Clinical Safety of Selected Ayurvedic Formulations in Management of Irritable Bowel Syndrome

ABSTRACT

Introduction: Irritable bowel syndrome (IBS) is a part of the larger group of functional gastrointestinal (GI) disorders that despite differences in location and symptom patterns share common features with regard to their motor and sensory physiology and central nervous system relationships. It generates a significant health care burden and can severely impair quality of life. It is characterized by symptoms of abdominal pain and discomfort that is associated with disturbed defecation. Ayurveda compares the symptoms of IBS with some of the diseases like Grahani (Ayurveda), 5 associated with disturbed defecation. Ayurveda compares the symptoms of IBS with some of the diseases like Grahani, Kaphaja Pravahika, Shokaja Atisara, Bhayaja Atisara, etc. Bilvadi Leha and Kutajarishta are two common Ayurvedic formulations that are currently used for the management of such diseases. However, the safety of these drugs was not evaluated until now.

Objective: Analysis of clinical safety and efficacy outcomes of Bilvadi Leha and Kutajarishta in IBS generated through multicenter open-label clinical studies at different CCRAS centers.

Materials and methods: Analysis of data collected from two different clinical studies was critically evaluated. Safety assessments were done through analyzing liver function tests (LFTs), alanine aminotransferase, aspartate aminotransferase, serum alkaline phosphatase, serum protein, albumin, globulin, and bilirubin, and kidney function tests (KFTs) before and after the trial period. Paired sample t-test was used for comparison. A p-value < 0.05 was considered significant. Drug compliance and adverse drug reaction/adverse events, if any, were noted.

Conclusion: The analysis of two different clinical studies clearly reveals that Bilvadi Leha and Kutajarishta are clinically safe, effective, and tolerable.

Keywords: Bhayaja Atisara, Bilvadi Leha, Grahani, Kaphaja Pravahika, Kutajarishta, Shokaja Atisara.


Source of support: Nil

Conflict of interest: None

INTRODUCTION

Irritable bowel syndrome is a GI disorder characterized by altered bowel habits in association with abdominal discomfort or pain in the absence of detectable structural and biochemical abnormalities. It basically happens due to alteration in GI motility, secretion, and sensation. The symptomatic analysis of IBS, points to Grahani, Kaphaja Pravahika, Shokaja Atisara, Bhayaja Atisara, etc., mentioned in Ayurveda classics which are characterized by altered bowel habits and other GI symptoms.

The pathogenesis of Grahani begins with the vitiation of Agni (digestive fire) in terms of its quality, quantity, and function. All metabolic physiological transformations in the body are carried out under the influence of Agni. Mandagni (quantitative, qualitative, and functional decrease of Agni) is the root cause of Ama Dosha, and it is a crucial factor for manifestation of most of the diseases. Ama Dosha, resulting from Mandagni, plays a pivotal role in the pathogenesis of GI disorders, such as Grahani Roga, Bhayaj Atisara, Shokaj Atisara, etc. Vitiation of Samana and Apana Vayu affects the enteric nervous system, alters the GI motility and hormone activity producing the symptoms of Grahani. All these diseases have psychological factors, such as fear and anxiety as etiology, and IBS also has psychological factors responsible for its origin.

The modern IBS therapies include bulk-forming agents, anti diarrheal, antispasmodics, antidepressants,
etc., which lack demonstrable efficacy. While considering the cost and potential risks (severe constipation, severe diarrhea, ischemic colitis) against potential benefits, potential risks outweigh the possible benefits. Therefore, exploring alternative medicines for therapeutic options, which are effective, economical, and safe, is needed.

Bilvadi Leha and Kutajarishta are two of the drugs used in diseases which are symptomatically similar to IBS and have been practiced by many practitioners. This set of studies was done to analyze the safety of Bilvadi Leha and Kutajarishta in IBS.

**Drug Profile**

The drugs that act on regulating the Agni and movement of Koshta must contain the following properties: Agnideepana (enhancing the digestive activity), Anapachana (eliminating undigested metabolic products), Vata Anulomana (regulating samana and apana and normalising its activity) and should act at the level of Koshta and modulate the altered GI activity. The set of two studies was done to analyze the safety of Bilvadi Leha and Kutajarishta in patients with IBS. Bilvadi Leha is a formulation mentioned in Sahasrayoga (Lehaprakaran-I), Kutajarishta is described in the context of Atisara in Bhaishajya Ratnavali (atisar adhikar).

