

## Efficacy and Safety of Straw Containing Probiotic (*Bacillus coagulans*) and Sennoside in Children Aged 5 to 12 Years Affected by Functional Constipation: A Pilot Study

Vikas D Gorad\*

Om Sai Clinic, Nerul, Navi Mumbai, Maharashtra, India

\*Corresponding Author: Vikas D Gorad, Om Sai Clinic, Nerul, Navi Mumbai, Maharashtra, India.

Received: March 02, 2020; Published: March 17, 2020

### Abstract

**Background:** We conducted an open-label, prospective pilot study to evaluate the efficacy and safety of straw containing Probiotic (*Bacillus coagulans*) and Sennoside in children aged 5 to 12 years affected by functional constipation (FC).

**Materials and Methods:** A total of 15 children aged 5 - 12 years affected by FC were administered M Sip Lax™ straw (sennoside 7.5 mg; *Bacillus coagulans* 1 billion colony-forming units (CFU); black salt 13 mg) once a day for three consecutive days. Efficacy and safety assessments were carried out at three follow-up visits: Visit 1 (Day 0, screening and enrollment), Visit 2 (Day 3+1, after three-day treatment with M Sip Lax™ straw), and Visit 3 (Day 6 or 7 after discontinuation of treatment). All patients were evaluated for baseline assessment, ROME III criteria, Bristol Stool Grading, Visual Analog Scale (VAS) score, total overall clinical condition, and investigators' and patients' assessment of the efficacy of treatment. Safety assessments included the incidence of adverse events, changes in vital statistics, and tolerability of the drug.

**Results:** A significant improvement was seen in ROME III criteria, Bristol Stool Grading, VAS score, and the total overall clinical condition of the subjects from baseline to Visit 2 ( $p < 0.05$ ). The drug was well tolerated with no adverse events or treatment discontinuation.

**Conclusion:** The findings of the pilot study indicate that M Sip Lax™ straw containing probiotic *B. coagulans* and stimulant laxative senna may be considered a natural, novel, well-accepted, safe, and effective initial treatment strategy for functional constipation in children.

**Keywords:** Open -Label; Prospective; Efficacy; Safety; Probiotic; Sennoside

### Abbreviations

CFU: Colony-Forming Units; FC: Functional Constipation; PEG: Polyethylene Glycol; SD: Standard Deviations

### Introduction

Constipation in children is a widespread, burdensome, and psychologically relevant issue, the treatment of which remains a global challenge [1]. The estimated prevalence ranges from 0.7 to 29.6% [2]. Constipation is also a common ailment in pediatric emergency clinics. Up to one-third of children aged six to 12 years report constipation during any given year, that is often accompanied by distressing physical effects, as well as psychological effects, on both children and their families [3]. Moreover, constipation is the primary complaint in 3%-5% of children who visit pediatric physicians [4]. Constipation is defined as FC if there is no underlying organic cause and is seen in approximately 95% of children with constipation. Functional constipation is associated with painful defecation, infrequent bowel movements, hard and/or large stools, and fecal incontinence and is often accompanied by abdominal pain [5]. These symptoms can have a significant impact on a child's well-being and health-related quality of life [6,7]. A questionnaire-based survey conducted among select practicing pediatricians and pediatric gastroenterologists in India found that FC constituted 30% of cases in pediatric gastroenterology

office practice, 4% - 5% of all referrals to pediatric gastroenterology tertiary care centers, and 0.8%-1% of all pediatric cases in medical colleges [8].

The pathophysiology of FC is multifactorial. In young children, an important etiological factor for FC is withholding of stool, which often leads to hard, painful, and/or frightening bowel movement. Withholding stool can lead to fecal impaction-the presence of a large fecal mass in either the rectum or the abdomen [5]. Psychosocial factors, behavioral disorders, such as autism spectrum disorders and attention-deficit/hyperactivity disorder, are associated with a higher risk of childhood constipation [9,10]. Other factors, including socio-economic status, child-rearing attitudes, and education, are considered to influence the pathophysiology of FC in children [5,11].

Fecal disimpaction with laxative therapies constitutes the mainstay pharmacotherapy in children affected by FC, alongside adjuvant therapies such as dietary and behavioral modification, toilet training, and family education [12,13].

