The use of two Comfort YCFs in the dietary management of toddlers with a history of functional constipation: a randomized controlled trial

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Abstract

Background: Pharmacological intervention with laxatives is the conventional treatment for functional constipation. Data to support the dietary management of functional constipation is lacking. This study compared the efficacy of two Comfort young child formulas with regards to the maintenance of healthy stooling parameters in toddlers with a history of constipation. It was registered in the Netherlands Trial Registry [identifier: NL7420 (NTR7653)], registration date 20/09/2018.

Methods: Ninety-five healthy toddlers, aged 12 to 32 months, diagnosed with functional constipation (Rome III criteria) were randomized to receive one of two study formulas after pharmacological treatment. For the first month of the intervention, subjects received a laxative in a decreasing maintenance dose alongside a test or control formula (maintenance phase). Subsequently, subjects only consumed formula for another month (post-maintenance phase). Stooling parameters were obtained weekly using the Bristol Stool Scale and modified Rome III Questionnaire on Paediatric Gastrointestinal Symptoms for infants and toddlers. Differences in percentages of hard stools (primary outcome) and other stooling parameters were analysed using analysis of covariance and Chi-Square methods.

Results: The overall percentage of hard stools was 5.02% in the test and 2.98% in the control group (n.s.). In the test group, these percentages dropped from 7.11% at the end of the maintenance phase, to 3.92% at the end of the post-maintenance phase (n.s.). In contrast, the % of hard stools in the control group was similar at the end of the maintenance (3.11%) and post-maintenance phase (2.77%; n.s.). No difference was found in the overall stool frequency between groups.

At the end of the maintenance phase, only 22% and 19% of toddlers consuming the test and control formulae, respectively, met 2 or more of the criteria for functional constipation. At the end of the study, this percentage decreased to 9% in the test group (p=0.057), whereas it remained similar in the control group (21%, p=0.1). The number needed to treat for functional constipation was 8.3 in favour of the test formula at the end of the study period. No laxative use was reported in either study group during the post-maintenance phase.

Conclusion: Both Comfort YCF support the maintenance of improved stooling over time in toddlers with a history of constipation. Children receiving the formula with intact protein tended to meet lower numbers of indicators of FC at the end of the study.

Background

Functional gastrointestinal disorders (FGIDs) are common health problems in infancy and early childhood. Even though they are mostly transient and do not require a medical treatment, they may be very distressing to a new parent as well as the child (1). These gastrointestinal disorders are often age-dependent and can be an accompaniment to a normal development (e.g., infant regurgitation), or they may arise from maladaptive behavioural responses to internal or external stimuli (e.g., in functional constipation, retention of faces is a learned response to painful defecation) (2). Gastro-oesophageal

reflux (regurgitation), constipation and infantile colic are among the most common disorders in infancy and early childhood and they can occur separately or in combinations (3). Both reflux and colic usually are linked with early infancy and self-resolve by the age of 12 months, however constipation often continues into the toddlerhood and peaks when the toilet training starts (mostly after 12 months) and often continues, in extreme cases even to the adulthood (4–6).

The prevalence of FC in children is difficult to determine with high dose of certainty, but most studies report it to range from 0.5 to 32%, with global pooled prevalence of 9.5% (7). There is no consensus regarding the geographical regions with highest prevalence of childhood FC. The common belief that constipation tends to be most frequent in North America and Europe(7), seem to be contradicted by epidemiological studies showing prevalence reaching as high as 30% in Taiwan (8), 26.8% in Colombia (9) and 22.5 in Saudi Arabia (10), indicating it is a global problem. Functional constipation (FC) is characterized by infrequent bowel movements, hard and/or large stools, painful defecation, and faecal incontinence, and is often accompanied by abdominal pain. FC is not caused by anatomic abnormality, inflammation, or tissue damage (11), but the exact cause is still unclear. Its pathophysiology is thought to be multifactorial. Risk factors include stress, dietary habits, physical activity, obesity, family history of FC, poor toilet training, psychological difficulties, child maltreatment, and dysbiosis of gut microbiota (12, 13). Withholding behaviour, i.e. avoiding stooling, is seen as the key factor of childhood constipation (14, 15).

In general, FGIDs have been linked to both short- and long-term (negative) effects on health and quality of life of young children as well as their caregivers. For example both children with FC as well as their families have lower health-related quality of life (16), while school aged- children had persistent fatigue with significant school absenteeism (17, 18). Moreover, the frequency of irritable bowel syndrome (IBS) was found to be significantly higher in a cohort of adults who suffered from FC during their childhood (55%) compared to controls without history of FC (23.5%) (4). Due to the magnitude of the problem, paediatric FC has also substantial impact on healthcare and medical costs. According to research conducted in USA, the estimated costs of paediatric FC are comparable to those of asthma and attention deficit hyperactivity disorder (19), while in Australia constipation in children is a significant cost burden costing public hospitals in Victoria approximately A$5.5 million/year (4.1 million USD or 6.6 million Eur) (20).

Conventional treatment for FC consists of pharmacological intervention (i.e. laxatives for stool disimpaction) in combination with non-pharmacological measures such as education and toilet training (21). The prevailing consensus among experts is that FC in children should not be treated by means of dietary intervention (11). This conclusion is drawn to a great extent due to the lack of sufficient high quality data to support efficacy of dietary treatments (11). However, experts also agree that proper balanced diets, with special focus on fibre and fluid intake, should be an integral part of the maintenance therapy of children that have been pharmacologically treated for FC (11, 22, 23).

