were conducted at days 1, 15 and 30. Body weight was taken on days 15 and 30.

2.2. Patients

Eligible patients were adults during early neurological rehabilitation with a primary diagnosis of ischemic stroke, intracranial hemorrhage, traumatic brain injury, hypoxic brain damage or critical illness polyneuropathy. At the point of enrollment all patients had to be clinical judged as being in need of enteral nutrition via PEG or NG for 30 days at least. Main exclusion criteria were: known allergy or intolerance against enteral nutrition compounds, dysfunction of fructose metabolism, severe chronic or acute comorbidities such as renal or liver insufficiency, required parenteral nutrition, gastrointestinal disorders, active tumor diseases, medical necessity of other enteral nutrition than those used for the study, unstable glucose levels in patients with diabetes mellitus, and nutrition through jejunal feeding tube (details see Supplementary Table 1).

2.3. Study interventions

Patients were randomly (1:1) assigned to either the INTERVENTIONAL or the CONTROL arm by means of a standardized procedure. The randomization was stratified by center and age group ($\leq$65 and >65 years) using a central randomization service (randomization lists were computer-generated using a randomly permuted block design).

CONTROL patients received a standard product based on powdered raw materials (Fresubin original fibre; alternatively Fresubin soya fibre in case of lactose intolerance or allergy against

milk protein). INTERVENTION patients received a commercial available natural food based product (HiPP chicken with carrot and calabash; alternatively HiPP turkey hen with maize and carrot in case of lactose intolerance) (details see Supplemental Table 2). All used tube feedings are special formula for enteral nutrition only, are nutritionally complete balanced and nutrient composition complies with the recommendations of the national society of nutrition. Based on the special consistency of all enteral tube feedings, which guarantee the passage through the feed line, the risk of blockages are limited. Daily calorie requirement was individually calculated using an age-class and gender specific basal metabolic rate formula [12,13]. This rate was adjusted by a physical activity factor ranging from 1.2 (completely inactive) to 2.0 (complex activity) or a disease factor of 1.2 (mild decubitus ulcer) or 1.5 (severe decubitus ulcer), whichever was higher.

2.4. Study endpoints

The primary endpoint was defined as the number of liquid, watery stools (type 7 according to BSC) that occurred during the 30 days observation period. Secondary endpoints were nutritional status (change in weight and BMI, biochemical markers like serum concentration of albumin), average daily caloric and liquid intake, stools frequency and stools consistency.

Safety endpoints consisted of type, frequency, severity and relationship of adverse events (AEs) with enteral nutrition, laboratory parameters (time course and values outside normal range), number of hypo-/ hyperglycemic episodes and control of blood glucose, number of previous and concomitant medications, neurological outcome (using the ERBI) and vital sign parameters. Safety and other study endpoints will be reported elsewhere.