Senna, an anthraquinone stimulant laxative and the main constituent of sennosides (found in leaves and pods), is a popular treatment for constipation owing to its natural origin, apparent low oral toxicity, and high effectiveness [14].

Probiotics are generally used for the treatment of diarrhea rather than constipation although studies have shown that probiotics, with their ability to produce lactic and acetic acids can influence the peristalsis of intestines by reducing colonic pH, and thus may have a beneficial effect in constipation as well [1,13]. *B. coagulans* specifically may have potential for treating constipation [15,16]. However, to our knowledge, no study has thus far investigated the combined efficacy of senna and probiotic *B. coagulans* in FC.

We conducted an open-label, prospective pilot study to evaluate the safety and efficacy of a novel straw containing Probiotic *Bacillus coagulans* and Sennoside (M Sip Lax™) for the treatment of functional constipation in children aged 5 - 12 years for a period of three days.

## **Methods**

Children aged 5 - 12 years affected by FC enrolled between January and February 2018 at Om Sai Clinic Sector 20, Nerul, Navi Mumbai were considered for the study. Functional constipation was diagnosed according to the Rome III criteria as having at least two of these symptoms [17]: < 3 defecations per week; history of excessive stool retention and painful or hard bowel movements; fecal incontinence > 2 times/week; withholding of stool; presence of a large fecal mass in the rectum; history of large-diameter stools. Children with suspected or proved organic causes of constipation, such as Hirschsprung's disease, hypothyroidism, or structural anomalies of the anal canal, sensitivity to study medication, those with any type of infection or fever or with type I diabetes, were excluded from the study. Informed consent was obtained at enrollment from the parents of all children. The study was approved by the Suraksha Ethics Committee.

The parents of the enrolled children were instructed to insert one M Sip Lax™ straw (sennoside 7.5 mg; *B. coagulans* probiotic 1 billion CFU; black salt 13 mg) in approximately 100 mL of water and make the child suck the contents through the straw completely each night for three consecutive nights. The clinician ensured that the guardians understood the methodology for taking sennoside with probiotic straw. Assessment of efficacy parameters was done at all the three visits during the study: Visit 1 (Day 1), Visit 2 (Day 3+1), and Visit 3 (Day 6 or 7) to evaluate patients at screening and enrollment, after three days of treatment, and at the sixth or seventh day of treatment discontinuation to assess the long-term effect of the drug, respectively.

## **Study assessments**

### **Primary efficacy variables**

The following primary efficacy variables were analyzed during the study period:

1. Rome III criteria assessment to assess improvement in constipation symptoms
2. Bristol stool grading assessment for stool consistency
3. Subjective global assessment of patient status regarding their constipation on Visual Analog Scale
4. Assessments of the overall clinical condition of the patient based on a five-point scale
5. Global assessment of the efficacy of treatment conducted by the physicians and patients at the end of the study, based on a five-point scale.

**Primary safety variables**

The primary safety variables included the incidence of adverse events, treatment-related adverse events, changes in vital parameters (such as body temperature, pulse rate, respiratory rate) from baseline to the end of treatment and global assessment of tolerability at the end of the study by the investigator and the patient’s guardian, based on a four-point scale, ranging from ‘poor’ (severe or serious adverse events necessitating stoppage of study medication) to ‘excellent’ (no report of adverse events).

**Statistical analysis**

Statistical analysis was carried out for all the efficacy parameters at the end of the study, i.e. the end of post-treatment follow-up (Visit 3) and end of study treatment (Visit 2). The analyses included determination of means and standard deviations (SDs) and t-test, with significance accepted at the 5% level. Results are expressed as mean ± SD.

**Results**

A total of 15 children with functional constipation were enrolled in the study; 15 children completed the study and were considered for statistical analysis. Of the total 15 enrolled children, eight (53.33%) were male and remaining seven (46.67%) female (mean age ± SD: 9.73 ± 1.48). There was no discontinuation or withdrawal during the entire study duration. The demographic data for the patients are shown in table 1.

Parameter		Observations (n = 15)
Total number of children enrolled in study		15
Total number of children who completed the study and were evaluated		15
Screen failure and discontinuation		None
Gender (%)	Male	8
	Female	7
Age in years (mean ± SD)		9.73 ± 1.48
Age in years (Coefficient of variation)		CV = 0.152

**Table 1: Demographics of patients.**

Before treatment, 13 of the 15 patients had type 2 stool, indicating mild constipation and two patients had type 1 stool, indicating severe constipation. A significant improvement in stool consistency was seen at Visit 2, with eight patients having type 4 and six patients having type 3 normal consistency of stools. At Visit 3 (after discontinuation of the drug for four days), mild constipation was seen in six patients, while six patients had normal stool even after discontinuation of treatment. Type 5 stool was observed in three patients (Figure 1).