The aim of this study was to assess the efficacy of two commercially available Comfort young child formulas (YCFs) with regards to the maintenance of healthy stooling parameters in toddlers with a history of constipation. In addition, effects of consumption of these formulae with respect to other symptoms, defined in the Rome III criteria for the diagnosis of FC in toddlers and young children, were examined.

Method

Study design and population

This was a multi-centre, randomised, controlled, open-label trial, where randomization of study participants to each of the two treatment arms was based on a computer-generated sequence in blocks of 10, performed by a third-party. A total of 95 full-term, formula-fed, otherwise healthy, toddlers that were diagnosed with and treated for functional constipation (Rome III), were included in the study (Fig. 1). All subjects had an appropriate for gestational age birthweight (between the 10th and 90th percentile), were formula fed prior to participating in the study and were between 12 and 32 months of age at the time of enrolment. Toddlers that were diagnosed with other gastrointestinal (GI) diseases (e.g. coeliac or Hirschsprung's disease, etc.), cow's milk protein allergy, or lactose intolerance were not eligible.

The sample size was calculated based on the desired significant difference in the primary outcome (% of total hard stools): 30% fewer hard stool occasions in the test group. During a two-tailed test, $\alpha = 0.05$ and $\beta = 0.20$ (power = 0.80), each group ideally comprising 42 subjects. Additional 6 (15%) dropouts = 48 per group.

The study protocol, information letter to parents/legal guardians and written informed consent forms were approved by the ethical committee of Clínica de Enfermedades Crónicas y de Procedimientos Especiales S.C. (record number: 001_2019). Upon completion of the study, parents received a €50 voucher as a compensation for their time. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and was registered in the Netherlands Trial Registry, [identifier: NL7420 (NTR7653)] registration date 20/09/2018.

Study products and procedure

Pre-study treatment consisted of 1.5g/kg bodyweight polyethylene glycol 3350 (Macrogol) (PEG). After treatment, subjects were enrolled and randomly assigned by the investigator paediatrician to receive one of two young child formulae (YCF) commercially available in Mexico in 2019, specifically designed for the dietary management of hard stools.

The test formula (FrieslandCampina, Friso) contained intact protein, 20% milk fat, a fibre mixture of GOS, inulin and CBG, 100% lactose and a probiotic (*B. lactis* HN019). The control formula (Abbott, Similac) contained partially hydrolysed whey (pHW), GOS, and lower lactose. See Table 1 for an overview of the

main functional ingredients of both formulae. Parents were instructed to provide their child with 3 servings of formula per day. Three servings of the test formula provided 1.74 grams of dietary fibre daily, whereas 3 servings of the control formula provided 1.39 grams.

Table 1
Composition of the study formulas (per 100 kcal).

		Test	Control
Protein	g	4.7 (intact)	3.17 (pHW)
Fat	g	4.43 (20% MF)	4.89 (vegetable)
Total fibre	g	0.478	0.232
GOS	g	0.26	0.232
Inulin	g	0.13	-
CBG	g	0.087	-
Lactose	g	6.5	0.27
Probiotic		*B. Lactis* HN019	-

pHW: partially hydrolysed whey; MF: milk fat

A total of 93 subjects completed the 8 week intervention with one of both Comfort YCF (Fig. 1). During the first 4 weeks of the intervention (maintenance phase), toddlers received a decreasing maintenance dose of PEG according to standard clinical protocol (see Fig. 2 for details). Subsequently, subjects only consumed formula for another 4 weeks (post-maintenance phase).

At baseline (V1), subjects' anthropometrics (body weight and length) were measured by the investigators or a research assistant and parents were asked to complete a simple food frequency questionnaire (FFQ), to assess the subjects' habitual food intake, especially with regards to dietary intake of fibres and fluids. During the intervention, parental-reported stooling parameters were obtained weekly using the Bristol Stool Scale (BSS) and modified Rome III Questionnaire on Paediatric Gastrointestinal Symptoms for infants and toddlers (QPGS-RIII, section E). In addition, parents were required to keep a milk diary, in which consumption of the study products was logged. Subjects and at least one of their parents visited the investigators every two weeks (V2, V3, and V4) to deliver all diaries and questionnaires and obtain new study products. After the eighth and final week of the intervention, anthropometrics (body weight and length) were measured by the investigator or a research assistant at the study site, and parents were asked to complete the FFQ again.

Bristol Stool Scale (BSS)

The Bristol Stool Scale (BSS) is a validated, visual scale, which enables parents to provide doctors and researchers with an accurate description of characteristics of their toddler's stools. The scale allows

classification of stool form in 7 types, ranging from “separate hard lumps like nuts” (type 1) to “watery, no solid pieces” (type 7) (24, 25). Type 1 and type 2 (“sausage-shaped, but lumpy”) stools are considered to be ‘hard stools’ and a sign of constipation. Parents were asked to complete the BSS every time their child defecated throughout the course of the study. If on any day the BSS was not completed, it was assumed that the subject did not have any bowel movements on that particular day. The BSS was used to assess overall frequency (%) of reported hard stools (type 1 and 2), overall stooling frequency, and percentage (%) of toddlers with hard stools. The frequency of hard stools was calculated as the number of hard stools divided by the number of total stools times 100.

QPGS-RIII (section E)

The Rome III Questionnaire on Paediatric Gastrointestinal Symptoms (QPGS-RIII) for infants and toddlers is a parent-reported questionnaire of their child’s symptoms, useful for diagnosing Rome III diagnoses for functional gastrointestinal disorders (FGIDs), like functional constipation (section E). The QPGS-RIII (section E) assesses the presence of different Rome III criteria for functional constipation, such as infrequent bowel movements, hard and/or large stools, painful defecation, and faecal incontinence, and is often accompanied by abdominal pain. For the purpose of this study, the QPGS-RIII (section E) was modified to ask parents about the past week, and parents were asked to complete the questionnaire at the end of every week. To be diagnosed with functional constipation, a child should meet at least 2 of the Rome III criteria.

