pISSN: 2234-8646 eISSN: 2234-8840
https://doi.org/10.5223/pghn.2018.21.1.28
Pediatr Gastroenterol Hepatol Nutr 2018 January 21(1):28-33

Original Article

PGHN

A Synbiotic Infant Formula with High Magnesium Content Improves Constipation and Quality of Life

Ioannis Xinias, Antonis Analitis*, Antigoni Mavroudi, Ioannis Roilides, Maria Lykogeorgou, Varvara Delivoria, Vasilis Milingos, Mayra Mylonopoulou, and Yvan Vandenplas†

*3rd Pediatric Department, Hippocration Hospital, Thessaloniki, *Department of Hygiene, Epidemiology and Medical Statistics, Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece, †Department of Pediatrics, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium*

Purpose: To evaluate the efficacy of synbiotic formula with partial whey hydrolysate and high magnesium content in infants presenting with functional constipation.

Methods: Sixty-five infants with functional constipation were included. Forty infants were treated during one month with parental reassurance and the intervention formula and were compared to a control group of 25 infants treated with parental reassurance only. Parents completed a quality of life (QoL) questionnaire at baseline and during the last week of the study.

Results: At inclusion, stool characteristics and QoL were similar in both groups. The control group was slightly older than the intervention group (7.5±3.9 vs. 6.2±3.6 weeks). At onset, stool composition was "hard and tight" (Bristol stool scale 1 and 2) in all infants. After one month, stool composition remained unchanged in the control group except in two infants that developed "creamy" stools (Bristol stool scale type 3 and 4). In the intervention group, stools remained "hard and tight" in 27.5%, and became "creamy" in 47.5%, "loose" (Bristol stool scale type 5) in 22.5% and "watery" (Bristol stool type 6 and 7) in 2.5%. The benefit of the intervention formula was estimated to be "very important" in 70%. The median scores for QoL improved significantly in the intervention group for all parameters and for one in the control group.

Conclusion: The intervention formula significantly improved functional constipation resulting in a better QoL of the parents and infants.

Key Words: Constipation, Hydrolysate, Magnesium, Prebiotics, Galacto-oligosaccharide, *Bifidobacterium animalis*

Received : September 12, 2017, Revised : October 3, 2017, Accepted : October 7, 2017

Corresponding author: Yvan Vandenplas, Department of Pediatrics, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium. Tel: +32-2-477-57-94, Fax: +32-2-477-57-83, E-mail: Yvan.Vandenplas@uzbrussel.be

INTRODUCTION

Functional gastrointestinal disorders such as regurgitation, colic and functional constipation are considered to be benign conditions in infants, although they are often a reason for parents to seek medical help and are as a consequence frustrating for parents and caregivers [1]. According to a review of the literature, functional constipation in infants occurs in 7.8% of infants (median value, P25-50: 3.8-15%) [2]. The prevalence rate of constipation in the first year of life was reported to be 2.9%, increasing up to 10.1% in the second year [3]. An expert panel concluded that the worldwide prevalence of functional constipation in infants age younger than 12 months is uncertain, but is estimated to be approximately 15%, depending on the type of feeding [2]. However, good quality data are lacking [2].The Rome IV consensus proposed diagnostic criteria for functional constipation in infants [4]. The following criteria have been proposed for apparently healthy infants stating that at least two of the following criteria must be present: i) two or fewer defecations per week, ii) history of excessive stool retention, iii) history of painful or hard bowel movements, iv) history of large-diameter stools, v) presence of a large fecal mass in the rectum [4].

During the second month of life the frequency of stooling decreases to half of the previous month [5]. Infants under one year of age are often referred for suspected functional constipation because of pain, consistency and frequency of stools. Accompanying symptoms may include irritability, decreased appetite, early satiety, which rapidly disappear following passage of stools [3]. The recommended management of functional constipation in infants focusses on parental guidance and reassurance, endorsed by an appropriate nutritional intervention [1]. In this study, the additional benefit of an infant formula with a partial whey hydrolysate, synbiotics (*Bifidobacterium lactis* and galacto-oligosaccharides (GOS) supplemented with magnesium was tested.

MATERIALS AND METHODS

This open study was conducted at the 3rd Pediatric Department, Hippocration Hospital of the Aristotle University of Thessaloniki from November 1, 2015 to November 30, 2016. An approval of the study protocol by the independent Ethical Review Board of the Aristotle University of Thesalonica was obtained (IRB no. 396/11-11-2017). Written informed consent was also obtained from all subjects.