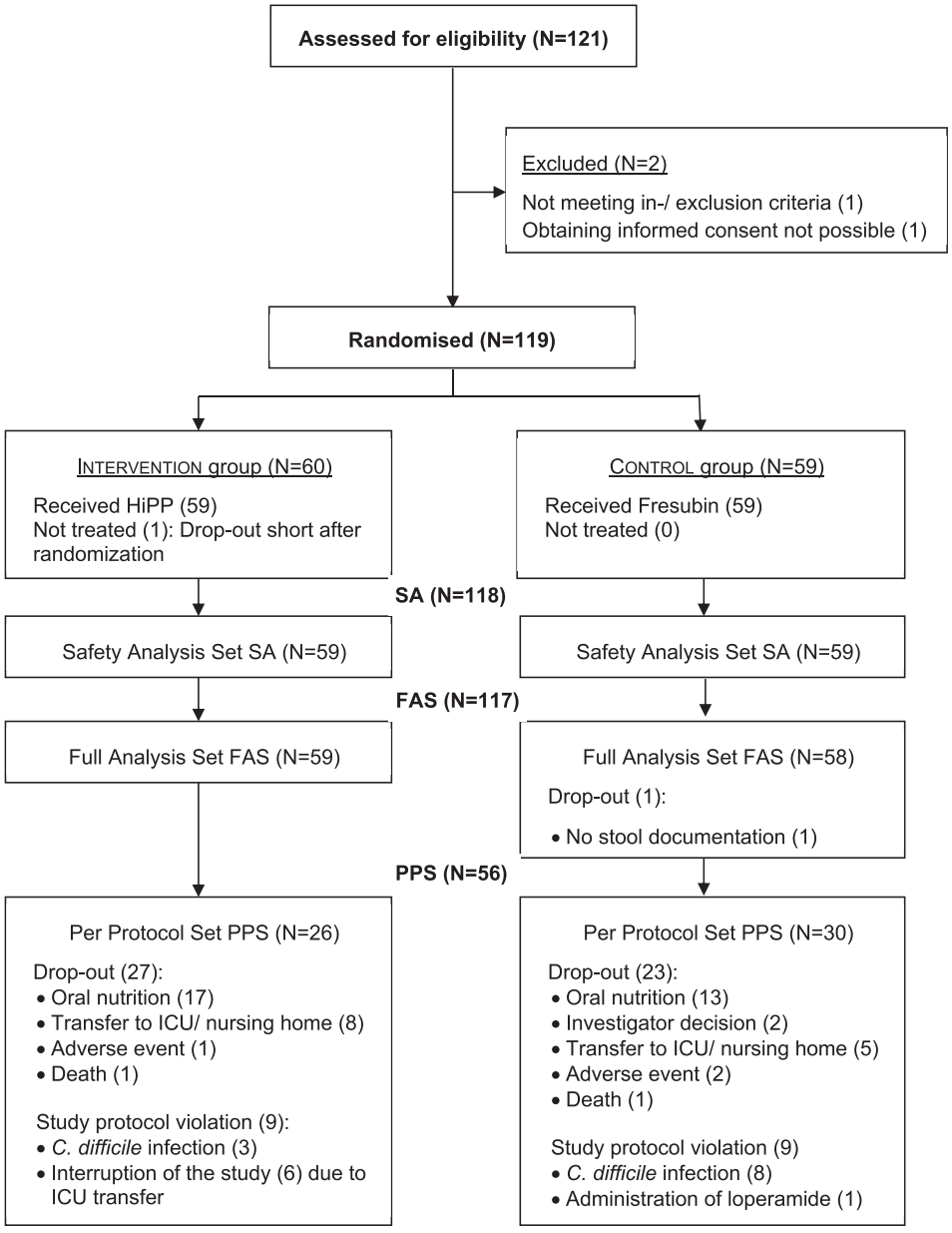

Fig. 1. Study flow chart. Patients could have multiple reasons for exclusion from the FAS.

2.5. Statistics

2.5.1. Sample size estimation

The study was powered on the primary endpoint. Based on an average number of type 7 stools of 15 in the CONTROL group and 7.2 in the INTERVENTION group (common standard deviation of 13.5) derived by internal pivotal studies, a one-sided *t*-test led to 48 patients per group (power 80%, type-I-error 2.5%). Taking into account a drop-out rate of 20%, a total of 120 patients were estimated to be required.

2.5.2. Analysis sets

The Safety analysis set (SA) was used for all safety parameters and included all patients who received enteral study nutrition at least once. Based on the intent-to-treat principle the Full Analysis Set (FAS) was defined as patients having at least one intake of the enteral nutrition under study conditions and at least one evaluation of stool characteristics after screening using the BSC classification scheme. Main conclusion of the primary endpoint was based on the FAS. The analysis of the primary endpoint was replicated using the Per Protocol Analysis Set (PPS) determined during a data review meeting. The PPS consisted of patients in the FAS with no major protocol violations. Secondary endpoint analyses were also conducted for the FAS and PPS. During the trial, some patients were diagnosed with *C. difficile* and were excluded from the FAS for additional subgroup analyses (subgroup FAS-Clost). The clinical rationale of the FAS-Clost population was to eliminate the effect of *C. difficile* associated diarrhea (CDAD) on stool consistency and defecation frequency.

2.5.3. Statistical analyses

For missing stool evaluations, values were imputed using the last value-carried-forward method (LOCF). The primary endpoint was analyzed with a negative binomial count model including treatment, center and age class as fixed factors. Number of days for which a stool evaluation was available was used as offset.

Additional sensitivity analyses of the main primary analysis were performed without using the LOCF method, looking at a shorter 15-day observation period, and finally including confounder variables such as the number and the application duration of antibiotics as further covariates in the multivariate model.

Continuous variables were analyzed using descriptive statistics, categorical parameters were evaluated using counts and percentages. Categorical parameters were examined using the Chi-Square-test or Fisher's exact test in case of small sample size or Mantel–Haenszel tests. Continuous parameters were compared using either non-parametric methods (Wilcoxon-two-sample test) or an analysis of variance model based on ranks. Inferential analyses for the main model used a one-sided significance level of 2.5%, all other tests applied a two-sided significance level of 5% and were of explorative nature.