Statistical analysis

Differences in percentages (%) of hard stools (primary outcome), stool frequency, and other stooling parameters were analysed using analysis of covariance (ANCOVA) and Chi-Square methods. Using ANCOVA, between-group differences and differences over time were examined with type of formula and week as fixed factors. Potential confounders were explored and included in the model where appropriate. Potential confounders that were considered included baseline characteristics (e.g. age, sex), study site, use of antibiotics and/or laxatives (during the post-maintenance phase), and estimated fibre and fluid intake, other than study formula. All analyses were performed for the maintenance phase (week 1–4), post-maintenance phase (week 4–8) and total study duration (week 1–8).

Results

Study population

Table 2 shows demographics of both study groups. Groups were well matched with regards to gestational age, birthweight, and baseline age and anthropometrics. In addition, similar numbers of subjects in each group attended childcare or had other significant caregivers, such as grandparents, siblings, and aunts.

Table 2
Demographics of subjects and their caregivers, presented by study group

	Test	Control
n	47[1]	48
Gender (n), count		
Male	22	27
Female	25	21
Gestational age (weeks), mean (SD)	39.02 (1.195)	38.97 (1.084)
Birthweight (grams), mean (SD)	3270.65 (407.510)	3142.29 (376.101)
Age at baseline (months), mean (SD)	21.12 (5.923)	20.43 (6.383)
Weight at baseline (kg), mean (SD)	11.05 (1.514)	11.34 (1.900)
Length at baseline (cm), mean (SD)	82.57 (6.098)	82.78 (8.626)
BMI at baseline (kg/m^2), mean (SD)	16.13 (1.875)	16.70 (2.739)
Age of mother (years), mean (SD)	27.19 (6.523)	27.13 (6.097)
Age of father (years), mean (SD)	29.73 (6.413)	29.30 (6.756)
Childcare (n), count		
Yes[2]	4	5
No	43	43
Other caregivers (n), count		
Yes[3]	12	13
No	35	35

[1]n = 2 dropouts after enrolment;[2]Childcare attendance: on average 5 days/week, range 2–7 days;[3]Other caregivers reported: grandparents, siblings, aunts; BMI: body mass index

In addition to the study groups being well matched at baseline, assessment of the simplified FFQ as well as the milk diary revealed no significant differences in feeding practices (i.e. estimated fibre and fluid intake) as well as study formula intake. Moreover, no antibiotic use was reported at any point throughout the intervention and none of the subjects were reported to use any laxatives during the post-maintenance period.

Bristol Stool Scale (BSS)

There were no significant between-group differences in any of the stooling parameters throughout the study. Overall, percentages of hard stools were low in both groups (see Fig. 3). The percentage of hard stools in the control group was 3.11 ± 5.75 and 7.11 ± 15.43 in the test group during the maintenance phase (n.s.) (vs.; n.s.), while in post-maintenance phase it was 2.77 ± 7.15 in the control versus 3.92 ± 10.43 in the test group.; n.s.), and throughout the study (2.98 ± 4.67 vs. 5.02 ± 10.06; n.s.). Furthermore, the weekly stooling frequency was comparable in both groups over the course of the study (9.76 ± 3.810 in the test group vs. 9.58 ± 3.504 in the control group). In addition, the percentage of subjects who were reported to have a hard stool on one or more occasions throughout the intervention were similar for the test (55.6%) and control (55.3%) groups. However, during the post-maintenance phase, this percentage was lower for the test compared to the control group (22.2% vs. 29.8%; n.s.).

QPGS-RIII (section E)

Prior to the intervention, all (100%) of subjects met 2 or more diagnostic criteria for functional constipation (Rome III). As shown in Fig. 4, the percentage of subjects meeting at least 2 of the Rome III criteria dropped significantly after medical treatment with PEG and the first week of intervention. At the end of the maintenance phase, around 20% of subjects in both groups (22% in the test group and 19% in the control group) met 2 or more Rome III diagnostic criteria for functional constipation. During the post-maintenance phase (weeks 5–8), 26.7% of subjects in the test group and 35.4% of subjects in the control group met 2 or more criteria at some point. Overall, weekly percentages of subjects meeting 2 or more criteria for FC remained low throughout the post-maintenance phase, but fluctuated between 9 and 19% in the test group, and 12.5 and 23% in the control group. In the test group, the percentage of toddlers meeting ≥ 2 FC criteria at the end of the study (week 8) was significantly lower than at the end of the maintenance phase (9% vs. 22%, $p = 0.057$), whereas no differences between week 8 and week 4 were observed for the control group.

Overall, there were no significant differences between groups, but, compared to week 1, the number of subjects meeting (2 or more) Rome III diagnostic criteria for FC decreased significantly over time in both groups ($p < .001$). Similar results were found when looking at individual Rome III criteria for functional constipation. No significant differences between groups were observed, but, compared to week 1, several parameters significantly improved with time ($p < 0.05$). These improvements include increased defecation frequency, lower occurrence of large diameter stools, and less stooling avoidance (see Table 3).