**OBJECTIVE**

Critical analysis and presentation of clinical safety outcomes of classical Ayurvedic formulations Bilvadi Leha and Kutajarishta in IBS, generated through multicenter open-label clinical studies at different CCRAS centers.

**MATERIALS AND METHODS**

Two different clinical trials, viz. Clinical Evaluation of Bilvadi Leha in the Management of IBS (trial 1) with CTRI number CTRI/2012/04/002577 and Clinical Evaluation of Kutajarishta in the Management of IBS (trial 2) with CTRI number CTRI/2014/09/005066, were done separately at three different centers. The formulations fulfilling the physicochemical standards and quality parameters and prepared as per standard operating procedures laid down in Ayurvedic Pharmacopia of India (Part II) were procured from good manufacturing practices-certified companies for both the studies. Both the clinical studies were also approved by institutional ethics committee and done in accordance with World Health Organization (WHO)—Good Clinical Practice Guidelines. Sample size used for analysis was 163 for trial 1 and 178 for trial 2.

Bilvadi Leha was given as the dose of 10 gm BD with lukewarm water after food (trial 1) and Kutajarishta was given as 25 mL BD with equal amount of water after food (trial 2). Follow-up was done every 2 weeks in both the trials to record the onset of any adverse reaction during the intervention. Total intervention period was 12 weeks. The data obtained from the completed clinical studies were analyzed retrospectively to assess the safety profile of Bilvadi Leha and Kutajarishta through LFTs and KFTs.

**Statistical Analysis**

Data of LFTs and KFTs collected at the beginning and at the end of the trial period were compared using paired t-tests. A p-value <0.05 was considered significant. Clinical symptoms have been reported as n (%) and have been compared as percentage change before and after the treatment.

**OBSERVATION AND RESULTS**

**Bilvadi Leha**

A total of 171 patients were enrolled in study I entitled Clinical Evaluation of Bilvadi Leha in the Management of IBS of which 22 patients dropped out in the course of the study. Among the total dropouts, 8 were not included for analysis. Last observation carried forward was applied on 14 patients who had completed at least two visits. Thus, data of 163 (171 – 22 + 14) patients were used for analysis. Among the dropout patients, no one quit the study for the reason of drug’s safety or palatability issues, so it is clear that the medicine had not any adverse effect on their health.

Among the total analyzed 163 patients, 66.9% were males and remaining 33.1% were females. The mean age of 163 patients was observed to be 42.88. Total 54% of the patients hailed from urban area. Maximum number of patients (47.8%) was doing desk work with less physical activity, and 84% were above poverty line. About 92.6% of the patients were able to read and write. The history of stress was identified in 50.9% of patients, and 55.8% of the population were vegetarian. Irregular bowel habits were seen in 92.0% patients. Loose stool consistency was seen in 67.5% cases.

Effect of Bilvadi Leha on disease-specific symptoms, IBS severity score, and WHO quality of life (QOL)-BREF score was statistically significant (p-value <0.001). Chronic or recurrent abdominal discomfort was present in 90.8% of cases at baseline, and after completion of treatment it remained only in 26.4%. Likewise, abdominal bloating was present in 89.6% cases at the baseline, which was reduced to 42.3% at the end of day 84. No significant adverse events or adverse reactions were observed during the study. Both, the LFTs and KFTs were found to be in normal limits before and after the trial.
Clinical Evaluation of Kutajarishta in the Management of IBS of which 10 patients dropped out in the course of the study. Last observation carried forward was applied on 8 patients who had completed at least two visits. Thus, data of 178 (180 – 10 + 8) patients was used for analysis. The dropout patients were not included in the study, as they could not turn up for follow-up in time due to their prior engagement out of the city. One patient reported increased frequency of bowels and did not continue the study.

Among those 178 patients, majority of patients were under the age group from 39 to 48 years, i.e., 37.6% (67 patients). About 60.7% of them were males and remaining 39.3% were females. Total 92.7% were literate, and remaining 7.3% were non-literate. Major symptoms noted in the patients were irregular bowel habits in 81.5% cases and loose stools in 81.5% cases. Effect of Kutajarishta on chief complaints, disease-specific symptoms, IBS severity score, and WHO QOL-BREF score was highly significant (p < 0.001), for example, chronic or recurrent abdominal discomfort or pain was present in 99.4% of cases at baseline, and after completion of treatment it was present in 24.7% of cases. Likewise, urgency of bowel movements was present in 86.5% cases at the baseline, which was reduced to 16.3% at the end of day 84. No significant adverse events or adverse reactions were observed during the study. Both, the LFTs and KFTs were found to be in normal limits before and after the trial. The data regarding demographic profile are given in Table 1, and safety parameters obtained from the three centers are given in Table 2 and Graphs 1 to 4.

