Clinical Trial: The Association Between Rifaximin And Partially Hydrolyzed Guar Gum Is More Effective Than Rifaximin Alone In Eradicating SIBO

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**Clinical Trial: The Association Between Rifaximin And Partially Hydrolyzed Guar Gum Is More Effective Than Rifaximin Alone In Eradicating SIBO**

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Functional GI diseases < Disease-based, Small intestine < Organ-based, Malabsorption < Topics, Probiotics/prebiotics < Topics
Clinical Trial: The Association Between Rifaximin And Partially
Hydrolyzed Guar Gum Is More Effective Than Rifaximin Alone In
Eradicating SIBO

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Preliminary data were exhibited at UEGW/WCOG Gastro 2009, London.
Abstract

Background:
Abnormal intestinal clearance is involved in the pathogenesis of small intestinal bacterial overgrowth (SIBO). It is known that partially hydrolyzed Guar gum (PHGG) affects intestinal motility. Eradication therapy of SIBO is based on antibiotic treatment: no data are available about the role of fibers supplementation in eradicating SIBO.

Aims:
To assess whether the association between PHGG plus rifaximin is more effective than rifaximin alone in the treatment of SIBO.

Methods:
50g-glucose breath test (GBT) was given to 500 consecutive patients. Patients with positive GBT and predisposing conditions to SIBO entered into the study, and were randomized to receive rifaximin 1200mg/die or rifaximin 1200mg/die plus PHGG 5g/die for 10 days. Patients completed a symptom questionnaire and GBT both in basal condition and 1 month after withdrawal of therapy.

Results:
Seventy-seven patients had SIBO. SIBO eradication rate was 62.1% in the rifaximin group (both on per-protocol and intention-to-treat analyses), and 87.1% (per-protocol, p=0.017) and 85.0% (intention-to-treat, p=0.036) in the rifaximin-plus-PHGG group. Clinical improvement was observed in 86.9% and 91.1% of eradicated cases in rifaximin and rifaximin-plus-PHGG groups, respectively (p=0.677).

Conclusion:
The association between rifaximin and PHGG seems to be more useful in eradicating SIBO compared to rifaximin alone.
INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is a condition mainly characterized by diarrhoea, bloating, flatulence and abdominal pain due to an abnormal amount of bacteria in the small intestine[1-4]. Gastric acid production, anatomical integrity of intestinal wall and peristaltic motility are main factors in preserving the fine equilibrium between host and bacteria. Therefore, predisposing conditions that alter the above mentioned mechanisms could heighten the number of bacteria in the small intestine and lead to the development of this syndrome. Furthermore, it has been proposed that gut microflora could play a role in the modulation of some inflammatory diseases. This was suggested by the higher incidence of SIBO among patients with Rheumatoid Arthritis[5] and Non Alcoholic Steatohepatitis[6] and by improvement of Rosacea after eradicating SIBO[7]. Although severe forms presenting remarkable malabsorption can be seen occasionally, the majority of clinical manifestations of SIBO are generally mild and make it hardly distinguishable from other conditions such as Irritable Bowel Syndrome (IBS) or Lactose Intolerance. This difficulty is clearly underlined by the heterogeneous results of several studies that reported IBS comorbidity with SIBO ranging widely from 10% to 80% [8-13].