Starter formula fed term born infants with an age range between 3 and 13 weeks suffering from constipation since at least one week without any clinical evidence for an organic cause were included. For the study purpose, functional constipation was defined different than the Rome criteria: less than 3 bowel movements per week with "hard and tight" stools (Bristol stool scale type 1 or 2) in exclusively formula fed infants. The characteristics of the infants at inclusion are listed in Table 1.

Exclusion criteria were besides a suspected organic cause for the constipation, breastfeeding (partial or exclusive), insufficient weight gain ($<$150 g/wk), the presence of blood in the stools, meconium produced after the first 24 hours of life, any other formula than a starter infant formula present on the Greek market.

When an infant met the inclusion criteria, parents were invited to participate in the study and if accepted, an informed consent was obtained. It was up to the parents and pediatrician to decide in consensus whether the infant would be included in the

Table 1. Patient Characteristics at Inclusion and after One Month

Characteristic	Intervention group	Control group	*p*-value
Patient no.	40	25	
Inclusion			
Age (wk)	1.4±0.8	1.7±0.9	0.173
Weight (g)	3,686±455	3,964±476	0.022
After 1 month			
Weight (g)	4,364±476	4,685±497	0.011
Weight gain (g)	678±207	722±118	0.342

Values are presented as number only or mean±standard deviation.

control or the intervention group. Physicians recommended inclusion in the control group (reassurance without any other intervention) as recommended in the guidelines as first option for each eligible infant [3]. Reassurance and anticipatory guidance was the only intervention in the control group, which remained on the standard infant starter formula the infant had been fed with. The intervention group was given the study formula (Table 2) besides the reassurance. The amount of intervention formula needed for one month was given to the parents. No infant received any additional medication, food supplement or probiotic. All parents received a diary and the same questionnaires.

Parents were given a questionnaire assessing quality of life (QoL) and information on defecation of the infant at inclusion and during the last week of the one month intervention period.

Change in stool composition was the primary outcome (Table 3). The assessment at the start and at the end of the study was done over a period of seven consecutive days. Baseline information was collected during one week after inclusion but before the intervention formula was started. The efficacy of the intervention was evaluated during the fourth (i.e., the last week) week of the study.

Parents had to fill in the parent form of a QoL questionnaire consisting of seven items regarding symptom duration and frequency, emotions, activities and different aspects related to the management of an infant suffering constipation. The scale assesses the burden of constipation on a scale ranging from 1 to 5 (very low burden=1 to extremely heavy burden=5). More specifically, the questions addressed the following domains: i) every day QoL, ii) sleep quality, iii) work-related QoL, iv) parent-child relationship, v) stress during everyday life, vi) QoL regarding social interaction with friends and relatives, and vii) overall QoL (Table 4). In addition, parents had to record information regarding defecation frequency and composition (Table 3). Stool composition was assessed by using a scale from 1 to 5 (hard=1; tight=2, creamy=3, loose=4, watery=5). During the follow-up visit after one month, the parents were asked to rate the evolution during the intervention by selecting one of the following options: a) very important benefit=1, b) important benefit=2, c) moderate benefit=3, d) very small benefit=4, and e) no benefit=5.

The non-parametric Wilcoxon test was used to investigate statistically significance of differences in scores between infants in the intervention and control groups at two time points, at inclusion and after one month intervention. T-test (paired and two-sample) was used in order to compare continuous variables between infants in the intervention and control groups, when normality assumption was not violated. Score changes between the intervention and the

Table 2. Composition of the Intervention Formula (per 100 mL)

Composition	Value
Energy (kcal)	66
Lipid (g)	3.2
Polyunsaturated fatty acids (g)	0.6
Carbohydrates (g)	7.5
Lactose (g)	3.8
Galacto-oligosaccharides (g)	0.5
Partially hydrolyzed whey protein (g)	1.5
Magnesium (mg)	8

Table 3. Stool Composition and Frequency at Inclusion and after One Month Intervention

	Intervention group	Control group	*p*-value
Patient no.	40	25	
Inclusion			
Stool composition			0.111
Hard and tight	40 (100.0)	23 (92.0)	
Creamy	0 (0.0)	2 (8.0)	
Frequency	2.0 (1.0-2.0)*	1.0 (1.0-2.0)†	0.01
After 1 month			
Stool composition			<0.001
Hard and tight	11 (27.5)	23 (92.0)	
Creamy	19 (47.5)	2 (8.0)	
Loose	9 (22.5)	0 (0.0)	
Watery	1 (2.5)	0 (0.0)	
Frequency	3.0 (2.0-3.0)†	1.0 (1.0-2.0)§	<0.001

Values are presented as number only, number (%), or median (interquartile range).
*,†$p<0.001$, †,§$p=0.278$.

