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Randomized Control Trials

Effect of synbiotic in constipated adult women – A randomized, double-blind, placebo-controlled study of clinical response☆

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SUMMARY

Background & aims: Synbiotic intake may selectively change microbiota composition, restore microbial balance in the gut and improve gastrointestinal functions. We have assessed the clinical response of chronically constipated women to a commercially available synbiotic, combining fructooligosaccharides with *Lactobacillus* and *Bifidobacterium* strains (LACTOFOS®).

Methods: Following 1 week of non-interventional clinical observation, 100 constipated adult women, diagnosed by ROME III criteria, were randomized to receive two daily doses (6 g) of synbiotic or maltodextrin (placebo group), for 30 days. Treatment response was evaluated by patient's daily record of evacuation (stool frequency, consistency and shape, according to Bristol scale), abdominal symptoms (abdominal pain, bloating and flatulence) and constipation intensity (Constipation Scoring System AGACHAN).

Results: Patients treated with synbiotic had increased frequency of evacuation, as well as stool consistency and shape nearer normal parameters than the placebo group, with significant benefits starting during the second and third weeks, respectively (interaction group/time, $P < 0.0001$). There were no significant differences in abdominal symptoms, but AGACHAN score was better in the synbiotic than in the placebo group.

Conclusions: Dietary supplementation with a synbiotic composed of fructooligosaccharides with *Lactobacillus* and *Bifidobacterium* improved evacuation parameters and constipation intensity of chronically constipated women, without influencing abdominal symptoms. NCT01286376

1. Introduction

Constipation is a chronic disease estimated to affect about 16% of the worldwide general population and to be 2–3 times more prevalent and symptomatic in women than men.[1] Constipation frequency appears to augment with increasing age, particularly after 65 years old, and large amounts of healthcare resources are expended on its diagnosis and treatment.[1,2] In addition, available therapies are unsatisfactory in one-third of patients.[2]

Although constipation disorder is usually defined as ≤3 bowel movements per week, patients often equate constipation with abnormal stool consistency, feelings of incomplete emptying, straining, and urge to defecate. Therefore, the ROME III criteria, developed in 2006, include these symptoms in diagnosing constipation.[3] In addition, for Rome III criteria patients should rarely pass loose stools without laxatives and have symptoms distinct from those of irritable bowel syndrome (IBS).[3]

Constipation can be a consequence of intestinal dysbiosis, with an increase of potentially pathogenic microorganisms and a decrease of potentially beneficial microorganisms.[4] These alterations may affect large bowel motility and secretory functions by changing the metabolic environment of the colon and the amount of available physiologically active substances.[4]

The ingestion of soluble fibers with prebiotic effects, such as inulin and fructooligosaccharides (FOS), stimulates the growth of beneficial bifidobacteria and lactobacilli in the colon.[5] Oral intake, at adequate concentrations, of specific strains of lactobacilli,

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bifidobacteria and other living commensal microorganisms, generically defined as probiotic, may be associated with health benefits, including improvements in bowel movements, permeability and microbial profile, improved function of intestinal immune barrier and prevention of colon cancer.[6]

The combination of probiotic strains and prebiotic fibers may provide synergistic effects, after which they are named: synbiotics.[7] The interaction between probiotics and prebiotics *in vivo* may improve the survival of probiotics.[7] Synbiotic intake has been shown to modify microbiota composition and restore intestinal microbial balance, which may have positive effects on gastrointestinal functions.[8]

This prospective, randomized, double-blind, parallel study was designed to evaluate the effects of a synbiotic, consisting of FOS, *Bifidobacterium lactis* and three different strains of *Lactobacillus*, on chronic constipation in women. Although the individual benefits of FOS and probiotic strains in the treatment of chronic constipation have been reported, the effects of the specific synbiotic associations we utilized have not yet been assessed.

Our aim was to evaluate the clinical response to synbiotic in chronically constipated women, through comparisons of changes in: (1) Frequency of bowel movements and stool consistency and shape; (2) Abdominal symptoms; and (3) Constipation states according to a standard constipation scoring system.

2. Methods

2.1. Ethical issues

The current study was registered in the Clinical Trials Database (ID: NCT01286376) and performed according to the ethical recommendations of the Declaration of Helsinki and the Ethical Committee of the Real e Benemérita Associação Portuguesa de Beneficência do Hospital São Joaquim, which approved the study protocol. All enrolled patients provided written informed consent.

