Efficacy and Safety of High Specific Volume Polysaccharide—A New Type of Dietary Fiber for Treatment of Functional Constipation and IBS-C

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(Received July 22, 2014)

Summary We investigated the efficacy and safety of a new type of dietary fiber (high specific volume polysaccharide) for use in treating constipation of different etiologies. Functional constipation patients and irritable bowel syndrome-constipation (IBS-C) patients were administrated high specific volume polysaccharide (HSVP) three times daily for a period of 2 wk to relieve their symptoms. Scores on a stool form scale, and patient reports of straining during a bowel movement, having sensations of an incomplete bowel movement or a blocked anorectum, and abnormal defecation intervals were recorded, graded, and scored by a functional constipation sample group. Similarly, a cohort of IBS-C patients reported their occurrence of abdominal discomfort or pain, abnormal stool formation, defecation frequency, and straining during a bowel movement. Additionally, both groups reported any adverse reactions associated with taking HSVP. All patients in both groups returned for follow-up visits, and no adverse reactions to treatment with HSVP were reported. In the functional constipation group, HSVP was effective for treating symptoms of constipation in 81.46% and 93.17% of patients after 7 and 14 d of dosing, respectively (both p<0.05). In the IBS-C group, symptoms of constipation were relieved in 71.67% and 88.34% of patients after 7 and 14 d of dosing, respectively (both p<0.05). High specific volume polysaccharide was shown be effective for treatment of functional constipation and IBS-C, without causing significant adverse events.

Key Words high specific volume polysaccharide, functional constipation, irritable bowel syndrome-constipation (IBS-C), constipation

Chronic constipation is a common disorder, with a median prevalence of 16% (range 0.7–79%) among adults throughout the world. Some studies have suggested that the prevalence of constipation is higher in the nonwhite than the white population (1), and comprises a variety of functional gastrointestinal disorders. Functional constipation is characterized by lumpy/hard stools, abnormal stool passage (straining during a bowel movement; feeling of an incomplete bowel movement or blocked anorectum) and other symptoms (2). Irritable bowel syndrome-constipation (IBS-C) is a type of IBS characterized by abdominal pain or discomfort, lumpy/hard stools, and abnormal stool passage (straining, or feeling of incomplete evacuation) (2, 3). Although the pathophysiology of constipation is multifactorial and not yet fully understood, considerable evidence supports involvement of the microbiome, immune function, diet, genetics, psychological distress, and recent environmental stress as contributing factors (4). Epidemiological studies have shown a positive correlation between the symptoms of constipation and dietary fiber intake (5), and fiber supplements have been shown to increase stool output and decrease transit time. Dietary fiber, and particularly wheat bran (Testa Triticum Tricum), which is a unique patent medicine composed of dietary fiber in China (6–8), is commonly recommended as a treatment for chronic constipation; however, this substance is very expensive. Additionally, economic factors often make it difficult to obtain conventional drugs. High specific volume polysaccharide (HSVP) is a polymerized polysaccharide extracted from the outer layer of Artemisia sphaerocephala Krasch (AsK) seeds by the Key Laboratory of Polymer Ecomaterials, Chinese Academy of Sciences. A proposed partial structure for HSVP is shown in Fig. 1 [(R can be one or several of the following groups: (3-α-Araf)n, T-α-Galp, T-α-Glcp, T-Araf or T-Arap)]. AsK seeds contain D-glucose, D-galactose, D-mannose, α-L-arabinose, and DL-xylose, and are a traditional Chinese herb and food additive with reported antidiabetic, detumescent, and antioxidant effects. They are also widely utilized as a thickener, stabilizer, water retention agent or film forming agent (8). In a mouse acute oral toxicity test, HSVP demonstrated an LD₅₀>10 g/kg, indicating its low level of toxicity. In China, Artemisia polysaccharide was extracted from AsK seeds in 1985 and showed a molecular weight of ~30 kDa. However, the molecular weight of HSVP is 50.82 kDa, which is much higher than those of other
common polysaccharides. This high molecular weight enables HSVP to absorb relatively large amounts of water.

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of The Second Hospital of Jilin University, China. Written informed consent was obtained from individual participants. Additionally, results of a micronucleus test, spermatogenetic aberration test, and Ames test were all negative (9). Key Laboratory of Polymer Ecomaterials, Chinese Academy of Sciences, has demonstrated that HSVP can increase fecal weight, water content, and volume, and decrease fecal rigidity. Here, we report the efficacy and safety of HSVP in treatment of functional constipation and IBS-C.