Analyses were performed with the software package SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient disposition

A total of 121 patients were screened of whom 119 patients were randomly assigned to one of the enteral tube feedings (60 (50.4%) patients to the INTERVENTION group and 59 (49.6%) to the CONTROL group, see Fig. 1). One patient dropped out immediately after randomization resulting in a total of 59 patients in each group (Safety analysis set (SA)) having received enteral tube feeding under study conditions. Because for one patient in the CONTROL group no BSC classification of stools was available, he was excluded from Full Analysis Set (FAS). The FAS (n = 117) was used as the sample for analyses. Screening characteristics and demographics of the FAS population did not differ between the groups (Table 1). Among these 117 patients (FAS) 27 (45.8%) in the INTERVENTION group and 23 (39.7%) in the CONTROL group dropped out early. The most common reason was improvement of the patients' status allowing oral nutrition (28.9% in the INTERVENTION group, 22.4% in the CONTROL group). Further reasons were transferal to an ICU (intensive care unit) or nursing home (8 patients in the INTERVENTION and 5 in the CONTROL group). Two patients died (one patient in each group), three more patients discontinued due to adverse events (enteral tubes had to be removed because of constriction of esophagus or swelling of vocal folds or reanimation) and two were excluded due to investigator's decision (feeding formula had to be changed because of weight loss or limited renal function). Besides early drop-out, main major protocol violations consisted of interruption of the study for more than three days, bacterial infections with *C. difficile* or continuous administration of loperamide. A total of 56 patients had no major protocol violations and were included in the PPS.

Table 1
Demographic and clinical characteristics at screening, FAS.

	INTERVENTION (n = 59)	CONTROL (n = 58)	p-value
Age (years) (Mean ± SD)	63.1 ± 14.40	62.6 ± 16.11	0.8963[a]
Number of patients ≤ 65 years, n (%)	29 (49.2%)	28 (48.3%)	0.9641[b]
Number of patients > 65 years, n (%)	30 (50.8%)	30 (51.7%)	
Gender: Male, n (%)	37 (62.7%)	32 (55.1%)	0.3208[c]
Body weight (kg) (Mean ± SD)	73.9 ± 17.27	72.8 ± 13.14	0.7467[d]
BMI (kg/m^2) (Mean ± SD)	24.9 ± 4.80	25.2 ± 4.60	0.8346[d]
Primary diagnosis[e]			
Ischemic stroke (IS)	18 (30.5%)	19 (32.8%)	1.0000[f]
Intracranial hemorrhage (ICH)	16 (27.1%)	19 (32.7%)	0.2421[f]
Traumatic brain injury (TBI)	17 (28.8%)	10 (17.2%)	0.2994[f]
Hypoxic brain damage	6 (10.2%)	9 (15.5%)	1.0000[f]
Critical illness polyneuropathy (CIP)[g]	4 (6.8%)	1 (1.7%)	0.3077[f]
Charlson Comorbidity Index (Mean ± SD)	1.5 ± 1.68	1.4 ± 1.40	0.8323[d]
Early Rehabilitation Barthel Index (Mean ± SD)	−124.6 5 ± 56.49	−131.4 5 ± 62.60	0.6283[d]

[a] ANOVA based on ranks, fixed factors treatment and center.
[b] Mantel–Haenszel Test, stratified by center (Breslow-Day).
[c] Mantel–Haenszel Test, stratified by age group and center (Breslow-Day).
[d] ANOVA based on ranks, fixed factors treatment, age group and center.
[e] At least one to be answered with 'yes'. Multiple replies possible.
[f] Fisher's exact test.
[g] One patient (CONTROL group) was included with Guillian Barre Syndrome subsumed under CIP.

Table 2
Caloric and liquid intake during the study, FAS.

	INTERVENTION (n = 59)	CONTROL (n = 58)
Daily caloric intake per patient (kcal/day) (Mean ± SD)	1725.7 ± 298.45	1708.7 ± 303.65
Daily total liquid intake per patient[a] (ml/day) (Mean ± SD)	2571.9 ± 495.52	2532.2 ± 343.62
Patients having received NFTF before entering the trial (n (%))	18 (30.5%)	18 (31.0%)
Flow rate (ml/h)[b]	122.7 ± 30.27	129.2 ± 33.64
Days under enteral study nutrition administration (Mean ± SD)	24.1 ± 10.97	24.5 ± 9.49
Days under observation (Mean ± SD)	31.0 ± 12.17	30.9 ± 10.51

[a] Including 80% liquid intake from enteral tube feeding.
[b] was calculated on the basis of all existing flow rates of each administrated tube food.

3.2. Administration of enteral tube feeding and compliance

32 patients in the INTERVENTION group and 35 in the CONTROL group were observed during the full study period. There were no statistically significant differences between INTERVENTION and CONTROL groups with respect to durations of tube feeding administration, average daily caloric intake und total liquid or flow rate (Table 2). Prior to their enrollment, 18 patients in each group had already received natural food based enteral nutrition (Table 2).

3.3. Main endpoint

Numbers of type 7 stools observed during 30 days differed significantly between the groups. The reduction of the number of liquid stools in the INTERVENTION ETF group was 61% compared to CONTROL ETF (IRR 0.39, 95% CI 0.24–0.64, p = 0.0001, Fig. 2). Table 3 shows the mean count of liquid stools: There was a mean of 6.8 ± 10.06 (IR 0.22) in the INTERVENTION group which was considerably lower than among patients in the CONTROL group (17.8 ± 17.72, IR 0.55, FAS) (Fig. 3). Sensitivity models confirmed statistically significant differences in all model variations even when looking at data without application of LOCF. IRR still improved when looking at the FAS-Clost or PPS. A shorter observational period of 15 days revealed a reduction of the number of type 7 stools up to 50% (FAS, FAS-Clost). Models adjusted for the covariates 'number' and 'duration of antibiotics' showed no significant confounding impact.

