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An open label, non-comparative pilot study to assess the efficacy and safety of a food supplement containing manna in pediatric functional constipation

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Summary. *Objective*. The primary objective of this study was to evaluate the efficacy and safety of the food supplement Physiomanna Baby® in pediatric patients with a history of functional constipation defined by Rome III criteria; secondary objective was to evaluate the adherence to the tested product in the enrolled children. *Methods*. The trial was designed as an open label, non-comparative pilot trial. In 3 Romanian sites (one community hospital and two private medical practice offices) 49 children (20 males, 29 females) aged 0 - 8 years were enrolled. The study was conducted between February 2016 and April 2016. The investigational product was administered as 1 g/kg in single daily oral administration from the first day and continued for a maximum of 3 days in the first week. If the constipation symptoms persisted, the children were treated in an additional cycle of treatment for a maximum of 3 days. *Results*. The number of Spontaneous Bowel Movements (SBM) per week has increased to normal after Physiomanna Baby® administration (from 1.80 ± 0.41 at baseline to 6.04±1.54 at day 8) evidencing a statistically significant difference (P-value <0.0001). The efficacy was also demonstrated in the subpopulation of children <4 years where the mean values per week increased from 1.69±0.47 at baseline to 6.15±1.59 SBM at day 8 (P-value <0.0001). According to Investigator Global Assessment of Efficacy (IGAE), Physiomanna Baby® shows immediate and excellent efficacy after one or two doses for 79.60% of the children, a very good efficacy after three doses for 12.24% and good efficacy after the second cycle of administration for 6.12% of children. Both Investigator Global Assessment for Safety (IGAS) and Patient Global Assessment for Safety (PGAS) were rated as 100% excellent for all patients. *Conclusions*. The food supplement Physiomanna Baby® provided immediate efficacy, offering to pediatricians a safe solution in the care of mild to moderate functional constipation, even if the study design characteristics were limited (pilot trial with a small sample size and without control group).

Key words: children, functional constipation, manna, food supplement, fiber

Introduction

Functional constipation is one of the most frequent pediatric gastrointestinal complaint with a prevalence ranging from 0.7% to 29.6% (1) and describes all children in whom constipation does not have an organic etiology (2). It is characterized by infrequent and painful defecation, hard or large stools, fecal incontinence and abdominal pain, causing a significant distress to both the child and family and is associated with a significant impact on health care (cost per year is 3 times than that in children without constipation) (3). One third of children with untreated chronic constipation continue to have problems beyond puberty, that will impact their social life (4).

Functional constipation in children has been defined by Rome III criteria (5,6) as presented in Table 1.

A medical history and complete physical examination was undertaken to confirm the diagnosis. The literature enphasises that laboratory or radiological investigations should only be performed in severe, refractive cases of constipation (7), to exclude an underlying disease or organic cause (present in less than 5% of cases) (8).

International guidelines underline that the first step in treatment should consist of education, dietary, and behavioural modifications. Actually, osmotic and stimulant laxatives represent the most frequent way to manage children constipation (9), even if scientific evidence does not yet support this practice and the risk of adverse events is possible (10-12). On the other hand, the role of fiber in the treatment is becoming well-known, because pediatricians would like to solve this affection in a less invasive approach as possible (13). Food supplements could represent useful tools for these problems (15). Natural plant exudates containing fibers like glucomanna have been used as the fiber supplement in such cases (16). One of the most promising candidates is Manna, an exudate containing oligosaccharides and polyols like mannitol with a mild laxative action (17).

Physiomanna Baby® is a food supplement containing Manna in addition to natural extract from Fennel (*Foeniculum vulgare*), Chamomile (*Chamomilla recutita*) and lemon balm (*Melissa Officinalis*) (18,19) that could play a role to treat functional constipation in children.

Despite the wide use of Manna and the consideration that many pediatrics already prescribe it to children, this product is almost absent in clinical trials. Therefore, we have planned the present pilot trial to have a preliminary assessment of Physiomanna Baby® efficacy and safety and to obtain data to calculate the sample size for future randomized studies.

Material and Methods

Design

The study was designed as a pilot, open label, non-controlled, multicenter trial with a prospective design on one cohort of pediatric patients.

Study population

The study included all infants aged less than 8 years addressed for functional constipation in one community hospital and two private medical practice offices located in Timisoara, Romania (Emergency Children Hospital "Louis Țurcanu"; Private Practice SCM Gados; Private Practice CMI Dr. Herteg) between February and April 2016. The diagnosis was made using the Rome III criteria (6) (Rome IV was not available at the time the study was performed).

To be included in the study, each subject had two or fewer SBM during the previous week and was otherwise in good health as judged by a physical examination at the baseline visit.