MATERIALS AND METHODS

Study design. We conducted a 2-wk study at The Second Hospital of Jilin University in China from June 2010 to October 2013. Eligible patients with complaints of constipation were randomly selected among out-patients and in-patients in our clinic. This study was approved by the Ethics Committee of The Second Hospital of Jilin University, and all enrolled patients provided their signed informed consent. All patients completed an investigator’s questionnaire to determine the severity of their symptoms at baseline (screening visit), and provided responses on a visual analogue scale (VAS) and Bristol scale (10) (Fig. 2 and Table 1). Additionally, the patients also used the VAS and Bristol scales to record the severity of their symptoms in a daily diary (before bedtime) during the 2-wk duration of our study. The patients were then assigned to a functional constipation group (110 females, 95 males; mean age 54 y, range, 20–66 y) or an IBS-C group (34 females, 26 males; mean age 50 y, range 18–60 y) for completion of the study. Patients in the functional constipation group provided evaluations of stool form (Bristol scale for stool form; Table 1), straining during a bowel movement, feelings of having an incomplete bowel movement, feelings of having a block anorectum (VAS, Fig. 2 and Table 2), and experiencing prolonged defecation intervals. Patients in the IBS-C group provided evaluations of stool form, frequency and duration of abdominal discomfort or pain, and straining during a bowel movement (Fig. 2 and Table 3). After 14 d of dosing with HSVP, the patients in both groups completed the investigator’s scale and were then prescribed medicinal charcoal tablets to investigate the effects on defecation intervals. All patients were continuously monitored for adverse events (AEs) on a daily basis. Other safety parameters (vital signs and clinical laboratory parameters) were ascertained on a weekly basis.

Subjects.

Inclusion criteria: Males and females aged ≥18 y and with a diagnosis of either functional constipation (Rome III criteria) or IBS-C (Rome III criteria) during the preceding 12 mo, and a mean baseline disease evaluation score ≥3 were eligible for inclusion in this study.

The Rome III diagnostic criteria for IBS-C were as follows: Recurrent abdominal pain or discomfort for at least 3 d/mo during the last 3 mo, and associated with two or more of the following characteristics:

1. Symptoms improved with defecation.
2. Onset was associated with a change in bowel habit.
3. Onset was associated with a change in frequency of defecation.

The individual criterion must have been met for 3 mo, and symptom onset must have occurred at least 6 mo prior to diagnosis. The patients were informed that the word “discomfort” refers to an uncomfortable sensation that would not be described as pain. When conducting
pathophysiology research and clinical trials, a pain/discomfort frequency ≥2 d/wk during a screening evaluation is recommended for subject eligibility.

The Rome III criteria for functional constipation state that criteria must be fulfilled for the last 3 mo, with symptom onset at least 6 mo prior to diagnosis. The symptoms must include two or more of the following:

1. Straining during ≥25% of defecations.
2. Lumpy or hard stools in ≥25% of defecations.
3. Sensation of incomplete evacuation for ≥25% of defecations.
4. Sensation of anorectal obstruction/blockage for ≥25% of defecations.
5. Manual maneuvers (e.g., digital evacuation, support of the pelvic floor) needed to facilitate ≥25% of defecations.
6. Fewer than three defecations per week.
7. Loose stools rarely present without the use of laxatives.
8. Insufficient criteria for irritable bowel syndrome.

Subject exclusion criteria: Subjects were excluded from participation in the study if they satisfied any of the following criteria.

1. Organic constipation was determined by examination with a fibro-colonoscope and an extensive series of screening investigations (parkinsonism, megacolon, rectocele, pelvic floor muscle spasms).
2. Drug or alcohol induced constipation.
3. Neurological and psychiatric disorders.
4. Prior physiotherapy due to defecation.
5. Use of a gastrointestinal motility drug in the preceding 12 mo.
6. Endocrine and metabolic disorders (hypothyroidism, hypercalcemia, diabetes mellitus, and diabetes insipidus).

Termination criteria: Patients were terminated from the study if they had taken a gastrointestinal motility drug during the observation period, experienced unbearable abdominal pain or discomfort during the observation, or were lost to follow-up.

**Treatment administration methods.** Subjects received oral administration of HSVP (5 g) dissolved in 150–200 mL of boiled water three times daily prior to meals for a period of 2 wk to relieve their symptoms. During the period of treatment, patients maintained their usual dietary intake, and completed the investigator’s scale at the end of 7 and 14 d of dosing. After 14 d of dosing with HSVP, the patients were prescribed Medicinal Charcoal Tablets (0.6 g) to be taken at breakfast time, and then recorded their defecation intervals.

