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By Dr. Amjad Atef Suliman Alhelo

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Ibs symptoms (Abdominal pain/discomfort, bloating/ distension, bowel movement difficulty) and changes in stool frequency and consistency were recorded daily and assessed each week. A safety assessment was carried out throughout the study.

Result: The proportion of responders, defined by an improvement of I.b.s symptoms (abdominal pain/ discomfort, bloating/distension, bowel movement difficulty) and changes in stool, was significantly higher (p value < 0.001) in the treated group than the placebo group (130 vs 47), (73.4% vs 27.64%).

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Conclusion: Saccharomyces cerevisiae is well tolerated and reduces irritable bowel syndrome symptoms with stool modification.

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I. Introduction

Irritable Bowel Syndrome (IBS) is the most common functional gastrointestinal disorder. IBS is characterized by chronic and/or recurrent abdominal pain or discomfort and altered bowel habits.

IBS has an estimated worldwide prevalence of 14% in women and 9% in men, and usually occurs before age 50 years.

IBS has been sub typed according to predominant bowel habit as:

- IBS with constipation.
- IBS with diarrhea.
- Mixed type.
- Unclassified.

a) *Rome III Criteria for IBS*

The criteria for a diagnosis of Irritable Bowel Syndrome (IBS) requires that a person be experiencing chronic abdominal pain or discomfort at least three days over the course of the last three months, with an onset of symptoms at least six months prior. These symptoms must also show:

- Pain symptoms are improved with a bowel movement.
- Symptom onset is related to a change in the frequency of stool.
- Symptom onset is related to a change in the appearance of stool.

Numerous pathophysiological mechanisms have been explained IBS, but the contribution of the gastrointestinal microbiota and variations in its composition and function have only recently begun to be evaluated as a significant component in the pathogenesis and pathophysiology of irritable bowel syndrome.

b) *Intestinal microflora*

Human intestine contains 1014 bacterial cells, which are 10 times higher than the number of cells in the human body. Seventy percent of our body normal microflora in the colon, which contains bacteria, fungi, viruses.

The number of bacteria increases from stomach (101 to 103 bacteria/g) to the colon (1011 to 1012 bacteria/g).

The small intestine contains mainly Gramm positive and aerobic bacteria, the large intestine contains predominantly Gram negative and anaerobic bacteria. 95% of intestinal bacteria are anaerobes, Bacteroidetes and Firmicutes.

c) *Benefits of intestinal flora*

Fermentation of undigested food, endogenous mucus producing short chain fatty acids, which are nutrients to the colonic epithelial cells and conservation of energy, absorption of NaCl and water, from the right colon, synthesis of vitamin K, control of epithelial cell proliferation, protection against pathogens by a barrier effect and training of the immune system.

Intrinsic and extrinsic factors that prevent overgrowth of bacteria in the small intestine, *intrinsic factors* include:

1. Gastric juice and bile.
2. Peristaltic movement which prevent adherence of bacteria.

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3. Normal gut defense including humoral and cellular mechanisms.
4. Mucin production by intestinal mucosa.
5. Gut antibacterial peptide.
6. Ileocecal valve preventing retrograde translocation of bacteria from colon to the small intestine.

Extrinsic factors include diet and drugs modulating gut flora, such as antibiotics and ppis and h2 blockers.

d) Evidences of Bacterial Disturbance Causing IBS

i. *Post-infectious IBS*

After acute gastroenteritis infectious etiology, up to 30% of patients complain of gastrointestinal symptoms for a long time, which meet irritable bowel syndrome criteria.

Probiotics is effective in restoring the intestinal microbiota in patients with post infectious irritable bowel syndrome.

ii. *Small Intestinal Bacterial Overgrowth and IBS*

A study undertaken at Cedars-Sinai Medical Center used 448 subjects who were referred by their doctors for detection of SIBO. After completing a questionnaire, the researchers determined that 202 subjects could be considered as having irritable bowel syndrome according to standard symptom criteria (see sidebar). Of these, 157 (78%) were positive for bacteria overgrowth using the LHBT.

The subjects' doctors then prescribed a 10-day course of antibiotics (e.g. Neomycin, ciprofloxacin, flagyl, or doxycyline) to eradicate their bacterial overgrowth. Of the 157 initially qualifying subjects, 47 were referred back by their doctors for a follow-up LHBT and were given a second questionnaire without being given the results of their LHBT. Of these 47 subjects, 25 achieved complete eradication, and 22 incomplete eradication of their SIBO. Antibiotic treatment significantly reduced hydrogen production in all 47 subjects, with greater reduction in hydrogen production seen in those subjects whose SIBO was completely eradicated.

iii. *Antibiotics and IBS (Iatrogenic IBS)*

Antibiotics significantly alter gut microflora causing imbalance of the intestinal microflora, for example many antibiotics causes pseudomembranous colitis.

a. *Antibiotics*

A risk factor for irritable bowel syndrome in a population-based cohort Krogsgaard LR1, Engsbro AL2, Bytzer P1, 3.