The presence of at least 10⁵ cfu/ml in jejunal aspirate culture is considered the gold standard test to diagnose SIBO, especially when colonic-type bacteria are isolated[1-4,14]. However, hydrogen breath tests are commonly used in clinical practice, being more acceptable to patients and giving quicker information to the clinician[15]. Among them, Glucose Breath Test (GBT) has proved to have the highest accuracy in diagnosing SIBO[14,16]. Once the bacterial overgrowth is diagnosed it can be successfully treated by locally active non absorbable antibiotics. Various studies have shown that rifaximin is successful in eradicating SIBO with no
or minimal side effects when compared to systemic antibiotics[7,15,17-21]. Of the predisposing conditions involved in SIBO pathogenesis, hypomotility seems to play a relevant role by impairing intestinal clearance and, as a consequence, the intestinal bacteria distribution[21-24]. Thus, we have hypothesized that adding a prebiotic such as partially hydrolyzed guar gum (PHGG) to rifaximin can be of help in the decontamination of small bowel. In fact, it can have a beneficial effect on intestinal motility and therefore, a synergic interaction between rifaximin and PHGG may lead to a higher eradication rate of SIBO. The primary end point of our study was to assess whether the association of rifaximin and PHGG was more effective than rifaximin alone in eradicating SIBO, while the secondary end point was to evaluate whether the combined treatment allowed to obtain a greater symptomatic improvement than rifaximin alone.

MATERIALS AND METHODS

Patients

From May 2007 to March 2010, 500 consecutive patients were referred to our centre to perform GBT because of gastrointestinal symptoms, such as modification in stool frequency, abdominal pain, bloating, flatulence, tenesmus, nausea and vomiting. In these subjects, the predisposing conditions for SIBO were: impaired intestinal motility due to medications (i.e. antidepressant drugs) (n=20), hypothyroidism (n=5), diabetes mellitus (n=4), Scleroderma (n=1), and Crohn’s Disease (n=3); acquired anatomical conditions such as resection of the ileum-cecal valve (n=3) or partial gastrectomy (n=1), adhesions due to major abdominal surgery (n=2). Also Rosacea (n=5), Non Alcoholic Steatohepatitis (n=4) and Rheumatoid Arthritis (n=1) were considered as disorders related to SIBO. Patients that underwent a previous treatment for SIBO and patients with basal H₂ sample >10ppm were excluded from the study. Moreover,
patients had to take neither antibiotic or Proton Pump Inhibitors (PPI), nor pre or probiotics for at least 10 days before the examination. Among these, we evaluated 390 patients who had both performed GBT and answered our questionnaire based on gastrointestinal symptom. In this investigation, we included the 77 patients (male/female: 15/62; mean Age 54; range 26-84 years) who had a positive GBT. These patients were randomized, by using a computer generated random list, to receive rifaximin 1200mg daily for 10 days or rifaximin 1200mg daily plus PHGG 5g/die for 10 days. All patients completed the questionnaire both in basal condition and 1 month after therapy. Adverse events were investigated during and 1 month after the end of treatment. Eradication of SIBO was assessed 1 month later after the end of treatment by a further GBT. The study was evaluated and approved by our Institutional Review Board.

Glucose Breath Test

The evening before GBT patients followed a diet containing boiled rice, meat and water alone. Then they fasted until the end of the test. Glucose was given in a dose of 50 g dissolved in 250ml of water. Breath hydrogen concentration, in parts per million (ppm), was measured by gas-chromatography (Quintron MicroLizer model DP plus, Milwaukee, USA) on samples of end expiratory air collected every 15 minutes for 2 hours. A basal sample was taken before glucose intake. Patients were asked to avoid cigarette smoking, food intake and physical exercise during test. A single peak of hydrogen excretion higher than 12 ppm was the cut-off value for test positivity.

Questionnaire

All patients completed an interview questionnaire, according to previous studies performed by our group[7,9,21] and by other Authors[25-27], based on 10 variables (diarrhea, upper and lower
abdominal pain/discomfort, bloating, flatulence, abdominal tenderness, weight loss, nausea, constipation, and tenesmus) scored from 0 (no symptoms) to 3 (severe), providing a global symptomatic score (GSS), calculated as the sum of all symptom scores, with a range from 0 to 30. A decrease of 50% in global symptomatic score after the end of therapy was arbitrarily considered as a significant improvement of symptoms, in agreement with other studies carried out by our group on this topic[7,9,21].

