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Development and Clinical Evaluation of Polyherbal Laxative Laxisen

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ABSTRACT

Constipation being one of the most common and frequently occurring symptoms of gastrointestinal disorders is high in prevalence rate, causing economic burden and badly effecting quality of life. Multiple research studies have been carried out to clinically evaluate, assess and address the treatment for both acute and chronic constipation in adults. However limited evidences are available for the efficacy of available treatment options for the management of constipation. This study is a prospective, open labeled, uni-center and observational clinical trial and was carried out at out-patient department of clinical medicine at Jinnah Medical Center, Korangi, Karachi, Pakistan to evaluate the clinical efficacy and safety of polyherbal formulation Laxisen in 35 patients with complaints of constipation.. The study drug was administered for 1- 2 weeks for acute and 1-6 weeks for chronic constipation patients. After following up patients for specified time period complete remission of constipation was observed and the drug was found significantly effective ($p < 0.003$). The mean weekly frequency of bowl movements was 9.95 for acute constipation while 9.23 for chronic constipation. Significant increase in frequency of the bowl movements was observed for all patients.

Keywords: Polyherbal Laxative formulation, Clinical Trial, Acute and Chronic Constipation, Cassia senna.

INTRODUCTION

Constipation is defined traditionally as three or less bowl movements per week. It is often a long-term and persistent problem and, although half of all constipation sufferers experience symptoms for three or more years, many[1] do not seek medical advice, opting instead for over-the-counter (OTC) remedies that they may continue to take for more than preceding three years[2,3]. However, dissatisfaction with OTC or prescription treatments is quite prevalent, mainly due to lack of efficacy (82% of participants in a US-based survey) and concerns regarding adverse events (AEs) (16%) [4]. The epidemiological survey has cited that prevalence of constipation in the worldwide general population ranges from 0.7% to 79% (median 16%) [5]. Terminalia chebula is used to treat digestive and urinary complaints as well as this plant material is added in triphala formulation[6] which relieves parasitic infection, fevers, flatulence, and constipation.

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Operculina terpethum is commonly used in constipation; abdominal pains along with other medicinal properties of roots have been cited in clinical studies [7]. Convolvulus scammonia extracts exert its effects in the duodenum mixes with excess bile and takes away bile due to its cathartic actions [8]. Cassia senna is well known herbal formulations for its laxative properties used throughout the world for the treatment of constipation. Two anthraquinone glycosides, sennoside A and sennoside B act as a pro drug molecule which acts on fecal bacteria and Senedin is released which is responsible for the characteristics properties of laxation [9]. Rosa damascena plant is also used as a gentle laxative [10] whereas the fruit bark and seed parts of Ficus hispida are emetic and laxative in action [11]. Ripe fruit of Vitis vinifera is laxative in nature [12]. The Laxisen composition is delineated here with in table1.

Table I : Composition of Laxisen

S. NO	INGREDIENTS	LATIN NAMES	PART USED	QUANTITY PER CAPSULE
1	Post halila zard	Terminalia chebula Retz.	Fruit	125 mg
2	Turbad sufaid	Operculina terpethum Linn.	Root	50 mg
34	Saqmonia	Convolvulus scammonia Linn.	Resin(Gum)	50 mg
4	Senna	Cassia senna	Leaves	150 mg
5	Gul-e-surkh	Rosa damascena	Petals	150 mg
6	Injeer zard	Ficus hispida	Fruit	150 mg
7	Maveez-e- munaqqa	Vitis vinifera	Fruit	150 mg
11	Sodium benzoate			0.5 mg
12	Potassium sorbate			0.5 mg

Chemical constituents and bioactivities

The parts of the herb Terminalia chebula used in Laxisen are leaves and fruits, the chemical constituents of these parts are anthraquinones, tannins, chebulic acid etc. In Chinese and Indian system of medicines, the uses of different parts of Terminalia chebula are as a laxative, astringent, improve bowel regularity and purgative [13]. The rhizome part of Convolvulus scammonia contains resins, dihydroxy cinnamic acid, ipuranol, ß-methyl-esculetin. The uses of this herb are described as cathartic, expectorant and purgative [14]. Cassia senna is used as a laxative, stimulant, cathartic typically in Chinese medicine [15]. The constituents of this herb are 1,8 dihydroxyanthracene sennosides, anthraquinone, ß-sitosterol, rhein, dianthrone glucosides, sennosides A, sennosides B, naphthalene glycosides, aloe-emodine, mucilage etc. Operculina turpethum elaborate different types of constituent such as glycosidic resin, terpethin and resin with purgative and cathartic biological activities [16,17]. The leaflets and fruit part of Vitis vinifera showed laxative properties, its fruit is used also in constipation and the main constituents are Linoleic, oleic, palmitic, stearic, malic acids, flavonoids, anthocyanins, tannins, monoterpene glycosides. Ficus hispida fruit contains furanocoumarins, citric acid, malic acid, mono saccharides and the uses of its fruit in folk medicine as laxative and digestive [18]. Rosa damascena is a gentle laxative and boiled extract used as laxative [19] whereas plant contains terpenes, glycosides, flavonoids, and anthocyanins [20-23].

METHODOLOGY

Study Design: The study was a prospective, open-label, non-comparative, uni-center, interventional and exploratory clinical trial.

Objectives

Primary Objectives:

Efficacy evaluation of the polyherbal formulation laxisen was the primary objective of the study. The trial was conducted on patients with constipation and changes in frequency of bowel movements and

stool form were noted. "Bristol stool form scale" [24,25] was used to evaluate the changes in stool form.