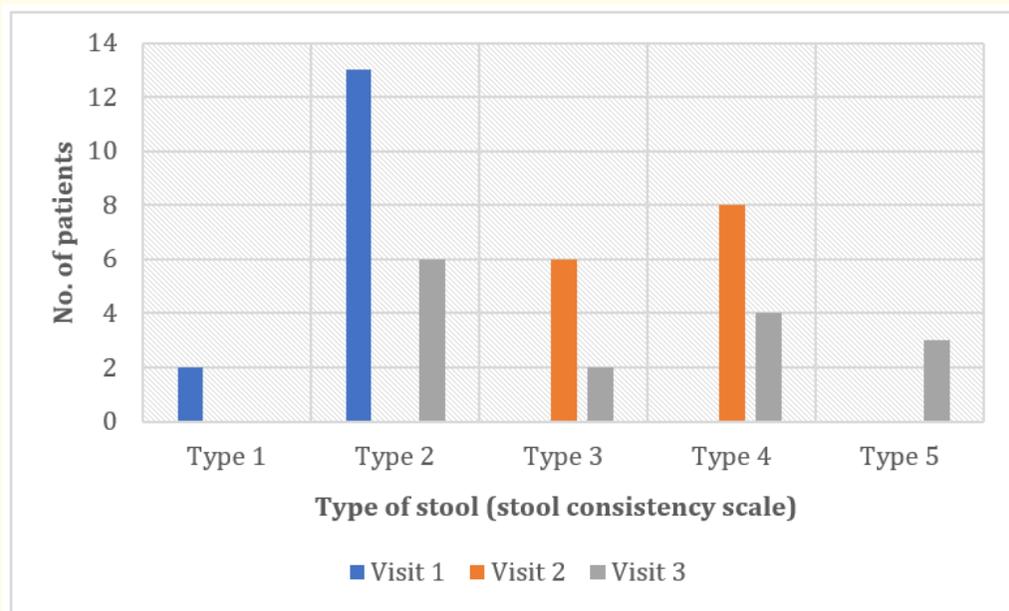


Figure 1: Bristol stool grading assessment for type of stool.

The mean total Rome III criteria score of M Sip Lax™ straw significantly reduced from 4.00 at the time of enrollment to 0.80 at Visit 2 ( $p < 0.05$ ). The score at Visit 3, after discontinuation of treatment for four days, was 2.53 (Table 2). There was a significant improvement in the mean effect of the drug on total Visual Analog Scale (subjective global assessment of patient’s status regarding their constipation) and the total overall clinical condition of children from baseline (Visit 1) to Visit 2 ( $p < 0.05$ ) following treatment with M Sip Lax™ straw for three nights (Table 2). Investigators and patients assessed the efficacy of treatment as ‘very good’ for 60% and 46% of patients and ‘good’ for 40% and 53% of patients, respectively.

Efficacy parameter	Visit 1 (Day 0) (Mean ± SD)	Visit 2 (Day 3+1) (Mean ± SD)	Visit 3 (Day 6/7) (Mean ± SD)
Total Visual Analog Scale	4.80 ± 1.01	2.40 ± 0.83*	3.47 ± 1.19
Total Rome III criteria score	4.00 ± 0.00	0.80 ± 1.21*	2.53 ± 1.41
Total overall clinical condition of patient	1.87 ± 0.35	4.47 ± 0.74*	3.40 ± 0.99

Table 2: Efficacy parameter assessment: Total visual analog on 5-point scale (1 = Very good improvement; 2 = Good improvement; 3 = Moderate improvement; 4 = Negligible improvement; 5 = Worse), total overall clinical condition of patient on 5-point scale (1 = Much worse; 2 = Worse; 3 = No change ;4 = Improved; 5 = Much improved) and Total Rome III criteria score. SD: Standard deviation. \* $p < 0.05$ .

There were no adverse events reported in this study. Vital measurements such as body temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure were within the normal range in all children monitored during this study. The tolerability of M Sip Lax™ straw was rated as ‘excellent’ by 86.67% and ‘good’ by 13.33% of patients.