**Statistical analysis**

Data are shown as mean values, ranges and rates. Data were assessed on both per-protocol (PP) and intention-to-treat (ITT) analyses. Fisher’s exact test was used to evaluate if the difference between the two groups was statistically significant in terms of both SIBO eradication rates and symptomatic relief. A p value <0.05 in a two-tailed test was considered significant. Statistical analysis was performed with GraphPad Software, QuickCalcs [San Diego, CA, USA], and with GNU Software, PSPP [Boston, MA, USA].

**RESULTS**

Table 1 shows the main demographic and clinical characteristics of the study population subdivided according to treatment received. There were no statistically differences between the two groups. Overall, eradication of SIBO was achieved in 57/77 patients (74.0%). In particular, SIBO eradication was obtained in 23/37 patients (62.1%; both PP and ITT analysis) treated with rifaximin alone, and in 34/39 (87.1%; PP) and 34/40 (85.0%; ITT) patients treated with rifaximin plus PHGG. SIBO eradication rates were significantly different between the two treatment arms on both PP (p=0.017; OR=0.241; 0.075, 0.781) and ITT (p=0.036; OR 0.289; 0.095, 0.884) analyses.
Figure 1 shows the flow of patients within the study, SIBO eradication rates and symptoms improvement. Among patients who obtained eradication, clinical improvement was observed in 86.9% and 91.1% of patients treated with rifaximin alone and rifaximin plus PHGG, respectively ($p=0.677$). On the other hand, among patients who did not obtain eradication, clinical improvement was observed in 7.1% (1/14) and 16.6% (1/6), respectively ($p=0.521$). The overall symptomatic improvement in the two treatment arms was 56.7% and 80% in patients treated with rifaximin alone and rifaximin plus PHGG, respectively ($p=0.1526$).

Pre-treatment mean symptomatic scores were: 4.21 in the study population (77/77), 4.19 among patients included in the rifaximin arm (37/77), and 4.22 among patients included in the rifaximin plus PHGG arm (40/77). Post-treatment mean symptomatic scores of the group that received rifaximin decreased from 4.10 to 1.85 among eradicated patients with symptomatic improvement (20/37), from 4.60 to 4.00 among eradicated patients without symptomatic improvement (3/37), and from 4.43 to 4.14 among patients who did not eradicated SIBO (13/37). Post-treatment mean symptomatic scores in the group that received rifaximin plus PHGG decreased from 4.23 to 1.81 among eradicated patients with symptomatic improvement (31/40), from 4.33 to 4.00 among eradicated patients without symptomatic improvement (3/40), and from 4.17 to 3.50 among patients without SIBO eradication (6/40).

No serious adverse events were reported during treatment.

**DISCUSSION**

In patients diagnosed with SIBO, a broad-spectrum antibiotic therapy is recommended in order to obtain eradication of intestinal bacterial overgrowth. Rifaximin is a locally active non-absorbable antibiotic whose efficacy in eradicating SIBO has been demonstrated by several studies[7,15,17-21]. Its use is often preferred to other antibiotics such as levofloxacin and
metronidazole because of its topical action and absence of adverse events[28]. In this study, we
aimed at evaluating whether adding PHGG to rifaximin was able to increase SIBO eradication
rate. Our hypothesis was based on the fact that antibiotics act only on intestinal bacteria, but
do not solve the conditions predisposing to SIBO. On the other hand, impaired intestinal
motility, by decreasing intestinal clearance, might promote the development of unfavourable
habitat for physiologic gut microflora and the invasion of small bowel lumen by colonic
bacteria.

Our results show that the association of PHGG and rifaximin was significantly more effective
than rifaximin alone in the eradication of SIBO. Thus, this association reached an eradication
rate of 87.1%, resulting significantly higher than rifaximin alone (62.1%). This finding suggests
that fiber supplementation positively interacts with rifaximin in SIBO treatment.