Due to the fact that antibiotic treatment is a confounding factor of diarrhea, both groups were investigated with regard to their antibiotic medication and influence on diarrhea. The number of patients receiving one or more antibiotic medications did not differ between both groups. In the INTERVENTION group 69.5% (41/59) of the patients needed antibiotic treatment compared to 75.9% (44/58) in the CONTROL group (FAS) (Table 4). Patients received an average of 1.5 ± 1.51 number of antibiotics in the INTERVENTION group, and 1.6 ± 1.51 in the CONTROL group (FAS) (Table 5). The FAS-Clost and PPS results were not different from FAS results. The rate of patients without antibiotic treatment or with 1, 2 or more antibiotics did not differ significantly between both groups (data not shown). As evident from Table 5, the mean days under antibiotic treatment did not differ between both groups.

Patients on antibiotics had more liquid stools (Table 4). The effect was statistically significant within the INTERVENTION group except for PPS. In the CONTROL group, no difference was detected. Between-group comparisons showed significant lower mean number of type 7 stools in the INTERVENTION group in each analysis population regardless of use of antibiotic medication (Table 4).

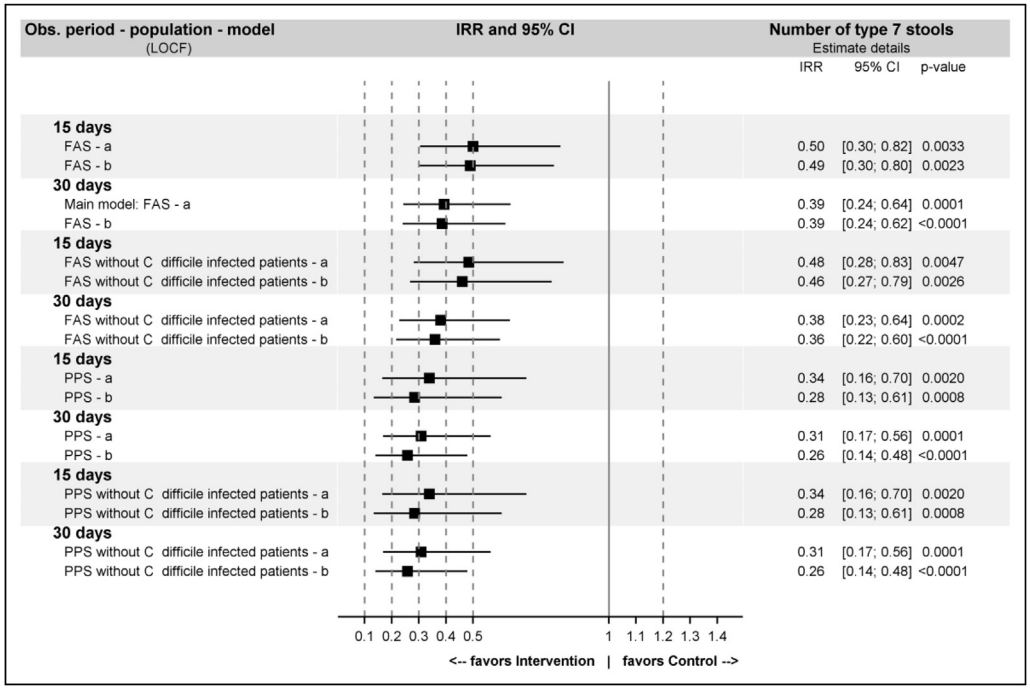

Fig. 2. Incidence rate ratios for the comparison of number of type 7 stools between treatment groups. Observational period distinguishes between 15 days and 30 days over which the number of type 7 stools has been summed up. Incidence rate ratio IRR, two-sided 95% confidence intervals and one-sided p-values are displayed on the right. [a] Negative binomial model with factors treatment, age group and center. [b] Negative binomial model with factors treatment, age group, center and covariates duration and number of antibiotics.

Table 3
Stool characteristics.