## Discussion

Chronic constipation has a negative impact on the quality of life and causes significant psychological distress [18]. Osmotic laxatives such as polyethylene glycol (PEG) and lactulose are the recommended first-choice pharmacotherapies for fecal disimpaction; however, they are associated with liquid stool and fecal soiling, which may impact the quality of life of patients and also require consumption of large quantities of water, which is inconvenient, particularly for children [19,20]. Moreover, some countries have no access to PEG [20]. In this purview, there is growing interest in the efficacy of alternative treatment strategies, including the use of probiotics and anthraquinones. We in this investigation, we decided to test a novel M Sip Lax™ straw formulation consisting of the probiotic *Bacillus coagulans* and the anthraquinone senna. Probiotics may confer beneficial effects in functional constipation through a number of mechanisms, including through the restoration of the altered intestinal microbiota and production of acids, which lowers the colonic pH, in turn, aiding the peristalsis of the colon and reducing the colonic transit time. Additionally, *B. coagulans* can convert bound bile into free bile salts, resulting in the influx of water into the intestine [21]. A study found that in children affected by FC, the addition of *B. coagulans* to mineral oil resulted in a greater improvement in several symptoms of constipation compared with mineral oil alone [21]. On the other hand, senna is on the World Health Organization's List of Essential Medicines. It is an inactive glycoside produced by plants; when ingested, it passes unabsorbed and unchanged down the small intestine and is hydrolyzed by colonic bacterial glycosidases to yield active metabolites. Senna's metabolism in the gut thus depends on the action of gut microbes and the addition of *B. coagulans* to M Sip Lax™ allows for a lower amount of senna to be used. These active metabolites increase the transport of electrolytes into the colonic lumen and stimulate myenteric plexuses, to increase intestinal motility, typically inducing defecation six to eight hours after oral dosing [18]. In a study conducted among constipated children with anorectal malformations, senna demonstrated greater efficacy than PEG in relation to the endpoints assessed, including presence of daily bowel movements, absence of fecal soiling, and a clean abdominal X-ray obtained after passing stool [19]. In yet another study, no statistically significant difference in treatment success was found between lactulose and senna [5]. The black salt present in the M Sip Lax™ straw further increases the influx of water, increasing fecal moisture content and making stools soft. Black salt also has a known anti-spasmodic effect, preventing potential muscle spasms because of the stimulant laxative. The synergistic effect of these ingredients would, therefore, result in the disimpaction of fecal matter; restoration of a healthy gut; reduction in abdominal discomfort and flatulence; and less painful defecation of feces. In our study, children aged 5 - 12 years were treated with M Sip Lax™ straw once a day for three consecutive days. Treatment with M Sip Lax™ straw for three days improved the frequency of bowel movement, and stools became soft. No abdominal pain was experienced while passing stools. The improvement in all the parameters was statistically significant. We also found that after discontinuation of treatment, about 20% of study patients experienced mild constipation at Visit 3. In view of this, the use of M Sip Lax™ for inducing disimpaction may be a suitable option, following which children could be put on a maintenance program to prevent symptom relapse. The maintenance program may include dietary intervention, behavioral modification, and maintenance therapy using standard laxatives. M Sip Lax™ straw was well tolerated by all 15 children who participated in the study. The novel formulation was very well accepted, with 100% treatment compliance, without a single missed dose. Not a single adverse event was documented during the study period. To our knowledge, this is the first study evaluating the combined effect of senna and probiotic *B. coagulans* in the pediatric population with FC.

## Conclusion

Constipation is one of the most common chronic disorders of childhood, affecting 1% to 30% of children worldwide. The symptoms of constipation, such as infrequent bowel movements or painful defecation, could have distressing physical and psychological effects on affected children and their parents. The goal of management is to clear fecal retention and maintain a regular bowel movement routine. In this pilot study, M Sip Lax™ straw containing the probiotic *B. coagulans* and stimulant laxative senna was found to be a natural, novel, well-accepted, safe, and effective treatment strategy for functional constipation in children, devoid of any adverse events. Further studies evaluating the efficacy of these agents with longer patient follow-up are needed to substantiate the results of this study.