Several studies have shown a beneficial effect on intestinal motility by use of alimentary
fibers[29]. In fact, alimentary fibers increase fecal mass and transit time, easing defecation.
They could be generally distinguished into two categories. Unsoluble fiber is minimally modified
in the intestinal lumen and mechanically increases fecal mass by retaining water, thus
decreasing transit time and improving defecation. Otherwise, soluble fiber is metabolized in the
large bowel, thus producing short chain fatty acids and leading to selective stimulation of
microbial growth which influences secondarily bowel functions[30]. This is an important
distinction because several studies conducted on IBS populations have shown that the global
amelioration of IBS symptoms is mainly associated with the use of soluble fibers rather than
with the insoluble ones. It was also found that insoluble fiber was no better than placebo at
improving IBS and, rather surprisingly, that a large amount of insoluble fiber may worsen IBS-
related symptoms [31,32].
In this study we used PHGG, a vegetable, water-soluble, dietary fiber that is derived from guar gum with a lower molecular weight than the original guar gum, whose safety has been largely proved[33-35]. Noteworthy, PHGG increases fecal acetate content and the colonic concentration of Lactobacilli and Bifidobacteria thus providing an important prebiotic action[36-41]. As PHGG is not used by these bacteria in vitro, it has been proposed that PHGG is degraded in human colon providing substrates that favour the selective growth of Bifidobacteria and Lactobacilli[41]. This is an important mechanism because it is proved that loss of anaerobes is associated with a depletion in short chain fatty acids and an increase in stool pH, allowing overgrowth of other bacteria which may contribute to altering intestinal function[42]. Moreover, acetate is one of the most important energy resources for colonocytes and is necessary to sustain colonic epithelial cell proliferation[43]. These factors are useful to preserve the mucosal integrity and to support its repairing process and, when altered, could lead to develop SIBO.

GBT and Lactulose Breath Test (LBT) are the most commonly utilized tests for SIBO. Although there is no universal agreement about which test should be performed to diagnose SIBO, in our study we used GBT because it is easier to interpret and more accurate in diagnosing SIBO than LBT[14]. This has been recently confirmed by the 1st Rome Consensus Conference that reported higher diagnostic accuracy for GBT with respect to LBT (71% vs 55%)[16]. In fact, glucose is highly absorbed in the proximal small bowel and rarely reaches the colon, showing a single “early” H₂ peak in case of SIBO. On the other hand, lactulose passes unabsorbed through the small bowel and reaches the large bowel where it is metabolized by colonic bacteria. Thus, lactulose investigates bacterial fermentation through the whole gut and can also be used as a measure of orocaecal transit. Nevertheless, being a non-absorbable carbohydrate, lactulose itself can accelerate small bowel transit that is a condition in which the “early” peak can merge
with the late “colonic” peak, thus making impossible to distinguish SIBO from colonic fermentation. Moreover, different portions of the given substrate might reach the colon at different times, thus causing two or more peaks in H₂ excretion that simulate SIBO[44]. GBT is associated with a lower incidence of false positive results when compared with LBT, and in healthy volunteers GBT shows an optimal intra-individual reproducibility[45].

Recently, studies on SIBO diagnosed by GBT and treated with rifaximin reported that the progressive increase in rifaximin dosage (from 600mg/day up to 1600mg/day for 7 days) may lead to an important gain in terms of SIBO eradication without enhancing the occurrence of side-effects[18,19]. Similar results were also achieved by Lombardo et al.[46] by prolonging high dose (1200 mg daily) rifaximin treatment to 14 days. These Authors studied two specific groups and achieved an eradication rate as high as 87% in PPI users and 91% in IBS patients. Although the setting of our study was slightly different (i.e, we included patients with all the predisposing conditions to SIBO, given the frequent coexistence of different GI disorders in them), nevertheless we obtained similar SIBO eradication rates by combining a shorter course of antibiotic treatment (1200 mg/day rifaximin for 10 days) with the supplementation of a soluble fiber such as PHGG.

Lastly, we observed that, although symptom improvement was higher among patients who obtained SIBO eradication with the combined therapy, this tendency failed to achieve statistical significance. This could be due to the fact that both groups underwent an active treatment, rifaximin, whose efficacy has been already proved, and therefore, clinical amelioration was very high in both groups.