**Efficacy evaluation methods.** Scores for reduced symptom rates were calculated as: (score after therapy − score before therapy)/score before therapy × 100%. Effectiveness was rated as excellent, effective, generally effective, or ineffective when the mean scores were reduced by ≥75%, >50% but <75%, ≥25% but <50%, and <25%, respectively. The rate of excellent effectiveness was calculated as: excellent effective rate = excellent effective sample size/total sample size. Accordingly, other rates of effectiveness were calculated as follows: effective rate = effective sample size/total sample size; generally effective rate = generally effective sample size/total sample size; ineffective rate = ineffective sample size/total sample size. Effectiveness rates were calculated as: effectiveness rate = excellent effective rate + effective rate.

**Safety evaluation methods.** Testa Triticum Tricum (Trifyba-Labaz, AstraZeneca AB) is a patent medicine composed of dietary fiber, and its use is associated with adverse events including bloating and berborigmo. In this study, bloating and berborigmo were reported as the main adverse events, and patients were continuously monitored by daily evaluations conducted from week 0 to week 2, followed by evaluations conducted every 5 d

### Table 2. Functional constipation group evaluation scale.

<table>
<thead>
<tr>
<th>Score</th>
<th>Stool form</th>
<th>Straining during a bowel movement (VAS)</th>
<th>Feeling of incomplete bowel movement (VAS)</th>
<th>Feeling of blocked anorectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Type 7–4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Type 3</td>
<td>1–2</td>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>2</td>
<td>Type 2</td>
<td>3–5</td>
<td>3–5</td>
<td>3–5</td>
</tr>
<tr>
<td>3</td>
<td>Type 1</td>
<td>6–10</td>
<td>6–10</td>
<td>6–10</td>
</tr>
</tbody>
</table>

### Table 3. IBS-C Group Evaluation Scale.

<table>
<thead>
<tr>
<th>Score</th>
<th>Abdominal discomfort or pain frequency</th>
<th>Abdominal discomfort or pain duration (h)</th>
<th>Abnormal stool form frequency</th>
<th>Straining during a bowel movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>never</td>
<td>0</td>
<td>never</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>occasionally</td>
<td>&gt;0, ≤1</td>
<td>occasionally</td>
<td>1–2</td>
</tr>
<tr>
<td>2</td>
<td>often</td>
<td>&gt;1, ≤3</td>
<td>often</td>
<td>3–5</td>
</tr>
<tr>
<td>3</td>
<td>frequently</td>
<td>&gt;3</td>
<td>frequently</td>
<td>6–10</td>
</tr>
</tbody>
</table>
between week 3 and week 4. Other safety parameters (vital signs and clinical laboratory parameters) were ascertained on a weekly basis.

Ethics consideration. *Artemisia sphaerocephala* Krasch (12) is a traditional Chinese herb and food additive; however, it is not regarded to be a medicine. The acute oral LD50 of >10 g/kg obtained from a mouse oral acute toxicity study suggests its extremely low level of toxicity. Additionally, results from mouse micronucleus, spermatic aberration and an Ames tests were all negative (9).

Statistical methods. Data were analyzed using SPSS for Windows, Version 11.0 (SPSS Inc., Chicago, IL). The paired *t* test and non-parametric test were used for determining the statistical significance of differences. A *p*-value <0.05 was regarded as statistically significant, and results are expressed as the mean ±SD. Results with an abnormal distribution of values are expressed as the mean (scope).

RESULTS

Functional constipation group scores for clinical outcomes

Patients in the functional constipation group demonstrated high rates of remission on days 7 and 14 of HSVP treatment (Fig. 3). The stool form score declined from 2.26 ± 0.81 to 1.08 ± 0.29 (*p*<0.05) on day 7, and further declined to 0.04 ± 0.26 on day 14. Scores for straining during a bowel movement score declined...
from 2.87 ± 0.41 to 1.00 ± 0.61 on day 7, and then declined to 0.38 ± 0.59 on day 14 (p < 0.05). Scores for sensing an incomplete bowel movement declined from 2.86 ± 0.43 to 1.11 ± 0.62 on day 7, and further declined to 0.55 ± 0.76 on day 14 (p < 0.05). Finally, scores for sensing a blocked anorectum declined from 2.45 ± 0.64 to 1.69 ± 0.66 on day 7, and further declined to 0.49 ± 0.57 on day 14 (p < 0.05). A comparison of scores at the 7 and 14 d time points showed continued significant decreases (p < 0.05). Additionally, the mean of defecation interval decreased from 151.68 (16–360) to 27.29 (8–47) on days 0 and 14, respectively.