	FAS				FAS - Clost				PPS			
	INTERVENTION		CONTROL		INTERVENTION		CONTROL		INTERVENTION		CONTROL	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
No. of defecations per patient[e]												
In total	59	46.4 ± 15.05	58	43.2 ± 15.14[a]	56	45.9 ± 14.77[a]	50	41.9 ± 14.54[a]	26	52.8 ± 17.04	30	44.7 ± 15.69[d]
Per day	59	1.6 ± 0.50	58	1.4 ± 0.51[a]	56	1.5 ± 0.49[a]	50	1.4 ± 0.49[a]	26	1.8 ± 0.57	30	1.5 ± 0.52[d]
No. of days with type 7 defecations[e]	59	4.2 ± 6.76	58	10.5 ± 8.83[b]	56	3.8 ± 6.34	50	9.6 ± 8.77[b]	26	2.6 ± 3.00	30	9.6 ± 7.60[b]
No. of days with ≥3 type 7 defecations[e]	59	0.8 ± 1.60	58	2.0 ± 3.46[d]	56	0.6 ± 1.02	50	1.7 ± 3.42[d]	26	0.6 ± 1.10	30	2.1 ± 4.13[d]
No. of type 7 defecations (unadjusted)	59	6.8 ± 10.06	58	17.8 ± 17.72	56	5.9 ± 8.46	50	16.0 ± 17.37	26	5.0 ± 6.54	30	17.5 ± 19.45
Multinomial models	n	IR (SD)	n	IR (SD)	N	IR (SD)	n	IR (SD)	n	IR (SD)		IR (SD)
Model a: Number of type 7 defecations (adjusted)[f]	59	0.22 (6.5)	58	0.55 (16.5)[c]	56	0.20 (5.9)	50	0.52 (15.6)[b]	26	0.16 (4.8)	30	0.52 (15.7)[c]
Model b: Number of type 7 defecations (adjusted)[g]	59	0.21 (6.3)	58	0.54 (16.3)[b]	56	0.19 (5.7)	50	0.52 (15.7)[b]	26	0.14 (4.2)	30	0.56 (16.4)[b]

[a] n. s.
[b] p-value < 0.0001.
[c] p-value < 0.001.
[d] p-value < 0.05.
[e] Tests of differences between treatments used a two-sided ANOVA based on ranks with fixed factors treatment, center and age group (two-sided).
[f] Incidence rate and estimated number of type 7 stools for 30 days. Derived from negative binomial count model with factors age group and center. P-values are one-sided for tests on differences.
[g] Incidence rate and estimated number of type 7 stools for 30 days. Derived from negative binomial count model with factors age group, center, number and duration of antibiotics. P-values are one-sided for tests on differences.

3.4. Secondary endpoints

3.4.1. Stool frequency and consistency

The total number of stools did not differ between both groups, except in the PPS showing a higher number of defecations in the INTERVENTION group (Table 3). Figure 4 illustrates the stool frequency distribution according to the BSC. Most frequent stool type in the INTERVENTION group was a normal type 4 stool with 36.7% while, the most frequent stool type of the CONTROL group was 7 with 36.7%. Excluding patients with *C. difficile*, there were 38.6% type 4 stools as most frequent type in the INTERVENTION group and 33.9% type 7 stools in the CONTROL group. In addition, administration of the INTERVENTION ETF reduced significantly the number of days with type 7 defecations (4.2 ± 6.76 vs. 10.5 ± 8.83, p < 0.0001 for FAS, 3.8 ± 6.34 vs. 9.6 ± 8.77, p < 0.0001 for FAS-Clost). There were only few days with ≥3 type 7 defecations in both groups, however significantly less in the INTERVENTION group (0.8 ± 1.6 vs. 2.0 ± 3.46, p < 0.05 for FAS, 0.6 ± 1.02 vs. 1.7 ± 3.42, p < 0.05 for FAS-Clost). PPS analyses confirmed these results.

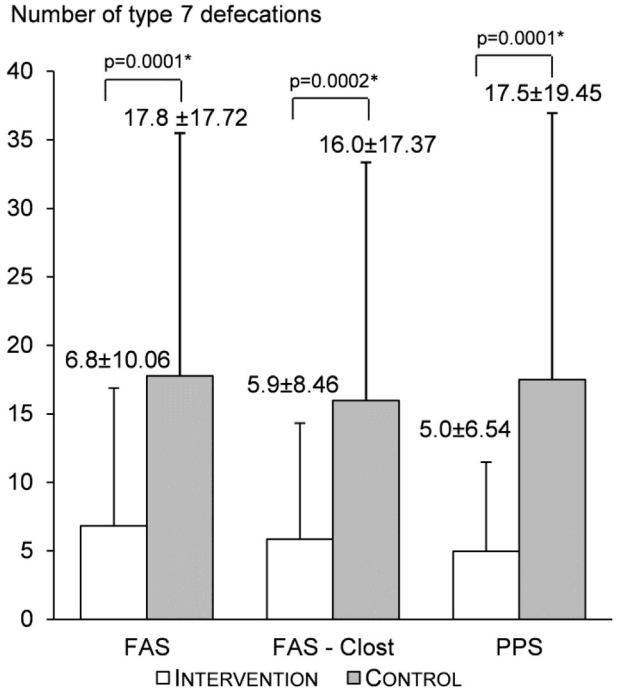

Fig. 3. Mean and standard deviation of number of type 7 defecations for analysis populations FAS and PPS and FAS subgroup without *C. difficile* infected patients (FAS – Clost). *One-sided p-values derived from negative binomial count model with factors treatment, age group and center.