Table 4. Quality of Life (Daily, Sleep Quality, Work Related) in the Intervention and Control Group

	Intervention group (n=40)		*p*-value*-†	Control group (n=25)		*p*-value‡-§	*p*-value*-‡	*p*-value†-§
	Before*	After†		Before‡	After§			
Daily			<0.001			0.003	0.259	0.002
Excellent	2 (5.0)	18 (45.0)		0 (0.0)	2 (8.0)			
Very well	19 (47.5)	16 (40.0)		10 (40.0)	14 (56.0)			
Moderate	18 (45.0)	6 (15.0)		14 (56.0)	9 (36.0)			
Poor	1 (2.5)	0 (0.0)		1 (4.0)	0 (0.0)			
Sleep			<0.001			0.077	0.577	<0.001
Excellent	3 (7.5)	15 (37.5)		0 (0.0)	0 (0.0)			
Very well	3 (7.5)	12 (30.0)		4 (16.0)	6 (24.0)			
Moderate	13 (32.5)	11 (27.5)		10 (40.0)	10 (40.0)			
Poor	21 (52.5)	2 (5.0)		11 (44.0)	9 (36.0)			
Work			<0.001			0.393	0.715	<0.001
Excellent	3 (7.5)	18 (45.0)		0 (0.0)	1 (4.0)			
Very well	9 (22.5)	17 (42.5)		8 (32.0)	6 (24.0)			
Moderate	19 (47.5)	5 (12.5)		10 (40.0)	12 (48.0)			
Poor	9 (22.5)	0 (0.0)		7 (28.0)	6 (24.0)			

Values are presented as number (%).

control group were compared. The non-parametric Mann-Whitney test was used in order to compare score changes between two independent samples based on the variable type. All tests were two-sided and the level of significance was set at 0.05. Statistical analysis was performed using STATA ver. 10 (2007; Stata Co., College Station, TX, USA).

RESULTS

The infants in the control group tended to be slightly older, but not significant, than the infants in the intervention group (7.5±3.9 vs. 6.2±3.6 weeks) (mean±standard deviation). Weight gain in the intervention and control group was comparable (Table 1). At inclusion, the composition of defecation did not differ. There was no drop out. Stool composition became only in the intervention group looser. Defecation frequency showed no statistically significant change in either group (Table 3).

At inclusion, there was no difference between QoL parameters between both groups. All median scores of the QoL questionnaire obtained at inclusion improved after one month in the intervention group, while only daily QoL improved in the control group (Table 4). As a consequence, there was a statistical significant difference for all parameters in the intervention group between inclusion and after the intervention, and between the intervention and the control group after the intervention.

DISCUSSION

A formula containing a partial whey hydrolysate, supplemented with *B. lactis* BB12 and GOS and with a high magnesium content (although within the regulatory ranges) improved significantly stool consistency in constipated infants. However, the infants in this study did not fulfill the Rome criteria.

The particular design of this study may be considered in some aspects to be a shortcoming. "No treatment" except reassurance is what is recommended in the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines [3]. However, there is little or no evidence for this recommendation as 'reassurance" as single intervention has not been studied. It is likely that parents of "less" constipated infants may have accepted to be included in this study arm, although according to baseline data there is no difference between both groups at inclusion. But if so, this

will only be of benefit for the outcome of the control group. Our results suggest that reassurance as single intervention does not improve functional constipation in infants.

Hydrolyzed protein may also be beneficial in the management of constipation, as it was shown that infants fed a hydrolyzed protein have more frequent defecations that infants fed intact protein [6]. There are data indicating that defecation is more frequent with a partial hydrolysate than with intact protein [6]. Prebiotics may be of benefit as well. Data suggest that prebiotics may decrease stool consistency in infants [7,8]. The tested formula was a pHF (partially hydrolysed formula) [7,8]. There are no data in literature in constipated infants evaluating a partial hydrolysate or prebiotics as single intervention. Although the majority of studies evaluating the efficacy of probiotics in infants with constipation are negative, some positive data with *Lactobacillus reuteri* DSM 17938 and *Bifidobacterium longum* have been reported [9,10]. There has been a negative trial with *B. lactis* DN173010 [11].

Magnesium is an appropriate, exceptionally safe and effective agent in the treatment of functional constipation which, in the salt form, can promote balanced water re-absorption from the large intestine mucosa, retaining the appropriate water amount, so that stools have a softer consistency without being loose [12]. As a result, the relatively increased volume of stools stimulates receptors in the intestinal mucosa, in order to promote even more the optimized by the use of probiotics and/or prebiotics large intestine contractility, thus reducing the large bowel transit time. Although is seldom used in Europe, it is very frequently used in the USA. Two independently performed trials showed that infant formula with a high magnesium content was effective in the management of infant constipation [13,14]. However, the magnesium content of all these formulae (including the one tested in this trial) is within the regulatory limits of standard infant formula and the Codex Alimentarius. As a consequence, there is no risk for elevated serum levels of magnesium. The range for magnesium content in infant formula according to the Codex Alimentarius and the European Commission Directive 2006/141/EC is 5-15 mg/100 kcal. The mean content in starter formulae ranges from 5 to 6 mg/100 mL or approximately 7.5-9 mg/100 kcal. The magnesium content in the intervention formula is 8 mg/100 mL or 12 mg/100 kcal (Table 2).