## Acknowledgement

We would like to thank Inzpera Healthsciences Limited for funding the study. We would like to thank AnaZeal Analyticals and Research Private Limited for their contribution to this study.

## Conflict of Interest

None.

## Funding

Funding for this study was provided by the sponsor, Inzpera Healthsciences Limited.

## Bibliography

1. Huang R and Hu J. "Positive effect of probiotics on constipation in children: a systematic review and meta-analysis of six randomized controlled trials". *Frontiers in Cellular and Infection Microbiology* 7 (2017): 153.
2. Rajindrajith S., et al. "Childhood constipation as an emerging public health problem". *World Journal of Gastroenterology* 22.30 (2016): 6864-6875.
3. Biggs WS and Dery WH. "Evaluation and treatment of constipation in infants and children". *American Family Physician* 73.3 (2006): 469-477.
4. Eltayeb AA., et al. "The use of botulinum toxin in children with chronic constipation". *International Surgery Journal* 4.6 (2017): 1845-1849.
5. Koppen IJ., et al. "Management of functional constipation in children: therapy in practice". *Pediatric Drugs* 17.5 (2015): 349-360.
6. Belsey Je., et al. "Systematic review: impact of constipation on quality of life in adults and children". *Alimentary Pharmacology and Therapeutics* 31.9 (2010): 938-949.
7. Faleiros FT and Machado NC. "Assessment of health-related quality of life in children with functional defecation disorders". *Journal of Pediatrics* 82.6 (2006): 421-425.
8. Yachha SK., et al. "Management of Childhood Functional Constipation: Consensus Practice Guidelines of Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition and Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics". *Indian Pediatrics* 55.10 (2018): 885-892.
9. McKeown C., et al. "Association of constipation and fecal incontinence with attention-deficit/hyperactivity disorder". *Pediatrics* 132.5 (2013): e1210-e1215.
10. Samsam M., et al. "Pathophysiology of autism spectrum disorders: revisiting gastrointestinal involvement and immune imbalance". *World Journal of Gastroenterology* 20.29 (2014): 9942.
11. Appak YÇ., et al. "Clinical findings, child and mother psychosocial status in functional constipation". *Turkish Journal of Gastroenterology* 28.6 (2017): 465-470.
12. Gordon., et al. "Osmotic and stimulant laxatives for the management of childhood constipation". *Cochrane Database of Systematic Reviews* 8 (2016): CD009118.
13. Sadeghzadeh M., et al. "The effect of probiotics on childhood constipation: a randomized controlled double blind clinical trial". *International Journal of Pediatrics* (2014): 937212.

14. Vilanova-Sanchez A., *et al.* "Are Senna based laxatives safe when used as long term treatment for constipation in children?" *Journal of Pediatric Surgery* 53.4 (2018): 722-727.
15. Ara K., *et al.* "Effect of spore-bearing lactic acid-forming bacteria (*Bacillus coagulans* SANK 70258) administration on the intestinal environment, defecation frequency, fecal characteristics and dermal characteristics in humans and rats". *Microbial Ecology in Health and Disease* 14.1 (2002): 4-13.
16. Minamida K., *et al.* "Effects of dietary fiber with *Bacillus coagulans* lilac-01 on bowel movement and fecal properties of healthy volunteers with a tendency for constipation". *Bioscience, Biotechnology, and Biochemistry* 79.2 (2015): 300-306.
17. Rasquin A., *et al.* "Childhood functional gastrointestinal disorders: child/adolescent". *Gastroenterology* 130.5 (2006): 1527-1537.
18. Portalatin M and Winstead N. "Medical management of constipation". *Clinics in Colon and Rectal Surgery* 25.1 (2012): 12-19.
19. Santos-Jasso K., *et al.* "Effectiveness of senna vs polyethylene glycol as laxative therapy in children with constipation related to anorectal malformation". *Journal of Pediatric Surgery* 52.1 (2017): 84-88.
20. Levy EI., *et al.* "Functional constipation in children: challenges and solutions". *Pediatric Health, Medicine and Therapeutics* 8 (2017): 19-27.
21. Saneian H., *et al.* "Comparison of *Lactobacillus Sporogenes* plus mineral oil and mineral oil alone in the treatment of childhood functional constipation". *Journal of Research in Medical Sciences* 18.2 (2013): 85-88.

**Volume 9 Issue 4 April 2020**

**©All rights reserved by Vikas D Gorad., *et al.***