3.4.2. Nutritional status

BMI did not decrease during the trial and there were no significant BMI differences between the groups. Both groups had an average BMI of 25 remaining stable (changes between −2% and +0.2%) over 30 days. In both study groups more than 90% of the patients started with a low serum albumin level (norm values 35–55 g/l, Safety Analysis Set). This high percentage remained constant throughout the whole study, both in the INTERVENTION and CONTROL group (mean serum albumin INTERVENTION 29.2 ± 4.00 g/l, CONTROL 27.9 ± 4.94 g/l).

4. Discussion

Diarrhea in enteral fed patients is a multifactorial disorder frequently resulting from morbidity or the use of medication such as antibiotics [4]. Although tube feeding formula per se is not generally regarded as the primary cause of diarrhea [4], changing the tube feeding is often the first step in the management of diarrhea. The present RCT analyzed the effect of a food-based tube feeding with one of its active ingredient from carrots (NFTF) in comparison to a standard tube feeding with fiber based on powdered raw material on the incidence of liquid watery defecations and diarrhea in critically ill neurological patients requiring long term enteral feeding.

For the first time – to the best of our knowledge – this RCT provides strong evidence that NFTF may significantly reduce the number of liquid stools (BSC type7) compared to standard tube

Table 4
Effect of antibiotic medication on number of type 7 defecations.

Antibiotics applied?	FAS (n = 117)				p-value[c]	FAS - Clost (n = 106)				p-value[c]	PPS (n = 56)				p-value[c]
	INTERVENTION		CONTROL			INTERVENTION		CONTROL			INTERVENTION		CONTROL		
	n	Mean ± SD[a]	n	Mean ± SD[a]		n	Mean ± SD[a]	N	Mean ± SD[a]		n	Mean ± SD[a]	n	Mean ± SD[a]	
Yes	41	8.4 ± 10.70	44	19.4 ± 18.31	0.0002	38	7.2 ± 8.70	36	17.3 ± 18.19	0.0008	22	5.6 ± 6.85	24	17.4 ± 20.59	0.0029
No	18	3.1 ± 7.43	14	12.6 ± 15.16	0.0469	18	3.1 ± 7.43	14	12.6 ± 15.16	0.0469	4	1.5 ± 3.00	6	18.0 ± 15.60	0.0477
p-value[b]		0.0092		0.0761			0.0153		0.1627			0.1462		0.6777	

[a] Represents mean number of type 7 stools with its corresponding standard deviation in the respective patient group.
[b] Wilcoxon-two-sample test (continuity corrected) within each treatment group on difference in mean number of type 7 stools between patients with and without intake of antibiotics.
[c] Wilcoxon-two-sample test (continuity corrected) between each treatment group on difference in mean number of type 7 stools within patients having taken antibiotics or having not taken antibiotics.

Table 5
Antibiotic treatment.

		INTERVENTION		CONTROL		p-value[a]
		n	Mean ± SD	n	Mean ± SD	
Number of antibiotics	FAS (n = 117)	59	1.5 ± 1.51	58	1.6 ± 1.51	0.3501
	FAS-Clost (n = 106)	56	1.5 ± 1.50	50	1.3 ± 1.23	0.6810
	PPS (n = 56)	26	2.0 ± 1.51	30	1.6 ± 1.38	0.5914
Duration of antibiotics in days	FAS (n = 117)	59	9.9 ± 10.21	58	11.5 ± 10.66	0.6966
	FAS-Clost (n = 106)	56	9.4 ± 9.85	50	9.2 ± 8.29	0.8308
	PPS (n = 56)	26	12.4 ± 10.16	30	10.8 ± 8.95	0.4286

[a] ANOVA based on ranks with fixed factors treatment, age group and center, two-sided p-value.