DISCUSSION
Irritable bowel syndrome is a functional GI disorder characterized by abdominal pain or discomfort, altered

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Bilvadi Leha</th>
<th>Kutajarishta</th>
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<tbody>
<tr>
<td>LFT</td>
<td>Baseline</td>
<td>Day 84</td>
</tr>
<tr>
<td>Conjugated bilirubin (mg/dL)</td>
<td>0.18 (0.113)</td>
<td>0.16 (0.096)</td>
</tr>
<tr>
<td>Unconjugated bilirubin (mg/dL)</td>
<td>0.49 (0.215)</td>
<td>0.49 (0.162)</td>
</tr>
<tr>
<td>SGPT (ALT) (IU/L)</td>
<td>26.39 (12.925)</td>
<td>23.78 (11.324)</td>
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<td>SGOT (AST) (IU/L)</td>
<td>26.85 (8.988)</td>
<td>25.81 (7.628)</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (IU/L)</td>
<td>148.02 (83.018)</td>
<td>118.11 (91.841)</td>
</tr>
<tr>
<td>Total protein (gm/dL)</td>
<td>7.23 (0.609)</td>
<td>7.23 (0.570)</td>
</tr>
<tr>
<td>Serum albumin (gm/dL)</td>
<td>4.32 (0.489)</td>
<td>4.21 (0.488)</td>
</tr>
<tr>
<td>Serum globulin (gm/dL)</td>
<td>2.92 (0.533)</td>
<td>3.02 (0.475)</td>
</tr>
<tr>
<td>KFT</td>
<td>Blood urea (mg/dL)</td>
<td>24.87 (5.276)</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine (mg/dL)</td>
<td>0.90 (0.150)</td>
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<tr>
<td></td>
<td>Serum uric acid (mg/dL)</td>
<td>5.18 (1.099)</td>
</tr>
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p-value <0.05 is considered significant; AST: Aspartate transaminase; ALT: Alanine transaminase
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bowl habit, and psychiatric symptoms, such as anxiety or depression in the absence of any detectable organic pathology. Movement of food and the faces in the intestines is either too slow or too fast. Although IBS does not cause any threat to life, it can be a long-lasting problem affecting the quality of life. Therefore, treatment of IBS is very important for improving the quality of life in such patients. In Ayurveda, we use drugs having properties like Ama Pachana, Agnideepana, Vatanulomana, and Sangrahi which have nature to treat conditions like Grahani, Kaphaja Atisara, Bhayaja Atisara, Pravahika, etc., which have symptoms similar to IBS. Thus, these two studies were done to see the safety and efficacy of Kuta-jarishta and Bilvadi Leha in the management of IBS.

On analysis, it was observed that majority of IBS patients were having desk work with minimal physical activity as their profession. Physical inactivity may have an indirect role in altering the intestinal motility and may lead to apana vayu vaigunya in koshtha producing alteration in bowel habits. The disease was found mostly in residents of urban region, which may be due to the unhealthy dietary habits and stressful life. Common symptoms manifested were chronic or recurrent abdominal discomfort or pain,
abdominal bloating, urgency of bowel movements, feeling of incomplete evacuation, passage of mucous, straining, distension of abdomen, etc., due to agnimandya leading to ama formation, which causes obstruction (srotosarodha) in the GI pathways. The IBS is a disease that responds well with proper alterations in diet (using food that are easily digestible without stress to GI tract), physical activity and with decrease in stress levels. But, once the disease manifests, maintenance of Agni and Vatanulomana is the right path to relieve symptoms.

In these studies, significant changes were noticed in the qualitative parameters, like Udar Shool (pain in abdomen), diarrhea, chronic or recurrent abdominal discomfort, abdominal bloating, feeling of incomplete evacuation, etc. The safety profile was analyzed through comparing the changes in LFTs and KFTs before and after the trial duration. Drug compliance and development of adverse effects/adverse drug reactions, if any, were scrutinized. In-depth observations revealed that there was not any change in the safety parameters like blood urea, serum uric acid, serum creatinine, total protein, serum globulin, serum albumin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and bilirubin levels in the body. All these parameters were found to be within the stipulated range after treatment also. Hence, it can be concluded that Bilvadi Leha and Kutajarishta are safe and effective in IBS.

