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RESEARCH ARTICLE

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

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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*, *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 multi-center 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*.

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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.[1] It basically happens due to alteration in GI motility, secretion, and sensation.[2,3] 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*[4] 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.[5] *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, antidiarrheal, 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.[6] 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), *Amapachana* (eliminating undigested metabolic products), *Vata Anulomana* (regulating *samana* and *apana* and normalising its activity) and should act at the level of *Kostha* 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*[7] is a formulation mentioned in Sahasrayoga (*Lehaprakaran*-1), *Kutajarishta*[8] is described in the context of *Atisara* in *Bhaishajya Ratnawali* (*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.

Kutajarishta

A total of 180 patients were enrolled in the study entitled 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 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 majority of them were having desk work. Also, 92.7% of them were having good socioeconomic status. Urban area-residing patients were 68.5%. Among the total, 68% of the patients were vegetarian. 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.

Table 1: Demographic profile of the patients in both clinical trials

Demographic profile	*Bilvadi Leha (n = 163)*	*Kutajarishta (n = 178)*
Sex		
Male	109 (66.9%)	108 (60.7%)
Female	54 (33.1%)	70 (39.3%)
Education		
Not able to read and write	12 (7.4%)	13 (7.3%)
Literate	151 (92.6)	165 (92.7%)
Socioeconomic status		
Below poverty line	26 (16.0%)	13 (7.3%)
Above poverty line	137 (84.0%)	165 (92.7%)
Diet		
Vegetarian	91 (55.8%)	121 (68.0%)
Nonvegetarian	72 (44.2%)	57 (32.0%)
Prakriti		
Vataja	1 (0.6%)	–
Pittaja	10 (6.1%)	–
Kaphaja	2 (1.2%)	–
Vata-Pittaja	91 (55.8%)	65 (36.1%)
Pitta-Kaphaja	56 (34.4%)	92 (51.1%)
Vata-Kaphaja	1 (0.6%)	23 (12.8%)
Sannipataja	2 (1.2%)	–
Patients completing the trial from different geographical locations		
Jammu	52 (31.9%)	59 (33.1%)
Mandi	53 (32.5%)	60 (33.8%)
Patiala	58 (35.6%)	59 (33.1%)

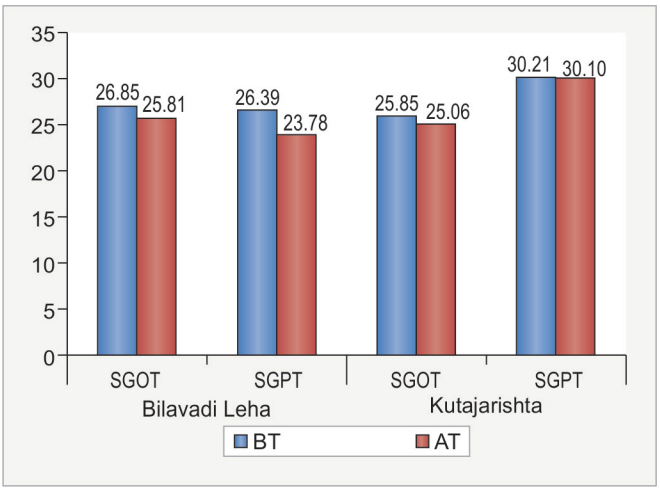
DISCUSSION

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

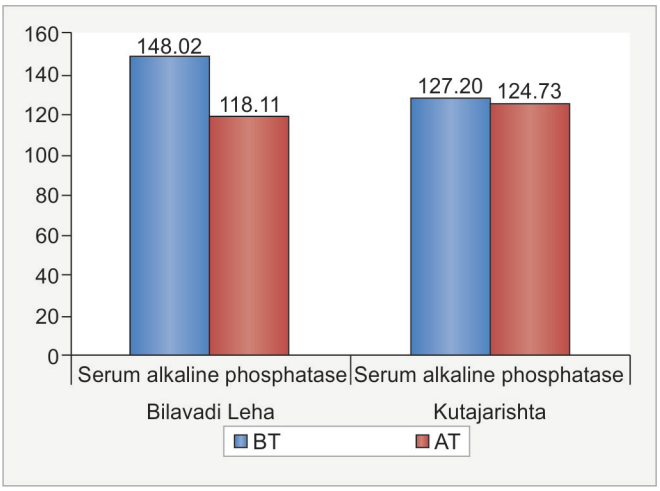
Table 2: Efficacy and safety profile of the patients in both the clinical trials