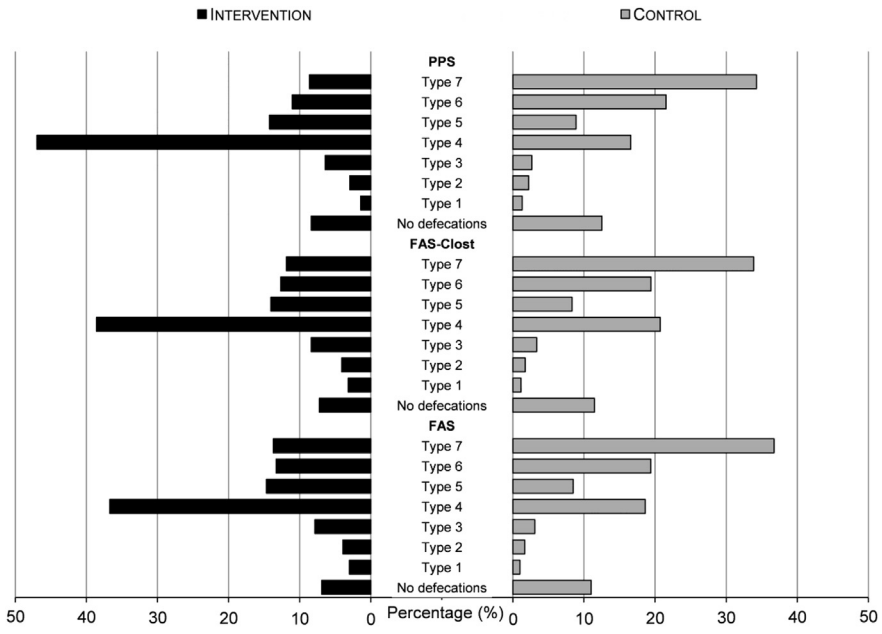

Fig. 4. Percentage of stool types according to Bristol Stool Type Chart. Y-axis displays percentage of stools in each category. Bars are grouped by the analysis populations FAS, PPS and subgroup FAS without *C. difficile* infected patients (FAS − Clost).

feeding by 61% (IRR 0.39, P = 0.0001). In addition, the INTERVENTION group had a significant reduction of 60% in mean days of diarrhea compared to the CONTROL group. Most frequent stool consistency in the INTERVENTION group was a normal type 4 stool (smooth and soft), while most frequent stool consistency in the CONTROL was type 7 (watery) stools.

4.1. *C. difficile* associated diarrhea (CDAD)

The toxin produced by bacterium *C. difficile* causes antibiotic associated diarrhea in about 10–25% of cases [14]. The incidence of CDAD in this study was 12.4%. To eliminate CDAD effects from our main parameter, we conducted a subgroup analysis (FAS-Clost) excluding patients with *C. difficile* infections. Significant differences of the number of type 7 BSC stools could still be demonstrated showing that even excluding patients with bacterial cause of diarrhea did not influence the main results (IRR = 0.38, p-value = 0.0002). Although a coincidence cannot be ruled out due to the small sample size, a smaller number of patients in the INTERVENTION group (n = 3) were diagnosed with CDAD than in the CONTROL group (n = 8). This possible protective effect should be investigated in future trials.

4.2. Antibiotic medication

CDAD is well known to occur under antibiotic treatment and antibiotic treatment itself often results in antibiotic-associated diarrhea [4,15–17]. In general, antibiotics are a major risk factor for diarrhea because of their negative effect on intestinal flora [18,19]. Alterations in the intestinal flora induced by antibiotics have been identified not only in patients eating but also in those being tube fed. These alterations may be associated with the increased prevalence of diarrhea [4–6]. The use of antibiotics is common among critically ill patients because of the high prevalence of pneumonia, urinary tract infection and other infections. In our trial, 69.5% (INTERVENTION) and 75.9% (CONTROL) of the patients had antibiotic treatment. The average duration was 1.4 weeks and a mean of 1.5 different antibiotics was prescribed. Surprisingly, the number of antibiotics and the treatment duration did not account for the differences in the number of type 7 defecations between INTERVENTION and CONTROL group in our statistical models, even an adjustment (by age, centre) led to smaller IRRs. However, a subgroup analysis focusing on patients treated with antibiotics confirmed the dominating effect of any kind of tube feedings: on an average, the frequency of type 7 stools was elevated two- to three fold under antibiotic treatment in both groups, but the differences in the number of type 7 defecations between INTERVENTION and CONTROL groups remained statistically significant lower.