An internet-based web panel representative of the Danish background population was invited to participate in a survey regarding the epidemiology of IBS in 2010, 2011 and 2013. A questionnaire based on the Rome III criteria for IBS were answered at all three occasions. In 2013, a question regarding use of antibiotics in the past year was included.

e) Results

In 2013, use of antibiotics was reported by 22.4% (624/2781) of the population. A higher proportion of individuals with IBS reported use of antibiotics compared with asymptomatic controls [29.0% (155/534) vs. 17.9% (212/1,184), $p < .01$]. For asymptomatic respondents in 2010 and 2011 ($n = 1004$), the relative risk of IBS in 2013 related with use of antibiotics was 1.9 [95% confidence interval (CI): 1.1-3.1]. Adjusting for sex by logistic regression, development of IBS was predicted by use of antibiotics with an odds ratio of 1.8 (95% CI: 1.0-3.2).

f) Conclusions

Antibiotics is a risk factor for IBS in asymptomatic individuals. Possible mechanisms should be investigated in future studies.

g) Probiotics

The World Health Organization define probiotics as "*live microorganisms, which when taken in adequate amounts, confer a health benefit on the host*", Probiotics can be bacteria, virus, parasites, or yeasts.

Probiotics benefit to the body by various mechanisms:

1. Pathogen suppression
2. Improvement of barrier function
3. Immunomodulation
4. Neurotransmitter production

Strain of *Saccharomyces cerevisiae* CNCM I-3856 secretes saccharolytic enzymes and assists intestinal flora by generating short-chain fatty acids that accelerate bowel movement. It also acts as a visceral analgesic, increasing resistance to pain by up to 40 percent. Additionally, it also acts as an anti-inflammatory to combat intestinal inflammation. To top it all off, the probiotic rebalances microbial composition in the gut as it has been shown to reduce harmful bacteria such as *Enterococcus spp.*, *Escherichia coli* and *Candida albicans*. The result is decreased inflammation, bloating, pain, discomfort, constipation all of which are symptoms of IBS.

II. Materials and Methods

a) Patients

Patients were selected in two investigative sites in Jordan, Jordanian Ministry of Health, and Saudi Arabia, Riyadh National Hospital from 1/09/2010 to 1/07/2015. Patients involved in the study were males and females between 18 and 75 years of age with a diagnosis of IBS according to the Rome III criteria.

A pain/ discomfort score strictly above 1 and strictly below 6, as determined on a pain/discomfort scale using arbitrary grading from 0 to 7.

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Patients had normal blood counts, complete blood count, liver function test, renal function, thyroid function, before participating the study.

Subjects were excluded if they had organic intestinal diseases, underwent treatments that influence ibs, or taking any medication or herbals or probiotics.