Table 3
Percentage of subjects meeting individual Rome III criteria for FC at several time-points

	Test				Control			
	Pre-study	**Week 1**	**Week 4**	**Week 8**	**Pre-study**	**Week 1**	**Week 4**	**Week 8**
Defecation frequency (≤ 2x/week)	60.9	8.5	6.5	6.5	61.7	20.8	0*	6.25*
Consistency (hard or very hard)	89.1	25.5	2.2	4.4	93.6	16.7	2.1	6.25
Faecal inconsistency[1] (yes)	37.0	17.0	4.3	8.9	51.1	12.5	14.5	10.4
Painful defecation (yes)	89.1	44.7	23.9	13.3	93.6	35.4	20.8	12.5
Large stool (yes)	50.0	31.9	8.7*	11.11*	53.2	27.1	12.5	12.5
Faecal impaction (yes)	60.9	21.3	10.9	8.9	51.1	20.8	12.5	4.2
Withholding behaviour	89.1	35	22*	9*,^	78.7	30	14*	16*
Once/week	Unknown	15	17	6	Unknown	11	7	11
Several times	Unknown	17	4	2	Unknown	14	6	4
Every day	Unknown	3	1	1	Unknown	5	1	1

**sign lower compared to week 1 ($p < .05$), ^sign lower compared to week 4 ($p < .05$), week 4 = end of maintenance phase; week 8 = end of post-maintenance phase;[1] passing stool whilst asleep.*

Safety parameters

Finally, no (severe) adverse events were reported throughout the study. Both groups exhibited healthy growth as indicated by mean weight-for-length (WFL) z-scores and body mass index (BMI) z-scores at the end of the intervention (see Table 4).

Table 4
Mean (SD) anthropometrics of both study groups at the start (baseline) and end of study

	Baseline		End of Study	
	Test	Control	Test	Control
n	47[1]	48	45	48
Weight (kg), mean (SD)	11.05 (1.514)	11.34 (1.900)	11.99 (1.630)	12.09 (1.897)
Length (cm), mean (SD)	82.57 (6.098)	82.78 (8.626)	86.02 (5.694)	84.68 (14.265)
WFL z-score	0.08 (1.120)	0.37 (1.243)	0.19 (1.036)	0.41 (1.463)
BMI (kg/m^2), mean (SD)	16.13 (1.875)	16.70 (2.739)	16.31 (1.847)	16.49 (2.521)
BMI-for-age z-score	0.14 (1.253)	0.47 (1.575)	0.16 (1.173)	0.42 (1.384)

[1]n = 2 dropouts after enrolment, WFL: weight-for-length, BMI: body mass index

Discussion

The study reported here assessed the efficacy of two different commercially available Comfort YCF in Mexico in 2019 with regards to their applicability in the dietary management of toddlers with history of functional constipation. Despite differences in the composition of the two study formulae (e.g. different protein fractions, fat blends, lactose and fibre content, and presence/absence of a probiotic), both study groups showed significant improvements in FC symptoms over time. As expected, total percentages of hard stools, as well as other symptoms related to FC decreased after initial pharmacological treatment with PEG. During the intervention, stooling parameters assessed in this study improved even further, and, most importantly, remained low throughout the post-maintenance phase. During the post-maintenance phase, none of the subjects were prescribed any laxatives. In contrast, in a study by Modin et al. (2018), on the use of PEG in maintenance treatment for childhood FC, the median time to the use of rescue medication in the control group, which discontinued use of PEG, was 27 days (range: 3–64 days) (26). Therefore, lack of laxative use in our study, supports the benefits of study formulas for maintenance of good stooling parameters beyond the pharmacological treatment period. No significant differences were observed between groups. Despite lack of significant differences between groups, the number needed to treat (NNT) for FC was 8.3 in favour of the test formula at the end of the study period. NNT estimates the effectiveness of a treatment (27), and in this case it indicates that 8.3 patients need to be given treatment formula to get one more patient better, comparing to control treatment.

Results showed that, during the post-maintenance phase, the overall reported (BSS) % of hard stools was around 3–4% in both study groups, affecting between 22.2 and 29.8% of subjects. In addition, 26.7% of subjects in the test group and 35.4% of subjects in the control group met 2 or more of the Rome III criteria

for FC at some point during the last 4 weeks of the study. Previous research has shown that after two months of primarily (87%) pharmacological treatment, around 37% of young children with FC remained constipated (28). In addition, Mill et al. stated that, even after 5 years of intensive treatment, 50% of children with FC remain symptomatic (21).

As introduced, experts believe that withholding behaviour is likely to be the most important factor for FC in toddlers and young children (14, 15). This is due to the fact that this conditioned habitual response to painful bowel movement leads to stools becoming harder and larger and thus more painful evacuation, thus perpetuating the vicious cycle. Additionally, retained stools cause chronic distention of rectum, which will in turn lead to overflow incontinence. Amongst other Rome III criteria, withholding behaviour improved significantly over time in both study groups. At diagnosis, around 80–90% of toddlers were reported to avoid stooling. At the end of the 2-month intervention, only 9 to 16% of all subjects were reported to exhibit withholding behaviour.