In conclusion, the combined use of rifaximin with PHGG allows us to obtain a higher eradication of SIBO as compared with the use of rifaximin alone. Therefore, the prebiotic effect of PHGG is
likely to provide a synergistic action with rifaximin inside the bowel lumen, by improving intestinal clearance and favoring the microflora balance.
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Acknowledgement

Declaration of personal interests:

Dr. Manuele Furnari was responsible for writing the manuscript, contributed data acquisition and participated in the statistical analysis; Dr Andrea Parodi designed the study and participated in the statistical analysis; Dr Vincenzo Savarino and Dr Edoaardo Giannini participated in the writing of the manuscript and partecipated in the statistical analysis; Dr Lorenzo Gemignani partecipated in the writing of the manuscript and contributed to data acquisition; Dr Simona Marenco, Dr Edoardo Savarino, Dr Lorenzo Assandri, Dr Valentina Fazio, Dr Simona Inferrera, and Dr Daria Bonfanti partecipated in patient management and data collection. All authors have seen and approved the final version of the manuscript. All authors declare that they have no conflicts of interest and that the work is original.

Table 1. Main demographic and clinical characteristics of the study population subdivided according to treatment receive.
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<td>- constipation (c)</td>
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<td>- nausea</td>
<td>6 (16.2%)</td>
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<tr>
<td>- tenesmus</td>
<td>4 (11%)</td>
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n: number of patients; BMI: body mass index; M: male; F: female.

**Figure 1** Flow diagram of the progress through the phases of a randomised trial of two groups (patients within the study, SIBO eradication rates, symptom improvement).
Assessed for eligibility (n=300)

Excluded (n=250)
  - Not meeting inclusion criteria (n=150)
  - Declined to participate (n=100)

Randomized (n=57)

Rifaximin (n=27)

Rifaximin + PHGG (n=40)

Dropout:
  - discontinued intervention: patient preference (n=1)

14 eradicated

33 not eradicated

20 improved

20 not improved

31 improved

31 not improved

GBT: glucose breath test; GSRS: gastrointestinal symptom rating scale.
Figure 1 Flow diagram of the progress through the phases of a randomised trial of two groups (patients within the study, SIBO eradication rates, symptom improvement).

GBT: glucose breath test; GSRS: gastrointestinal symptom rating scale.

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# CONSORT 2010 checklist of information to include when reporting a randomised trial*

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<td>Blinding</td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>11b</td>
<td>If relevant, description of the similarity of interventions</td>
<td>N/A</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant flow (a diagram is strongly recommended)</td>
<td>13a</td>
<td>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
<td>18</td>
</tr>
<tr>
<td>Recruitment</td>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
<td>4</td>
</tr>
<tr>
<td>14b</td>
<td>Why the trial ended or was stopped</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>Baseline data</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
<td>17 (table1)</td>
<td></td>
</tr>
<tr>
<td>Numbers analysed</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
<td>6,7</td>
<td></td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
<td>6,7</td>
<td></td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
<td>N/A</td>
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<tr>
<td>Harms</td>
<td>All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Discussion</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
<td>N/A</td>
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<tr>
<td>Limitations</td>
<td>Generalisability (external validity, applicability) of the trial findings</td>
<td>8-10</td>
<td></td>
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<tr>
<td>Generalisability</td>
<td>Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
<td>8-10</td>
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<tr>
<td>Interpretation</td>
<td>Other information</td>
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<tr>
<td>Registration</td>
<td>Registration number and name of trial registry</td>
<td>N/A</td>
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<tr>
<td>Protocol</td>
<td>Where the full trial protocol can be accessed, if available</td>
<td>N/A</td>
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</tr>
<tr>
<td>Funding</td>
<td>Sources of funding and other support (such as supply of drugs), role of funders</td>
<td>N/A</td>
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</tbody>
</table>