	Bilvadi Leha			*Kutajarishta*		
Parameters	*Baseline*	*Day 84*	*p-value*	*Baseline*	*Day 84*	*p-value*
LFT						
Conjugated bilirubin (mg/dL) bilirubin (mg/dl) bilirubin (mg/dl)	0.18 (0.113)	0.16 (0.096)	0.047	0.14 (0.096)	0.14 (0.089)	0.966
Unconjugated bilirubin (mg/dL)	0.49 (0.215)	0.49 (0.162)	0.910	0.55 (0.242)	0.55 (0.305)	0.860
SGPT (ALT) (IU/L)	26.39 (12.925)	23.78 (11.324)	<0.001	30.21(14.948)	30.10 (15.350)	0.916
SGOT (AST) (IU/L)	26.85 (8.988)	25.81(7.628)	0.093	25.85 (8.152)	25.06 (8.661)	0.242
Serum alkaline phosphatase (IU/L)	148.02 (83.018)	118.11 (91.841)	<0.001	127.20 (71.525)	124.73 (66.722) (90.40)	0.291
Total protein (gm/dL)	7.23 (0.609)	7.23 (0.570)	0.988	7.12 (0.551)	7.09 (0.582)	0.523
Serum albumin (gm/dL)	4.32 (0.489)	4.21 (0.488)	0.008	4.11 (0.386)	4.06 (0.376)	0.115
Serum globulin (gm/dL)	2.92 (0.533)	3.02 (0.475)	0.086	2.99 (0.525)	3.02 (0.565)	0.517
KFT						
Blood urea (mg/dL)	24.87 (5.276)	25.09 (5.937)	0.626	24.76 (6.594)	24.30 (6.136)	0.446
Serum creatinine (mg/dL)	0.90 (0.150)	0.86 (0.158)	0.002	0.93 (0.512)	0.92 (0.454)	0.871
Serum uric acid (mg/dL)	5.18 (1.099)	5.22 (1.102)	0.593	5.41 (1.1258)	5.35 (1.170)	0.585

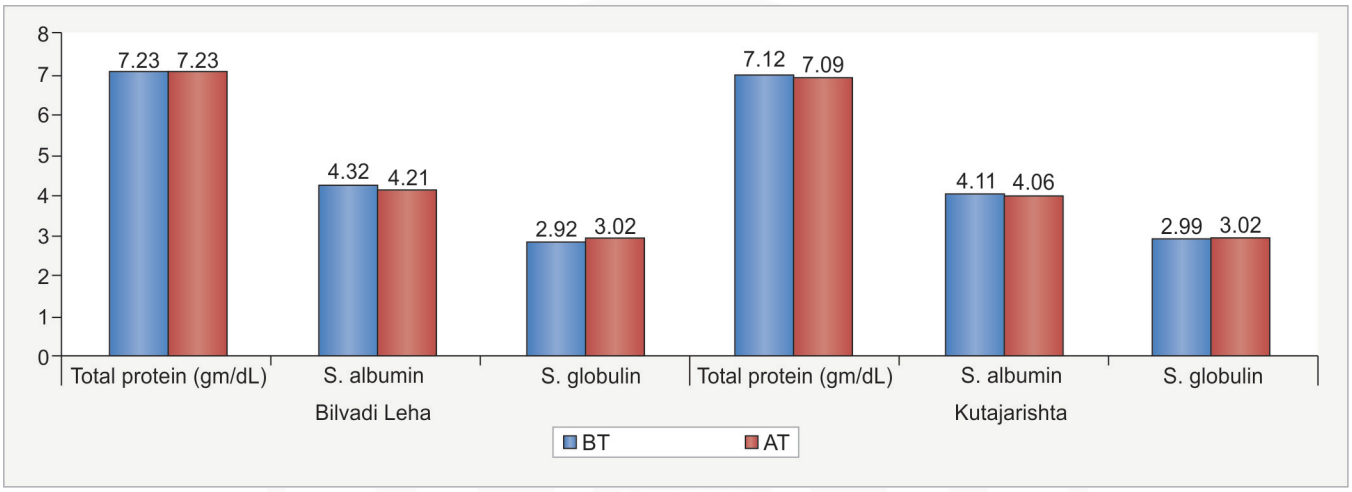
p-value <0.05 is considered significant; AST: Aspartate transaminase; ALT: Alanine transaminase