The exclusion criteria consisted of any organic cause for constipation, history of known obstruction

Table 1. Rome III criteria for functional constipation

Age <4 years[a]	**Age ≥4 years**[b]
1. <3 defecations per week	1. <3 defecations in the toilet per week
2. ≥1 episode of fecal incontinence per week after acquisition of toileting skills	2. ≥1 episode of fecal incontinence per week
3. History of excessive stool retention	3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements	4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum	5. Presence of a large fecal mass in the rectum
6. History of large diameter stools, which may obstruct the toilet	6. History of large diameter stools, which may obstruct the toilet

[a] *Must fulfill ≥2 criteria for ≥1 month prior to diagnosis;* [b] *Must fulfill ≥2 criteria at least once per week for ≥2 months prior to diagnosis, with insufficient criteria for diagnosis of irritable bowel syndrome*

or perforation, congenital malformations able to produce constipation (i.e. Hirschsprung's disease, imperforate anus, children with cerebral palsy), the use in the 4 previous weeks of concomitant medication, herbs or dietary supplements that can cause constipation; TSH clinically significant elevation or abnormal plasma electrolytes; positive Fecal Occult Blood Test (FOBT); known allergy to manna, mannitol or other Physiomanna Baby® ingredients. No enrolled child had participated in a clinical trial in the past 30 days and a written informed consent was signed by parents before enrollment.

Food supplement in study

At baseline, the parents received all the necessary tested product for one subject (1 jar containing 100 g manna food supplement in powder). A second additional jar was available as a back-up.

Physiomanna Baby® (Iuppa Industriale S.r.l. - Alice Bel Colle (AL), Italy) was prescribed as a weight-dependent dose of 1 g/kg body (half of the little spoon attached to the jar). The food supplement was orally administered by the parents once a day mixed in water. It was recommended that the child drink plenty water during the day. The administration started from the first day of study and continued for a maximum of 3 days in the first week (1st cycle); if the constipation symptoms persisted the food supplement administration should continue for additional 3 days during the second week (2nd cycle).

Framework of the study

Two mandatory onsite visits (at baseline and day 8), and three phone contacts (on day 2, 3, and 4) were performed if the efficacy endpoint was reached within the first week of administration (Figure 1).

When the target was not reached after the first week and therefore Physiomanna Baby® administration was continued in the second week, three more phone contacts (on day 9, 10, and 11) and a final visit on day 14 were performed. In addition, Investigators could ask the children and their parents for any number of unscheduled visits.

The parents were taught how to administer and when to stop the investigational food supplement, and how to record the number of stools per day during the whole study period. Parents were also instructed to contact the Investigator if any adverse events occurred.

Outcome variables for Efficacy

Assessment of efficacy consisted of the number of Spontaneous Bowel Movements (SBM) recorded per day and per week; SBM was defined as BM not preceded by a 24 h administration with a laxative or enema.

During the trial, the administration of Physiomanna Baby® continued if 2 SBM or less occurred in the last 7 days. When the number of SBM increased to 3 times a week or more the parents stopped the administration and the Investigator planned the final visit in the same week.

At the final visit, the Investigator Global Assessment for Efficacy (IGAE) was registered for each child using the following 4-point scale: 0 = worse: no

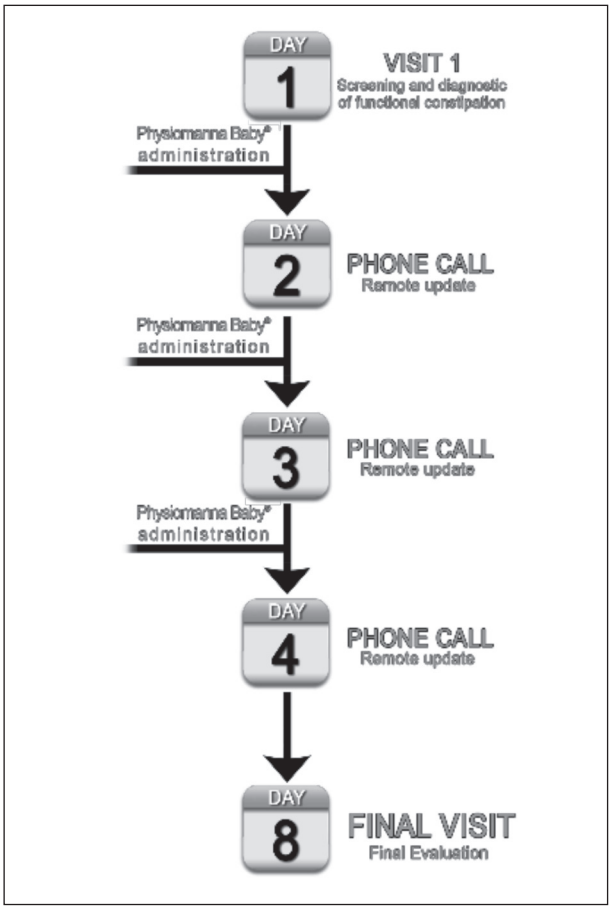

Figure 1. Study flow chart

effect of treatment; 1 = good: the treatment effect appeared after the second cycle of administration, only; 2 = very good: the treatment effect occurred after three days of administration; 3 = excellent: the treatment effect occurred after one or two days of administration.