In this research we used the BSS as well as the QPGS-RIII (section E). Results showed overall low percentages of hard stools using the BSS as well as % of children with FC based on Rome III criteria. Whilst neither assessment tool showed significant differences between groups, there were some discrepancies in results from both measures. The number of subjects meeting 2 or more Rome III criteria for FC as well as the frequency of hard stools were slightly lower in the test group based on the QPGS-RIII, whilst overall % of hard stools was slightly lower in the control group based on the BSS. A study assessing the agreement of both measures in relation to stool consistency as well as the prevalence of FC found similar differences (29). Authors reported fair agreement between the 2 methods with regards to stool consistency ($\kappa = 0.335$, $p < .001$). However, they did report excellent agreement between the BSS and Rome III criteria for assessing the prevalence of FC (29). Differences in parental reports of stool consistency using these two measures might be due to the fact that the BSS provides a visual stimulus, making it easier for parents to identify the consistency of their toddler's stool. In addition, using the BSS, consistency for every stooling occasion is recorded, whereas in the case of the QPGS-RIII, parents are presented with multiple choice answers to best describe the usual appearance of their child's stool (e.g. "hard or very hard", "not too hard and not too soft"). The current study had several limitations. First, the intervention period, especially the post-maintenance phase, was relatively short. Therefore, no conclusions can be drawn with regards to the long-term efficacy of Comfort YCF. Furthermore, the study was only blinded to the statistician, but not the PIs or parents/caregivers of the subjects. The effects observed in this study maybe specific to the tested formulas, and therefore should not be generalised to other products available on the market. Finally, one of the three study sites, in addition to providing study formulas, educated parents and caregivers on ways to increase dietary fibre intake, whereas the other 2 sites did not. This did not lead to any differences in study outcomes, as neither 'study site' or 'estimated fibre intake' were found to have a significant effect in data analysis. Lack of finding any effect of potential differences in fibre intake could also be contributed to the use of a simplified FFQ, which was inadequate to properly assess dietary fibre intake.

Conclusion

Both Comfort YCF support the maintenance of improved stooling over time in toddlers with a history of constipation. Children receiving the formula with intact protein tended to meet lower numbers of indicators of FC at the end of the study.

Abbreviations

ANCOVA Analysis of Covariance

BMI Body Mass Index

BSS Bristol Stool Scale

FC Functional Constipation

FGID(s) Functional Gastrointestinal Disorders

GI Gastro-intestinal

MF milk fat

NNT Number needed to treat

PEG Polyethylene Glycol

pHW Partially hydrolysed whey

QPGS-RIII Questionnaire on Paediatric Gastrointestinal Symptoms

RIII Rome III

WFL Weight-for-length

YCF(s) Young Child Formula(s)

Declarations

Ethics approval and consent to participate

The study protocol, information letter to parents/legal guardians and written informed consent forms were approved by the ethical committee of Clínica de Enfermedades Crónicas y de Procedimientos Especiales S.C; (Michocan, Mexico) (record number: 001_2019). Upon completion of the study, parents received a €50 voucher as well as 4 complementary tins of study products as a compensation for their time. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the

International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and was registered in the Netherlands Trial Registry [identifier: NL7420 (NTR7653)], registration date 20/09/2018.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Denise Hofman, Miriam Contreras, and Urszula Kudla are employees of FrieslandCampina at the time of manuscript creation. Daniel Alfonso Cisneros Sevilla, Darelia Alelí Topete Ángel, Sergio Díaz Madero, and Joshué David Covarrubias Esquer report no conflicts of interest.

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Author's contributions

J.D.C.E., S.D.M., U.K. and M.C.F. contributed to the design of the study. D.A.C.S., J.D.C.E. and S.D.M recruited and followed-up subjects. D.A.T.A., M.C.F., D.H., and U.K. supervised the implementation of the clinical trial. D.H. analyzed the data and wrote the draft manuscript. All authors reviewed the manuscript.

References

1. Vandenplas Y, Hauser B, Salvatore S. Functional Gastrointestinal Disorders in Infancy: Impact on the Health of the Infant and Family. Pediatr Gastroenterol Hepatol Nutr. 2019;22(3):207.
2. Heine RG. Allergic gastrointestinal motility disorders in infancy and early childhood. Pediatr Allergy Immunol. 2008 Aug;19(5):383–91.
3. Bellaiche M, Oozeer R, Gerardi-Temporel G, Faure C, Vandenplas Y. Multiple functional gastrointestinal disorders are frequent in formula-fed infants and decrease their quality of life. Acta Paediatr Int J Paediatr. 2018;107(7):1276–82.
4. Khan S, Campo J, Bridge JA, Chiappetta LC, Wald A, di Lorenzo C. Long-Term Outcome of Functional Childhood Constipation. Dig Dis Sci. 2007 Jan;52(1):64–9.
5. Afzal NA, Tighe MP, Thomson MA. Constipation in children.Ital J Pediatr. 2011 Jun;37:28.
6. Zeevenhooven J, Koppen IJN, Benninga MA.The New Rome IV Criteria for Functional Gastrointestinal Disorders in Infants and Toddlers. Pediatr Gastroenterol Hepatol Nutr [Internet]. 2017 [cited 2018 Jun 26];20(1):1. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5385301/