CONCLUSION
Irritable bowel syndrome is a condition that significantly affects the quality and productivity of life. Nidana Parivarjana and synchronizing the harmonious activity of Agni and Vata in the intestine are the key factors in managing IBS. Kutajarishta and Bilvadi Leha act by regulating the activity of Doshas and Agni in Koshta. From this study, it can be concluded that in spite of the differences in gender, socioeconomic status, age group, Prakriti, and geographic region, Kutajarishta and Bilvadi Leha proved to be very much safe, effective, and tolerable in the management of IBS. No adverse reactions or adverse events pertaining to drug interaction were noticed during the trial period.

REFERENCES
हिन्दी सारांश

आई.बी.एस. में बच्चन आयुर्वेदिक रोगों की नैदानिक सुखशाक्ति एवं फर्मेको- एपिडेमियोलोजिकल अवलोकन

रेतुः सिंह, 5पुंड़ूः पांडा, 6लक्षण वान गुरुके, 7हरभस सिंह, 8चुंद्रेंद्र के. सार्म, 9कृष्ण कुमारी

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7आग राज सार्म, 8एम. राव, 9रिकु तोंगर, 10छेत्रा चौहानी, 11श्री कबूरु, 12गुणवत्ता सूरैय खान

13बबतायाद, 14प्रदीप दुआ, 15राकेश राणा, 16रिचा सिंहल, 17आदित्य खुमर

कृपया नोट कीजिये: कार्यालय की तौर पर उद्ध रोग के समूह में से आई.बी.एस. एक प्रमुख रोग है, विशेषतः एवं लक्षणों में अत्यंत होने के बाद मैं क्रिया प्रणाली, संबंधी प्रणाली तथा केंद्रीय लस्टिक तंत्र के आचरण पर इनका सामान्य स्वरूप है। आई.बी.एस. का होना व्यापक पर एक रूपांतरण प्रभाव है, जो नीति की स्वायत्त ग्राहक प्रणाली को तुलनात्मक पुष्टि है। इस विषय में कुछ प्रमुख लक्षण इस प्रकार हैं, उदाहरण के लिए- उद्धर में सूक्ष्म, क्षण बढ़ता जीवन का होना, पेट का पुर्यों इलाज के साथ-साथ जीवन तंत्र करते में कठिनाई का होना।

आयुर्वेद में आई.बी.एस. के लक्षणों के समक्ष सम्प्रति एवं लक्षणों वाली कुछ विभेदों का वर्षन विस्तुत रूप से किया गया है जैसे- प्रकृति दोष, कवक प्रासारिक, शरीर अतिरिक्त, मधु अतिरिक्त इत्यादि। विलादि लेख एवं कुट्जा इतिहास दो आयुर्वेदिक विभेदों हैं जिनका उपयोग उपलब्धित व्यापियों की संकल्पना में बुद्धानुसार से किया जाता है।

अध्ययन एवं जटिलता: बहुमंजियता नैदानिक अभ्ययन/अवलोकन द्वारा विल्याम लेख एवं कुट्जा इतिहास की निरस्पदता को आई.बी.एस. में ब्यवस्थित करना।

सामग्री: गुणवत्ता के सभी मानकों की माती-माता जांच करने के परिबाट जी.एम.प्र. नैदानिक कंपनी से दोनों विभेदों, विल्याम लेख एवं कुट्जा इतिहास को प्राप्त किया गया। यह.सी.आर.एस. के अध्ययनों तथा सृष्टियों में अलग-अलग नैदानिक अभ्ययनों से प्राप्त आंकों से स्वस्थ प्रक्रिया ग्रहण तकनीक टेस्ट (से.एफ.टी.) एवं अन्नवेदी टीकन टेस्ट (के.एफ.टी.) का अभ्ययन के पूर्व और परस्पर परीक्षण किया गया। विभेद का प्रतिकृत प्रभाव (ए.सी.एस.एस.एल.) एवं प्रतिकृत परिस्थितियों (ए.डी.) परीक्षण के दौरान इंकार किया गया। सभी मानकों के प्रक्रिया दिन से 84वें दिन के बीच में हुए परीक्षण का युग कुछ दिन टेस्ट द्वारा तुलनात्मक अभ्ययन किया गया। सभी मानकों को पूरी अवधि के दौरान टेस्ट कीमा में पाया गया।

निकाय: दोनों नैदानिक अभ्ययनों के द्वारा स्वयं रूप से इम्प्रेस नं कि विल्याम लेख एवं कुट्जा इतिहास आई.बी.एस. के रोगियों में सुरक्षित एवं प्रभावी है।