Outcome variables for Safety

As far as tolerability of the tested product was concerned, the Investigators monitored the occurrence of any adverse event during the study. Investigator Global Assessment for Safety (IGAS) was registered for each child using a 4-point scale: 0 = worse; 1 = mild; 2 = good; 3 = excellent.

In addition, at the final visit was also recorded the Patient Global Assessment for safety (PGAS) that, in children less than 4 years old, was performed directly by parents. The used 4 point scale was the following: 0 = worse tolerability; 1 = mild tolerability; 2 = good tolerability; 3 = excellent tolerability.

Adherence

The patients' parents were reminded of the importance of strictly complying with the instructions received from the Investigator. The evaluation of product's administration adherence was performed as secondary outcome checking diary cards and checking the unused content of the returned bottles.

Statistical analysis and sample size

The null hypothesis of the study was that there will be no statistically significant difference between the number of SBM recorded in the week immediately before enrollment and the number reported after 1 or 2 weeks of Physiomanna Baby® administration.

Since this trial was planned as a pilot study, a prior estimation of sample size was not performed. To have 45 evaluable patients (a sample size often used for the new tested product in trials on pediatric functional constipation (20-22)) it was estimated that the subjects included in the study could be about 50.

SBM per week were analyzed comparing pre- and post- study administration status by using a Wilcoxon paired test for matched samples. Statistical significance level was set at 5%.

Quantitative variables (i.e. demographic) were described through counts, mean, standard deviation (SD), standard error, 25, and 75 percentiles, minimum and maximum. Statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) with an intention to treat approach.

Ethical aspects

The study has been approved on February 10th, 2016 by the Comisia de Etică a Colegiului Medicilor Timiș (Timișoara, România). The study was conducted under the ethical principles for medical research involving human subjects of the Declaration of Helsinki. The informed consent was obtained in writing from parents before performing any study specific procedures. The study was registered on www.ClinicalTrials.gov with identification number NCT02732743.

Results

Of 50 children included in the trial, one resulted as a screening failure and forty-nine (20 males and 29 females) were analyzed. Only one patient was withdrawn during the study period due to prohibited medication assumption: therefore, 48 children (mean age 3.51±2.31 years) completed the study and were considered as evaluable.

Table 2 underlines the consistent number of children less than 12 months (12 on 49) enrolled.

During study monitoring, no protocol deviations were recorded.

In the population analysed, mean SBM weekly frequency was 1.80±0.41 at baseline visit and after Physiomanna Baby® administration it increased to

Table 2. Patients distribution at baseline by gender and demographic

Age range	Female	Male	Total
1-6 months	4	3	7
6-12 months	3	2	5
1-5 years	16	9	25
5-8 years	6	6	12
TOTAL	29	20	49

Table 3. Spontaneous Bowel Movements evolution

	Children <4 years		Children ≥4 years		All	
	Baseline Visit	**Day 8**	**Baseline visit**	**Day 8**	**Baseline visit**	**Day 8**
N	26	26	23	23	49	49
Mean± Std Dev	1.69±0.47	6.15±1.59	1.91 ±0.29	5.91±1.50	1.80 ±0.41	6.04±1.54
Std Err	0.09	0.32	0.06	0.31	0.06	0.22
Min-Max	1-2	2-8	1-2	2-8	1-2	2-8
Percentiles 25	1	6	2	6	2	6
Percentiles 75	2	7	2	7	2	7

6.04±1.54 on day 8 (P-value <0.0001, by using a Wilcoxon signed rank test) (Table 3).

This positive result was also confirmed considering separately the two sub-population of children less or more than 4 years (Figure 2).

In the younger group after Physiomanna Baby® administration, the mean values per week increased from 1.69±0.47 to 6.15±1.59 SBM (P-value <0.0001), and in the children >4 years from 1.91±0.29 to 5.91±1.50 (P-value <0.0001). A Wilcoxon Signed-rank test at a 5% significance level was used to assess the differences between age groups.

In both the analyzed subpopulations the results belonging to males were slightly better than those of females, even if no statistically difference between gender was evidenced.

Table 4 shows the mean increase of SBM during the study period (from Baseline to Day 8).

Approximately 85% of the subjects have gained 3 or more SBMs during the first week of study period (3 SMB/week is limit indicated for functional constipation by Rome III criteria).