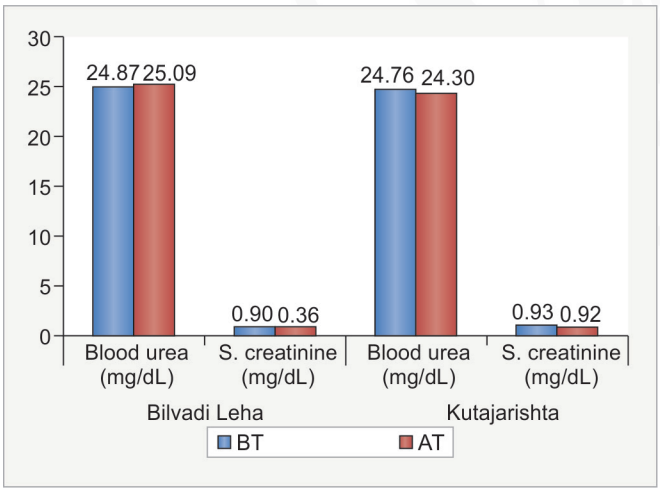
Graph 1: Liver function tests (SGOT and SGPT) before and after the trial



Graph 2: Liver function test (serum alkaline phosphatase) before and after the trial in both the studies



Graph 3: Liver function test (total protein, serum albumin, and serum globulin) before and after the trial in both the studies



Graph 4: Kidney function test (blood urea and serum creatinine) before and after the trial in both the studies

bowel 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 *Kutajarishta* 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 (*srotoavarodha*) 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, *Prakrti*, 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.

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हिन्दी सारांश

आई.बी.एस. में चयनित आयुर्वेदिक रोगों की नैदानिक सुरक्षा एवं फार्मेको–एपिडीमियोलोजिकल अवलोकन

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भूमिका: कार्यात्मक तौर पर उदर रोग के समूह में से आई बी एस एक प्रमुख रोग है, स्थिति एवं लक्षणों में अंतर होने के बाद भी क्रिया प्रणाली, संवेदी प्रणाली तथा केन्द्रीय तंत्रिका तंत्र के आधार पर इनका सामान्य स्वरूप है। आई.बी.एस. का होना स्वास्थ्य पर एक प्रतिकूल प्रभाव है, जो जीवन की स्वाभाविक कार्य प्रणाली को नुकसान पहुचाता है। इस बिमारी के कुछ प्रमुख लक्षण इस प्रकार है, जैसे– उदर में शूल, कभी बद्ध कभी द्रव मल का होना, पेट का फूलना इत्यादि के साथ–साथ मल त्याग करने में कठिनाई का होना।

आयुर्वेद में आई.बी.एस. के लक्षणों के समकक्ष सम्प्राप्ति एवं लक्षणों वाली कुछ व्याधियों का वर्णन विस्तृत रूप से किया गया है जैसे – ग्रहणी दोष, कफज प्रवाहिका, शोकज अतिसार, भयज अतिसार इत्यादि। बिल्वादि लेह एवं कुटजारिष्ट ऐसी दो आयुर्वेदिक औषधियां हैं जिनका उपयोग उपर्लिखित व्याधियों की चिकित्सा में बहुतायत से किया जाता है।

अभिप्राय एवं उद्देश्य: बहुकेंद्रीय नैदानिक अध्ययन/अवलोकन द्वारा बिल्वादि लेह एवं कुटजारिष्ट की निरापदता को आई.बी.एस. में स्थापित करना।

साधन: गुणवता के सभी मानकों की भली–भांति जांच करने के पश्चात जी.एम.पी. प्रमाणित कंपनी से दोनों औषधि योगों, बिल्वादि लेह एवं कुटजारिष्ट को प्राप्त किया गया। सी.सी.आर.ए.एस. के अधीनस्थ तीन संस्थानों में अलग–अलग नैदानिक अध्ययनों से प्राप्त आंकड़ों से विश्लेषण किया गया जिसमें बिल्वादि लेह एवं कुटजारिष्ट के सुरक्षा मापदण्डों को आई.बी.एस. में जैवरासायनिक परिक्षण लीवर फंक्शन टेस्ट (के.एफ.टी.) और किडनी फंक्शन टेस्ट (के.एफ.टी.) का अध्ययन के पूर्व और पश्चात परीक्षण किया गया। औषध का प्रतिकूल प्रभाव (ए.डी.आर.) एवं प्रतिकूल परिस्थिति (ए.इ.) परिक्षण के दौरान इंगित किया गया। सभी मापदण्डों के प्रथम दिन से 84वें दिन के बीच में हुए परिवर्तन का युग्म युक्त टी टेस्ट द्वारा तुलनात्मक अध्ययन किया गया। सभी मापदण्डों को पूरी अवधि के दौरान निर्दिष्ट सीमा में पाया गया।

निष्कर्ष: दोनों नैदानिक अध्ययनों के द्वारा स्पष्ट रूप से इंगित है कि बिल्वादि लेह और कुटजारिष्ट आई.बी.एस. के रोगियों में सुरक्षित एवं प्रभावी हैं।