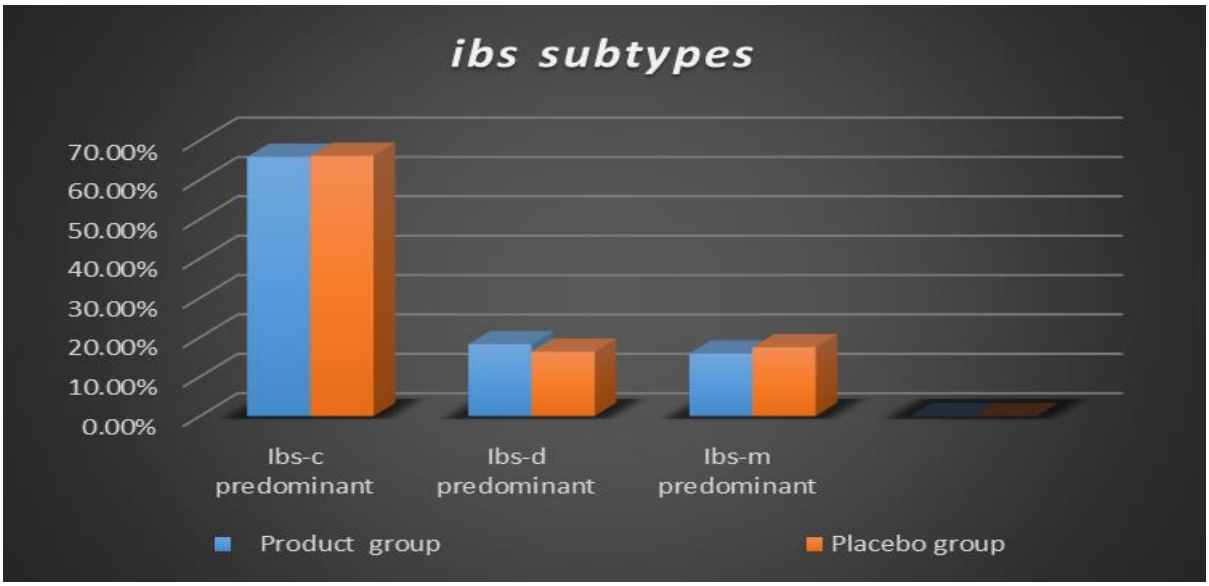


Figure 1

b) Study design

This is 4-week double-blind placebo- controlled clinical study randomizing two parallel group of IbS patients 177 experimental and 170 placebos, During a four week period, scores for abdominal pain/discomfort (defined as a non-comfortable sensation corresponding to a continuum between discomfort and pain), bloating And flatulence, difficulty with defecation, stool frequency, and consistency were recorded.

Dietary recommendations were explained to each patient, After verification of the inclusion/exclusion criteria, eligible IBS patients were randomized to consume daily, for 4 weeks, two tablets of s.cerevisiae CNCM I-3856 (1000 mg) with meal and placebo (calcium gluconate 500 mg). Patients were followed weekly and provided consent before inclusion in the study.

c) Study products and compliance evaluation

The products studied were presented in all tablets of active product and placebo was without flavour, and had the same size, colour. They were to be taken orally, two tablets a day with launch and dinner time with a glass of water. The probiotic preparation specifically 1000mg per tablet of S. cerevisiae CNCM I-3856, and the placebo consisted of calcium gluconate 500 mg.

d) Assessment of symptoms and study endpoints

Ibs symptoms evaluated daily and assessed each week during the 4-week study according to a 7-point Likert scale.

Abdominal pain/discomfort scores were first analyzed, where the score at week 0 (W0) to (w4).

Secondary outcome measures were the weekly scores of bloating/distension and bowel movement difficulty, recorded daily in the same condition using the 7-point Likert scales Changes in stool frequency and consistency were followed daily using the Bristol Stool Scale (ranging from 1, corresponding to separate hard lumps, to 7 for entirely liquid stools).

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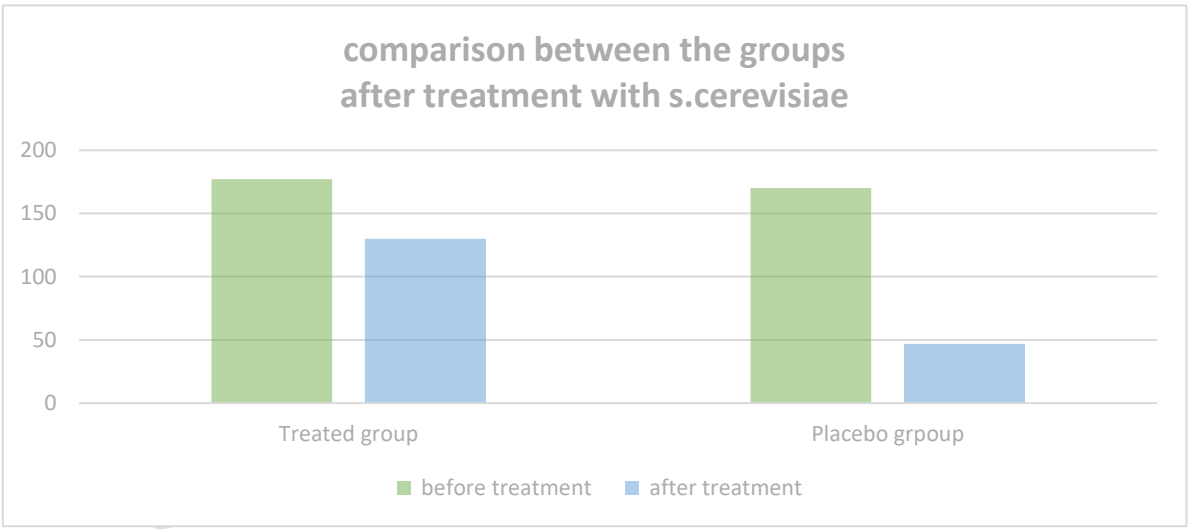


Figure 2

e) Safety variables

Adverse events were recorded by patients and immediately transmitted to the investigator to estimate their severity.

f) Randomization and statistical methods

Randomization and statistical analyses were conducted using *SPSS* software.

Each subject included at the visit (V1) received in a random manner one of the two products (placebo or active).