A major shortcoming of the present study is the open-label design. However, it is virtually impossible to blind studies with infant formula as the formulas that are compared often have differences in texture, smell and taste. Another limitation of this clinical trial is that the data rely on subjective observations made by the parents. Future clinical trials should benefit from more objective observations. Moreover, in this study—as in other studies evaluating a formula change—several interventions are evaluated concomitant. The tested formula differs from starter infant formula in four different aspects: a protein hydrolysate, probiotics, prebiotics and more magnesium. As a consequence, the effectiveness of each intervention on itself is not known. The bias risk of this study is important as the study was open.

In conclusion, this clinical trial supports the beneficial effects of a formula with a partial whey hydrolysate, high magnesium content, supplemented with a probiotic (*B. lactis*) and prebiotic (GOS) for functional constipation treatment in formula-fed infants. These data need to be confirmed by a double-blind, prospective, randomized trial.

ACKNOWLEDGEMENTS

This study has been supported by Rontis, providing free formula in the intervention group for the study period. Yvan Vandenplas has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Aspen, Biocodex, Danone, Nestle Nutrition Institute, Nutricia, Phacobel, Rontis, United Pharmaceuticalst. The co-authors did not report any potential conflicts of interest.

REFERENCES

1. Vandenplas Y, Benninga M, Broekaert I, Falconer J, Gottrand F, Guarino A, et al. Functional gastro-intestinal disorder algorithms focus on early recognition, parental reassurance and nutritional strategies. Acta Paediatr 2016;105:244-52.
2. Vandenplas Y, Abkari A, Bellaiche M, Benninga M, Chouraqui JP, Çokura F, et al. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. J Pediatr Gastroenterol Nutr 2015;61:531-7.
3. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr 2014; 58:258-74.
4. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2016;150:1443-1455.e2.
5. Tunc VT, Camurdan AD, Ilhan MN, Sahin F, Beyazova U. Factors associated with defecation patterns in 0-24-month-old children. Eur J Pediatr 2008;167: 1357-62.
6. Hyams JS, Treem WR, Etienne NL, Weinerman H, MacGilpin D, Hine P, et al. Effect of infant formula on stool characteristics of young infants. Pediatrics 1995; 95:50-4.
7. Savino F, Maccario S, Castagno E, Cresi F, Cavallo F, Dalmasso P, et al. Advances in the management of digestive problems during the first months of life. Acta Paediatr Suppl 2005;94:120-4.
8. Bekkali NL, Bongers ME, Van den Berg MM, Liem O, Benninga MA. The role of a probiotics mixture in the treatment of childhood constipation: a pilot study. Nutr J 2007;6:17.
9. Coccorullo P, Strisciuglio C, Martinelli M, Miele E, Greco L, Staiano A. Lactobacillus reuteri (DSM 17938) in infants with functional chronic constipation: a double-blind, randomized, placebo-controlled study. J Pediatr 2010;157:598-602.
10. Guerra PV, Lima LN, Souza TC, Mazochi V, Penna FJ, Silva AM, et al. Pediatric functional constipation treatment with Bifidobacterium-containing yogurt: a crossover, double-blind, controlled trial. World J Gastroenterol 2011;17:3916-21.
11. Tabbers MM, Chmielewska A, Roseboom MG, Crastes N, Perrin C, Reitsma JB, et al. Fermented milk containing Bifidobacterium lactis DN-173 010 in childhood constipation: a randomized, double-blind, controlled trial. Pediatrics 2011;127:e1392-9.
12. Izzo AA, Gaginella TS, Capasso F. The osmotic and intrinsic mechanisms of the pharmacological laxative action of oral high doses of magnesium sulphate. Importance of the release of digestive polypeptides and nitric oxide. Magnes Res 1996;9:133-8.
13. Chao HC, Vandenplas Y. Therapeutic effect of Novalac-IT in infants with constipation. Nutrition 2007;23: 469-73.
14. Infante DD, Segarra OO, Redecillas SS, Alvarez MM, Miserachs MM. Modification of stool's water content in constipated infants: management with an adapted infant formula. Nutr J 2011;10:55.