IBS-C group scores for clinical outcomes
Scores in the IBS-C group decreased with HSVP treatment on both days 7 and 14 (Fig. 4). The score for frequency of abdominal discomfort or pain declined from 2.30 ± 0.77 to 1.15 ± 0.72 (p < 0.05) on day 7, and then to 0.53 ± 0.62 on day 14. The mean score for duration of abdominal discomfort or pain declined from 2.40 ± 0.74 to 1.48 ± 0.87 on day 7, and further declined to 0.57 ± 0.83 on day 14 (p < 0.05).

The score for frequency of abnormal stool forms declined from 2.27 ± 0.73 to 1.05 ± 0.77 on day 7, and further declined to 0.35 ± 0.48 on day 14 (p < 0.05). The score for straining during a bowel movement declined from 2.30 ± 0.72 to 1.35 ± 0.88 on day 7, and further declined to 0.22 ± 0.42 on day 14 (p < 0.05). A comparison of scores at the 7 and 14 d time points showed a significant decreasing trend in symptoms of constipation (p < 0.05).

Effectiveness rates
Patients in the functional constipation group showed total effectiveness rates of 81.47% and 93.17% at days 7 and 14, respectively (p < 0.05), and excellent effectiveness rates of 14.15% and 80.00% at days 7 and 14, respectively (p < 0.05). The rates of effective effectiveness in the group were 67.32% at day 7 and 13.17% at day 14 (p < 0.05). The total rates of effectiveness in the IBS-C group were 71.67% at day 7 and 88.34% at day 14 (p < 0.05). Excellent effectiveness was shown in 21.67% and 66.67% of patients at days 7 and days 14 (p < 0.05), respectively, while effective effectiveness was shown in 50.00% and 21.67% of patients at days 7 and 14, respectively (p < 0.05) (Fig. 5).

Safety outcomes
All patients in both groups were follow-up. No occurrence of bloating or berborigmo was reported during 14 d, and all patients had stable vital signs and clinical laboratory parameters. There were 2 lung infections during the induction period; however, these cases were not considered to be related to HSVP.

DISCUSSION

Our results showed that HSVP was effective for treating constipation. Symptoms in both the functional constipation group and IBS-C group were relieved by oral administration of HSVP. In the functional constipation group, HSVP softened stools, relieved straining during bowel movements, relieved the feeling of having an incomplete bowel movement or a blocked anorectum, and also decreased the interval between defecations. Patients in the IBS-C group reported relief from abdominal discomfort or pain, having abnormal stool forms, and straining during bowel movements. The use of most traditional laxatives is accompanied by increased rates of morbidity and adverse events, and little evidence is available regarding their safety and efficacy in the long-term treatment of chronic constipation. The long-term use or abuse of laxatives may cause drug resistance, drug dependence, colon melanosis, and even cancer. Although stimulating laxatives such as bisacodyl, sodium picosulphate, and sennosides have been tried, these agents were introduced in an era when high-quality trials were not performed, and their effectiveness and long-term safety have not been determined in placebo-controlled trials. While complex interactions between
the central and enteric nervous systems often circumcribe the effectiveness of specific therapies, the use of dietary fiber for treating functional constipation and IBS is honored. Additionally, HSVP cannot be absorbed by the intestines, and can be used to stimulate defecation with almost no toxic side effects. We therefore believe that HSVP can be prescribed as a safe treatment for constipation.

The pathophysiology of constipation is multifactorial, and not yet fully understood. However, an individual’s diet, microbiome, immune function, genetics, level of psychological distress, and recent exposure to environmental stress all contribute to development of functional constipation and IBS-C. Our study is limited by its small number of patients and the lack of demographic and behavioral information for the participants. Such information includes the presence of co-morbidities, a history of recent exposure to environmental stress, smoking or psychological distress, and information on the educational levels of the patients.

In conclusion, HSVP represents a new type of dietary fiber which can be used to treat functional constipation and IBS-C without significant adverse effects.

REFERENCES

9) Bai SN, Yong TW, Yun XF. 2000. Survey and prospect of the studies on the extraction of oil and glue from artemisia. Pressure Vessel Technol 18: 17–23.