7. Koppen IJN, Vriesman MH, Saps M, Rajindrajith S, Shi X, van Etten-Jamaludin FS, et al.Prevalence of functional defecation disorders in children: a systematic review and meta-analysis. J Pediatr. 2018;198:121–30.
8. Wu T-C, Chen L-K, Pan W-H, Tang R-B, Hwang S-J, Wu L, et al. Constipation in Taiwan elementary school students: a nationwide survey. J Chinese Med Assoc. 2011;74(2):57–61.
9. Chogle A, Velasco-Benitez CA, Koppen IJ, Moreno JE, Ramírez Hernández CR, Saps M. A Population-Based Study on the Epidemiology of Functional Gastrointestinal Disorders in Young Children [Internet]. Vol. 179, The Journal of Pediatrics. 2016 [cited 2018 Oct 31]. Available from: www.jpeds.com
10. AlGhamdi M, Alfetni A. Prevalence and factors associated with functional constipation among children attending well baby clinic IN Aladel primary health care center IN Makkah al-Mukarramah, 2016, cross sectional. Int J Adv Res. 2017;5:1175–85.
11. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and Treatment of Functional Constipation in Infants and Children. J Pediatr Gastroenterol Nutr. 2014 Feb;58(2):265–81.
12. Rajindrajith S, Devanarayana NM, Perera BJC, Benninga MA. Childhood constipation as an emerging public health problem.World J Gastroenterol. 2016;22(30):6864.
13. Avelar Rodriguez D, Popov J, Ratcliffe EM, Toro Monjaraz EM.Functional constipation and the gut microbiome in children: preclinical and clinical evidence.Front Pediatr. 2021;966.
14. Vriesman MH, Koppen IJN, Camilleri M, Di Lorenzo C, Benninga MA.Management of functional constipation in children and adults. Nat Rev Gastroenterol Hepatol [Internet]. 2020;17(1):21–39. Available from: https://doi.org/10.1038/s41575-019-0222-y
15. Levy EI, Lemmens R, Vandenplas Y, Devreker T. Functional constipation in children: challenges and solutions. Ped Health [Internet]. 2017;(8):19–27. Available from: http://dx.doi.org/10.2147/PHMT.S110940
16. Rajindrajith S, Devanarayana NM, Benninga MA. Quality of life and somatic symptoms in children with constipation.2013;
17. Wang C, Shang L, Zhang Y, Tian J, Wang B, Yang X, et al.Impact of functional constipation on health-related quality of life in preschool children and their families in Xi'an, China. PLoS One. 2013;8(10):e77273.
18. Bakker RJ, van de Putte EM, Kuis W, Sinnema G. Risk factors for persistent fatigue with significant school absence in children and adolescents. Pediatrics. 2009;124(1):e89–95.
19. Liem O, Harman J, Benninga M, Kelleher K, Mousa H, Di Lorenzo C. Health utilization and cost impact of childhood constipation in the United States. J Pediatr. 2009;154(2):258–62.
20. Ansari H, Ansari Z, Lim T, Hutson JM, Southwell BR. Factors relating to hospitalisation and economic burden of paediatric constipation in the state of V ictoria, A ustralia, 2002–2009. J Paediatr Child Health. 2014;50(12):993–9.

21. van Mill MJ, Koppen IJN, Benninga MA. Controversies in the Management of Functional Constipation in Children. Curr Gastroenterol Rep [Internet]. 2019;21(6). Available from: http://dx.doi.org/10.1007/s11894-019-0690-9
22. Poddar U. Approach to Constipation in Children. INDIAN Pediatr. 2016;319(15).
23. Morais MB, Vítolo MR, Aguirre AN, Fagundes-Neto U. Measurement of low dietary fiber intake as a risk factor for chronic constipation in children. J Pediatr Gastroenterol Nutr. 1999 Aug;29(2):132–5.
24. Lane MM, Czyzewski DI, Chumpitazi BP, Shulman RJ. Reliability and validity of a modified Bristol Stool Form Scale for children. J Pediatr. 2011;159(3):437–41.
25. Lewis SJ, Heaton KW. Stool Form Scale as a Useful Guide to Intestinal Transit Time. Scand J Gastroenterol [Internet]. 1997 Jan 8 [cited 2018 Mar 25];32(9):920–4. Available from: http://www.tandfonline.com/doi/full/10.3109/00365529709011203
26. Modin L, Walsted AM, Dalby K, Jakobsen MS. Polyethylene glycol maintenance treatment for childhood functional constipation: a randomized, placebo-controlled trial. J Pediatr Gastroenterol Nutr. 2018;67(6):732–7.
27. Wen L, Badgett R, Cornell J. Number needed to treat: a descriptor for weighing therapeutic options. Am J Heal Pharm. 2005;62(19):2031–6.
28. Borowitz SM, Cox DJ, Kovatchev B, Ritterband LM. Treatment of Childhood Constipation by Primary Care Physicians : Efficacy and Predictors of Outcome. 2017;115(4).
29. Koppen IJN, Velasco-Benitez CA, Benninga MA, Di Lorenzo C, Saps M. Using the Bristol Stool Scale and Parental Report of Stool Consistency as Part of the Rome III Criteria for Functional Constipation in Infants and Toddlers. J Pediatr. 2016;177:44-48.e1.