4.3. Tube feeding composition

The impact of food-based tube feeding on diarrhea has not been studied so far, but several studies investigated the effect of high fiber diets on diarrhea. Different meta-analyses [15,16,20] demonstrated that high fiber enteral tube feedings may ameliorate diarrhea among patients not in intensive care unit. A study on an inpatient sample receiving a fiber free ETF via postpyloric tube feeding demonstrated a nine times higher risk of CDAD as compared to non-tube-fed patients [21]. It is well known that high fiber diet has an impact on the intestinal flora resulting in a decrease of diarrhea [22–25]. This may be explained by the fact that high fiber tube feeding is the basis of colonic fermentation and selectively stimulates the growth and/or activity of intestinal bacteria associated with health and well-being [26]. Colonic bacteria can produce short chain fatty acids (SCFA) from soluble fibers, which are energy substrates for colonic mucosal cells. SCFA may lower colonic pH, preventing an infection with enteropathogens [27]. All tube feedings used in this study contained similar amounts (10–20 g/l) of mixed fibers. However, the composition of the fiber mixture differed between the two groups. While NFTF contains 0.5 g/100 ml oat fiber (insoluble), inulin (soluble) as well as natural fibers from carrots, the standard ETF fiber consisted of cellulose, wheat dextrin (soluble) and inulin (soluble). In comparison to the CONTROL, the NFTF formulation contains 8% carrots, delivering a daily amount of 120 g carrots (corresponds to 4.3 g of fibers) in 1.5 l tube feeding. The NFTF also contains many other components from carrots such as pectins and acidic oligosaccharides, for which protective effects have been shown in previous studies [28–30]. Since the beginning of the 20th century, carrot soup has been used in the treatment of small children's diarrhea [30]. The beneficial effect on diarrhea is caused by an anti-adhesive effect of acidic oligosaccharides and was identified in 1997 for the first time [31]. Later on, an in-vitro study showed that acidic oligosaccharides, in particular trigalacturonic acids from carrots, may block adherence of various enteropathogenic microorganisms to human liver cells and human intestinal mucosa [29]. Carrots contain factors leading to bifidogenic effects in vivo an in vitro [28,32]. It has been demonstrated for infants suffering from enteritis [28] that oral realimentation solution with carrots, rice and electrolytes is more effective in reducing diarrhea than a glucose-electrolyte solution with rice but without carrots. Bifidobacteria were the predominant bacteria in the feces on day 4 of the realimentation period [28] when the carrot soup was given. Bifidobacteria shows antimicrobial activity against many enteropathogens [33] and their reduction [7] has impaired the ability of gastrointestinal microbiota to inhibit pathogens [34], which increased the colonization with pathogens such as *C. difficile*. Replacement of depleted intestinal microorganisms with pro- or prebiotics may be beneficial in maintaining favorable microbiota and a homeostatic environment in the colon [35].

In another RCT with critically ill patients, it could be demonstrated, that banana flakes (4,5 g fiber/day or 2 g pectin/day) ameliorate diarrhea in enteral fed patients [36] to the same degree as in control patients receiving antidiarrheal medications. Interestingly, this study showed a beneficial effect of banana flakes on the treatment of CDAD. Although the results did not reach statistical significance probably due to a small sample size, only 12% patients of the banana flake group were tested positive for *C. difficile* toxin in comparison to 36% in the control group. The authors hypothesized that pectin and other fermentable substances in banana might contribute to the beneficial effect of banana on diarrhea.

It remains unclear whether the beneficial effect of NFTF relates to anti-adhesive effects of acidic oligosaccharides in carrots or other prebiotic ingredients in carrots like pectin or other food ingredients in the food mixture. This should be evaluated in further studies.

4.4. Strength and limitations

The strength of the study was that patients were exclusively tube fed patients in standardized settings. In addition, the observational period of the study (average 31 days) and the period under complete enteral nutrition (average 24 days) were considerably longer than in previous trials [37]. In addition, there was daily data recording of each stool evacuation with its corresponding consistency via the validated BSC [10]. However, due to a temporary transfer to another hospital (i.e. reimplantation of the skullcap), the stool documentation was not continuous for some patients. In addition, we could not ensure that nutrition was continued according to the study protocol during their stay within the acute care hospital. Consequently, a length of stay of more than three days in the acute hospital was defined as reason for not entering the patient into the PPS. Evaluation of stool consistency relied on direct observations by experienced nursing staff and thus remained subjective, which might result in bias. Although the staff was highly motivated, some episodes of diarrhea may have been missed or recorded incorrectly. The number of days with $\geq$3 type 7 defecations [11] was small for both groups, but very similar to another study with enteral fed patients after stroke [37]. A further limitation of the study is that it was not possible to blind ETF appropriately and that the absence of blinding might reduce the quality of the results. Furthermore, there was no weighing of stools in our study. The high drop-out rate of 44% (INTERVENTION) and 51% (CONTROL) was mainly due to an early return to normal oral feeding before discharge to other rehabilitation units providing lower intensity care or to nursing homes.

5. Conclusion

Diarrhea remains an important issue among long-term tube fed critically ill patients. Tube feeding based on natural food components may be an effective prophylaxis and treatment of diarrhea,

thus contributing to a better quality of life, more effective rehabilitation treatment and a decrease of nursing and hospital costs.

Statement of authorship

SBS conducted the study in one of the study centers, performed the data collection and data entry, coordinated the double data control and wrote the paper. ASV, RW and JDR were principal investigators, read, improved and finally approved the paper. WK was the director of the study and helped writing the paper. AEK was responsible for the data analysis and the preparation of the figures and partly tables. In addition, AEK wrote the statistical sections of the paper, read and improved the paper.

Role of funding source

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Conflict of interest

SBS job position was funded to 50% by HiPP GmbH & Co. Vertrieb KG during study performance.

AEK has received consulting fees and honoraria from company HiPP GmbH & Co. Vertrieb KG.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.01.007.

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