2.2. Patients

Adult (aged 18–75 years) literate female patients from GANEP – Human Nutrition of the Real e Benemérita Associação Portuguesa de Beneficência do Hospital São Joaquim with bowel constipation, as diagnosed by ROME III criteria,[3] were screened between May 2010 and February 2011 for eligibility to participate in our study. Exclusion criteria were bowel constipation due to pharmacologic interventions; diagnosis of gastrointestinal diseases (e.g., cancer, previous abdominal surgery, inflammatory bowel diseases) by endoscopic or radiologic evaluation 5 years before or after the symptoms started; disorders of respiratory, cardiologic, renal, hepatic, gastroenterological, hematologic, neurologic or psychiatric functions; other diseases that, in the opinion of the investigator, could significantly affect intestinal transit; lactose intolerance or allergy to any ingredient of fiber supplements; dependence on laxatives; alcohol or drugs use; regular use of antidepressants, opioid narcotic analgesics, anticholinergic or anti-spasmodic agents; use of investigative drugs one month before or during the study; regular use of medications affecting intestinal motility; regular intake ($\geq$3 times/week) of products containing pre or probiotics (e.g. yoghurts, dairy drinks, supplements); and antibiotic ingestion in the last 3 months. A computer-generated (GraphPad statistical software) sequence with a block size of 10 patients (1:1 allocation) was employed by an independent investigator to assign the participants to either of the groups (synbiotic and placebo). The patients were enrolled and assigned by one exclusive investigator (L.C.L.) and randomization sequence was concealed until the end of statistical analysis.

2.3. Synbiotic treatment

After a week of non-interventional clinical observation, all included patients were randomized to receive two daily doses of 6 g LACTOFOS® (synbiotic group) or maltodextrin (control group), each diluted in 100 ml of water with a minimum of 4 h between doses, for 30 days. Each LACTOFOS® sachet contained 6 g of fructooligosaccharide (FOS) and 10^8–10^9 bacteria of the strains *Lactobacillus paracasei* (Lpc-37), *Lactobacillus rhamnosus* (HN001), *Lactobacillus acidophilus* (NCFM) and *Bifidobacterium lactis* (HN019). The control and experimental sachets were prepared by the manufacturer of LACTOFOS® and were identical in appearance, taste and smell.

2.4. Baseline demographic and clinical data

One week before treatment, each patient was interviewed by a trained dietitian. Data regarding body weight and height, waist circumference (WC), body mass index (BMI), percentage of fat, water, lean mass and bone were collected using the MEA Slim® – 02.510 balance (Plenna). Regular physical activity was also recorded.

2.5. Clinical response evaluation

Clinical response to treatment was evaluated throughout the study period. Each patient kept a self-report daily record of evacuation data, abdominal symptoms and constipation intensity, after being instructed by one exclusive trained dietitian (L.C.L.) during a first consultation, immediately before treatment. Patients were monitored weekly by phone calls, to verify synbiotic/placebo consumption, any issues regarding recording of data, and to assess adverse events. After treatment, patients attended a final consultation with the same dietitian to verify the reported data and patient impressions regarding treatment.

2.6. Evacuation categorization

Analysis of evacuation included determination of stool frequency, consistency and shape. Stool consistency and shape were classified by the patient using the scale of Bristol,[9] which classifies stool form into seven categories: 1, nut-like; 2, lumpy sausage; 3, sausage with cracks; 4, smooth snake; 5, soft blobs; 6, fluffy pieces; and 7 watery. Stool consistency and shape were assessed by determining the average difference from category 4 (smooth snake), which was regarded as ideal stool form and consistency.

2.7. Abdominal symptoms categorization

Patients recorded their perception of abdominal pain, bloating and flatulence according to four classifications of symptoms (0, no symptoms; 1, tolerable symptoms; 2 bothersome symptoms; 3, symptoms impairing daily activities). For each patient, intestinal symptoms were recorded as the highest score per week.

2.8. Grading of constipation intensity

Constipation intensity was determined using the AGACHAN Constipation Scoring System,[10] which considers at the same time the following set of symptoms: frequency of bowel movements, difficulty/straining to evacuate, pain on evacuation, sensation of incomplete evacuation, abdominal pain, time taken to start the evacuation, type of assistance (digital assistance or enema) for evacuation, attempts per day and duration of constipation. The