Figures

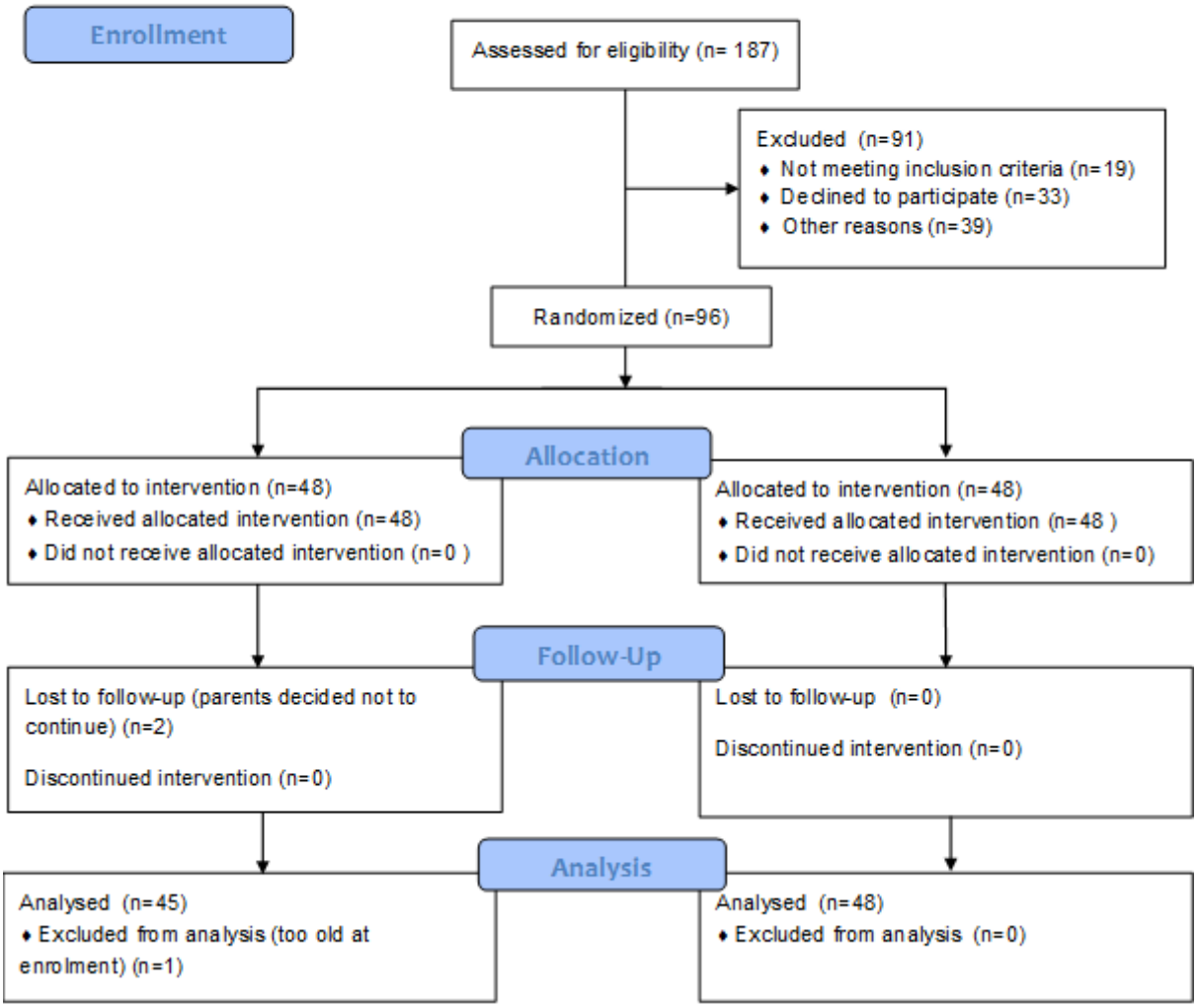

Figure 1

Participants flow-chart, from potential enrolment until completing the study.

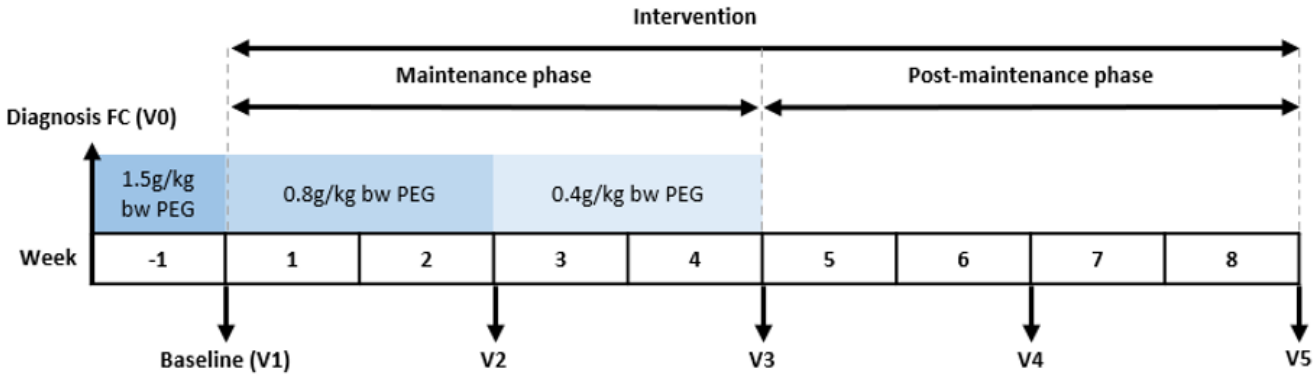

Figure 2

Study flow-chart (bw: body weight; PEG: polyethylene glycol; V: visit).