Only for 3 on 48 patients was necessary to repeat the treatment during the second week and no relapse of functional constipation was evidenced from day 14 to day 21.

IGAE evidenced a significant performance of Physiomanna Baby® in the management of functional constipation: 79.6% of children were rated as excellent, 12.24% as very good and 6.12% as good.

No adverse event was evidenced during the trial period and also IGAS was rated as 100% excellent.

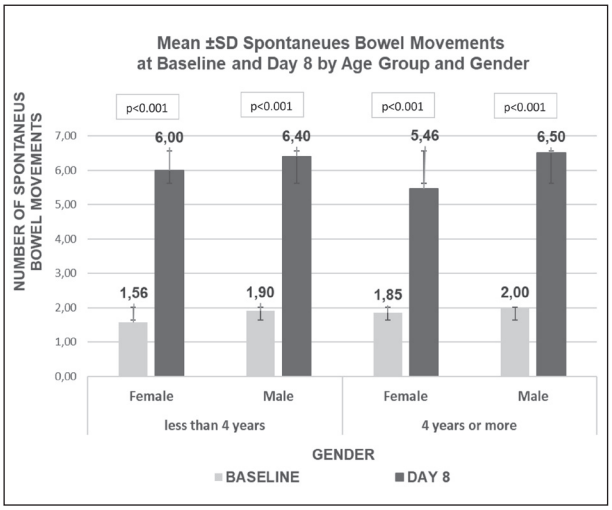

Figure 2. Spontaneous Bowel Movements mean ±SD values at Baseline visit and Day 8 for age 2 groups (Less than and More than 4 years) and by Gender. P-values were obtained by performing Wilcoxon Signed-rank tests at a 0.05 significance level.

Table 4. Spontaneous Bowel Movements change from Baseline visit to day 8

	Children <4 years	**Children ≥4 years**	**All**
N	26	23	49
Mean± Std Dev	4.46±1.65	4.00±1.41	4.24±1.55
Std Err	0.31	0.29	0.22
Min-Max	0-6	0-6	0-6
Percentiles 25	4	4	4
Percentiles 75	6	5	5

These positive evaluations were confirmed by patient diaries data where tolerability was considered as excellent in 100% of the cases by means PGAS.

The adherence to product's administration was 100%.

Discussion

The emotional and psychological attitude of parents (expressed by anxiety and questionable therapeutic behavior) plays an important role in daily management of pediatric functional constipation. For such a frequent gastrointestinal disease (for example, it is 7 times higher than asthma in children 7–8 years of age (23)), usually there is no need for drug treatment. But, all too often, parents and healthcare providers, seem scared in front of a slight prolonged functional constipation.

Therefore, providing a correct information to parents can be very important because, in absence of a doctor's advice, they risk to rely to ineffective remedies based on popular tradition or bought directly based on media advertising. When choosing between the different therapeutic options, the doctor will obviously evaluate the child's needs (possibly combining them with the parental ones) and likely prescribe an effective approach. At the same time, however, the doctor must strike a balance between the expected benefits and the safety of the treatment in children. In this context, functional constipation treatment should: reduce the children' symptoms, improve the frequency and consistency of stools, reduce discomfort, abdominal pain, and restlessness and, at the same time, ensure the clinician about prescribing a product that is safe and non-toxic. Considering the above factors, in children with functional constipation the use of osmotic and stimulant laxatives should be reserved for the most severe cases (24) and used under medical supervision, due to the risk of adverse events (which can be serious, though rare), whereas folk remedies do not offer sufficient guarantees of the expected activity. Moreover, utmost safety is essential for infants, and a safe food supplement like Physiomanna Baby® able to resolve the constipation symptoms in 45 out of 49 children treated by one administration cycle only (single dose or two), and assure the absence of constipation relapse after an additional week, should be considered as an important therapeutic tool for the pediatrician. This indication is also strengthened by the findings of its tolerability in the treatment of constipation, a disease present in 17% to 40% of children in the first year of life (4). In this regard, Physiomanna Baby® administration was found to be totally safe, without any adverse events also in a population with mean age of 3.51±2.31 years.

These preliminary results, even with the limits given by the design of a pilot study (small sample population and without control group), show that Physiomanna Baby® is beneficial in the care of children with mild to moderate constipation. Follow-up studies should be designed to assess if it can prevent chronic constipation and recurrent impactions.

Conclusions

For children with acute or mild chronic functional constipation, with no chronic digestive diseases and no organic diseases, Physiomanna Baby® could offer to the pediatricians a safe and clinically tested solution in the care of pediatric functional constipation. It could be prescribed in weight-dependent doses as maintenance therapy to achieve regular evacuation, to avoid recurrent constipation, to maintain soft stools and to reduce the laxative intake.

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