Block randomization was performed by type of subject (with predominant constipation) (IBS-C), with predominant diarrhea (IBS-D), or mixed symptoms (IBS-M)) with dynamic allocation software using the block permutation technique.

The AUCs (W1-W4) of the abdominal pain/discomfort scores, bloating/distension scores, and bowel movement difficulty scores was calculated and analyzed.

III. Results

a) Primary outcome measures

Abdominal pain/discomfort scores, expressed in AU on a scale from 0 (no symptoms) to 7 (severe symptoms), Intra group analysis revealed a significant reduction of the score in the probiotic groups throughout the 4 weeks of treatment period (W0–4); this led to a mean score reduction of (130 vs 47), (73.4% vs 27.64%) compared with baseline, respectively in the product group ($p < 0.001$) in both treated groups.

IV. Discussion

The present randomized double-blind placebo-controlled study demonstrates, in Jordanian population and Saudi population, that S. cerevisiae CNCM I- 3856 is safe and improves abdominal pain/discomfort. In IBS and other patients fulfilling the Rome III criteria, the 4-week clinical trial was performed according to the recommended designs of treatment trials for functional gastrointestinal disorders in order to demonstrate statistical superiority of a treatment with S. cerevisiae for IBS patients.

Based on these data and expecting a 45.76% therapeutic gain over placebo for the score assessing abdominal pain/discomfort, 347 IBS patients were randomized and treated for 4 weeks with either S. cerevisiae CNCM I-3856 at a daily dose of 2000 mg 1000mg bid, or placebo 500 mg calcium gluconate.

After the first week of the study abdominal pain in the treatment group significantly decreased, score of 1 was 40 percent at the first week, and at the second week was 54 percent, and at the third week was 63 percent, and at the fourth week score of 1 was 70 percent. As a result, (abdominal pain/discomfort, bloating/distension, bowel movement difficulty and changes in stool frequency and consistency) had improved, if we compare treated group and the placebo group (130 vs 47), (73.4% vs 27.64%).

Probiotic administration is considered safe and acceptable strategy in IBS. Most studies evaluating the effects of probiotics in IBS patients have been performed with bacterial strains of lactobacilli and/or bifidobacteria. Despite the numerous advantages offered by yeast compared to bacteria, including antibiotic and phage resistances, as well as higher natural resistance against gastric acid and bile salts, and stronger capacity to regulate the immune response, only two clinical trials assessed the effect of yeast in patients with IBS.

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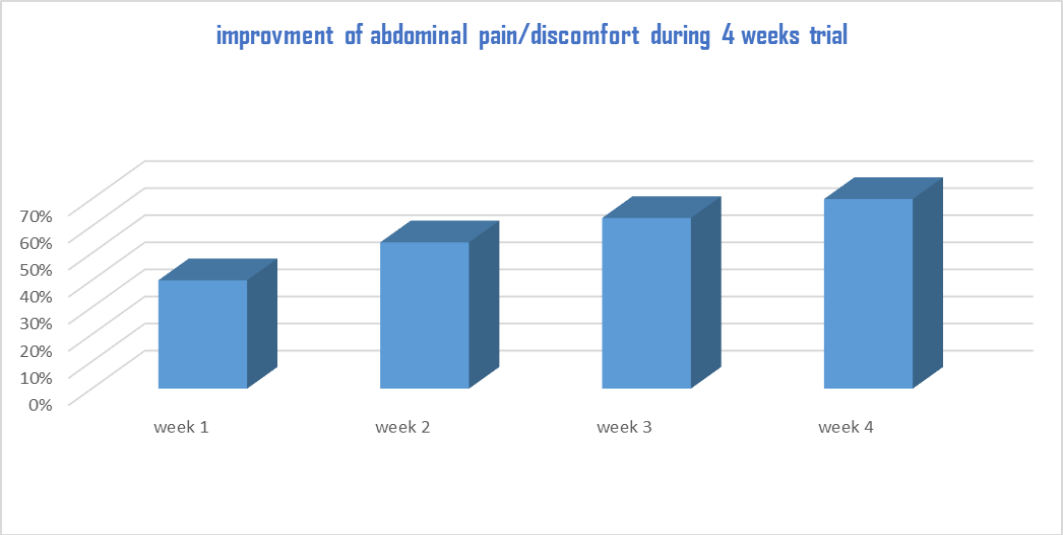


Figure 3

V. Conclusion

In conclusion, S. cerevisiae CNCM I-3856 at 2000 mg/day, conveniently delivered bid by two tablets 1000 mg, is well tolerated and reduces abdominal pain/discomfort scores with altering stool frequency and consistency. Further clinical studies are warranted to confirm that S. cerevisiae could be a new promising candidate to improve abdominal pain/digestive discomfort in subjects with IBS.

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