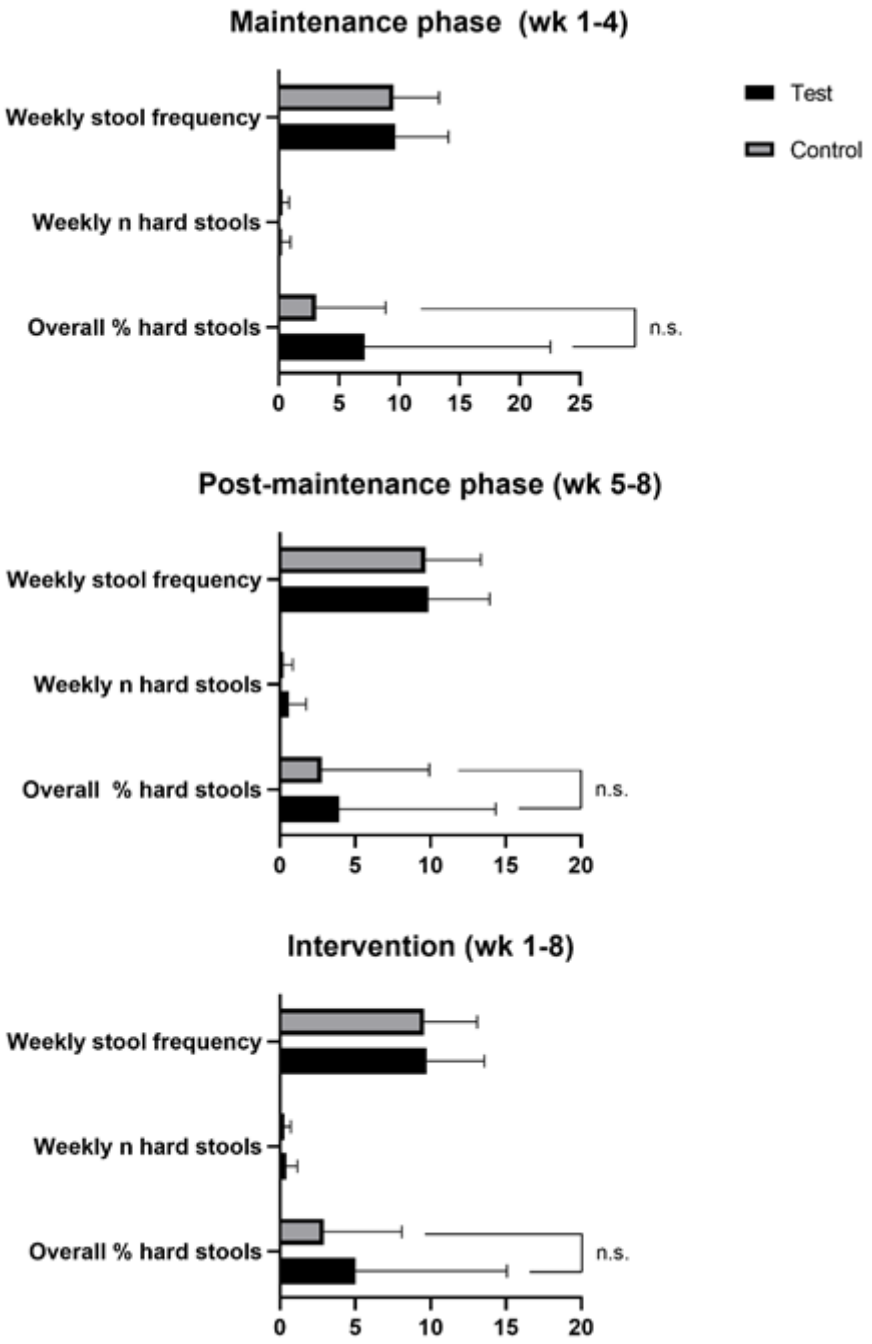

Figure 3

% hard stools in both groups during the maintenance phase, post-maintenance phase, and entire intervention.

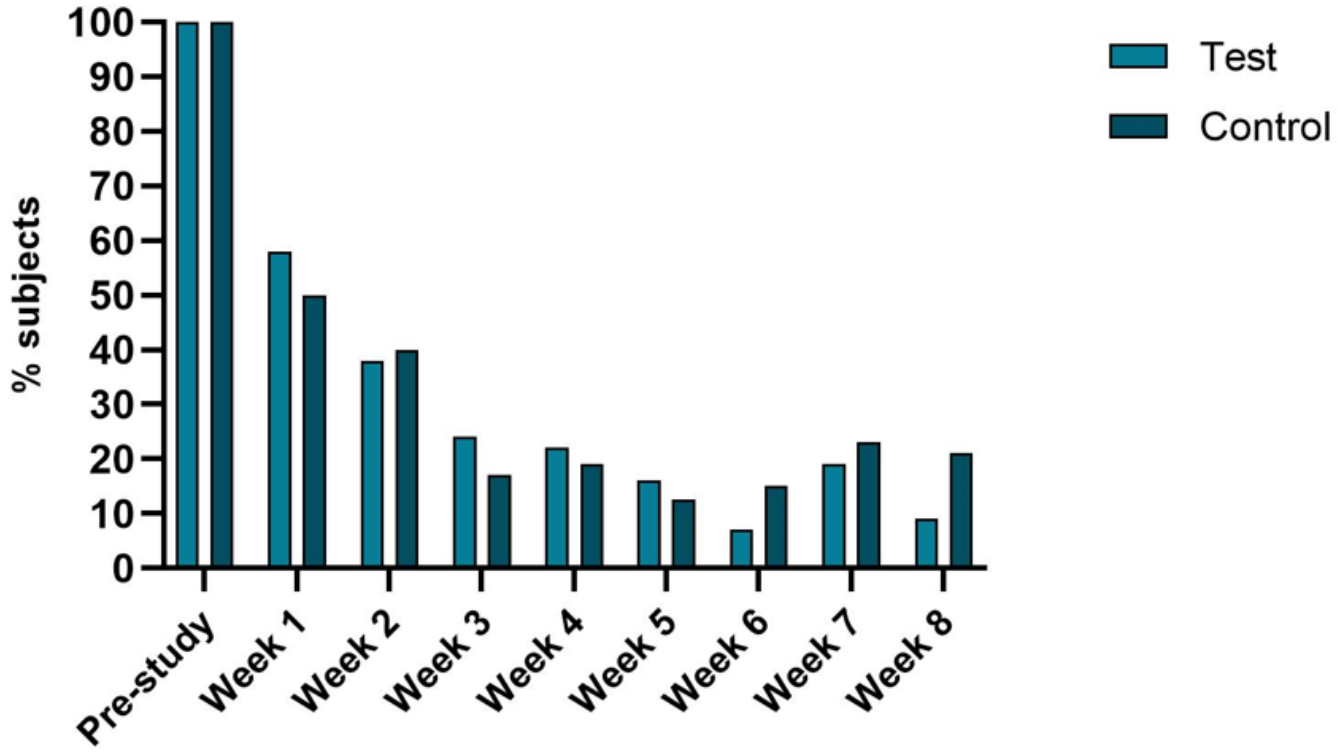

Figure 4

% of subjects meeting at least 2 of the Rome III criteria