Secondary Objectives:
Secondary objectives of the clinical research study were to evaluate the efficacy of polyherbal formulation by assessing improvement in symptoms (i.e., straining on defecation, sensation of incomplete evacuation, time spent on the average for evacuation of bowel), other related symptoms. The safety and side effects were also assed in patients.

Investigational Product:
Laxisen is a polyherbal formulation in capsule form and its composition is shown in table 1. The formulation was manufactured according to current Good Manufacturing Practice (cGMP).

Institutional ethics committee approval and regulatory compliance

The study protocol and all the related documents were reviewed and approved by ethical committee of Jinnah University for Women, Karachi, Pakistan.

Patient Recruitment and Sample Selection
The patients sample was selected from the outpatient's clinical department of Jinnah Medical Center, Korangi, Karachi, Pakistan.

Inclusion Criteria:
Those patients meeting the "Rome III diagnostic criteria for constipation" were included in the study. According to the Rome III criteria for constipation, a patient must have experienced at least 2 of the following symptoms over the preceding 3 months:

- Fewer than 3 bowel movements per week
- Straining
- Lumpy or hard stools
- Sensation of anorectal obstruction
- Sensation of incomplete defecation
- Manual maneuvering required to defecate

Patients presenting a stool form score of a range of 1 to 3 on the "Bristol Stool Form Scale" were also included. Informed consent of all the patients included in the study was taken from the participants and they were asked to fill a self-administered questionnaire. Patients who agreed to follow the study protocol were included in the study.

Exclusion Criteria:
- Severe cardiac, renal or hepatic impairment
- Severe psychiatric disturbance
- Suffering from diabetes and hypertension
- Mental disorder preventing adequate informed consent
- Dilatation of the bowel (megarectum or pseudo-obstruction)
- Concomitant medication with drugs known to cause constipation
- Known pregnancy, suspected pregnancy, or trying to conceive
- Currently breastfeeding
- Currently participating (or within 1 month) in any other study

Study Procedure:
Patients were asked for screening visit. After taking informed consent, they were recruited for study. Those patients suffering from acute or chronic constipation were screened and diagnosis was carried out on the basis of clinical history, Rome-III questionnaire and Bristol stool form scale. Patients were given a washout period of week and they were advised not to use any drug for constipation. Those patients were recruited in the study who fulfilled the inclusion criteria at the baseline visit only. All the main symptom and associated symptoms of constipation were assessed using Bristol stool form scale. All the patients were advised to note their daily bowel evacuation time, other details and other symptoms. The study participants were provided with a bottle containing capsules varying in numbers because of the varying dose for different symptoms. Those with symptoms of acute constipation were given study drug for maximum of two weeks while those with symptoms of chronic constipation were

given dose for maximum of six weeks. Patients were advised to use medication regularly and in case they failed to give follow up on time (delayed for maximum of three days). All the study participants were advised to refrain from all those medications that are known to cause constipation (like aluminum containing ant acids and opioid analgesics and antidepressants). No diet modifications were advised during the study period. All the participants were advised to visit for follow up on the 7th, and 14th days for acute patients and 7th, 14th, 21th, 28th, 35th and 42nd days for chronic patients after the screening visit (day 0). Participants who failed to visit for follow up on specified time were allowed to visit within three days of grace time being given to them. Those failing to comply with the given time for follow up and delayed time of three days were considered as dropouts. Symptoms of the study participants were assessed using the Bristol stool form scale and VAS at every follow-up visit. The investigator's evaluation and patient's evaluation for the overall improvement were carried out on 1st to 2nd follow up for acute constipation and 1st to 6th follow up for chronic constipation. The investigator as well as patients assessed the tolerability of the study drug on last follow up visits for both acute and chronic constipation accordingly. The Investigator also assessed the drug compliance on each follow up visit. During the study period all the participants were monitored for possible adverse effects. At last follow up visit all the patients were checked for the normal physiologic functions. After 2 weeks for acute and 6 weeks for chronic constipation the patients were asked to stop the trial drug. After the stoppage of the study drug all the patients were given a non-laxative period of one week to observe the relapse of the symptoms of constipation.

Statistical Analysis:

SPSS software 22 was used for the statistical analysis of the data. Data of the quantitative variables was expressed in terms of mean or median ± SD. Data representing categorical variables were compared by "Chi-square test". p-values were reported at 95 % confidence interval on the basis of two-sided significance test.

RESULTS

Out of 30 patients 18 patients were evaluated for acute and 12 for chronic constipation and they strictly followed the protocol guidelines and complete data was acquired for assessment of study variables. Out of 30 study subjects 16 were males and 14 were females where as 60 % of the patients included in the study were presented with symptoms of acute constipation while 40 % of the study patients were presented with chronic constipation. The severity of constipation of patients included in this study has been represented in Fig 1.

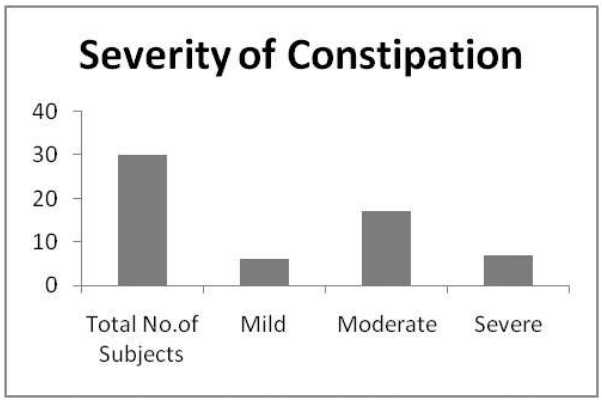

Figure 1 : Severity Of Constipation In Patients

The mean age of the study patients was 41.83 with standard deviation of 11.624. Graphical representation of age and sex distribution of patients is given in Fig 2 and Fig 3 respectively.

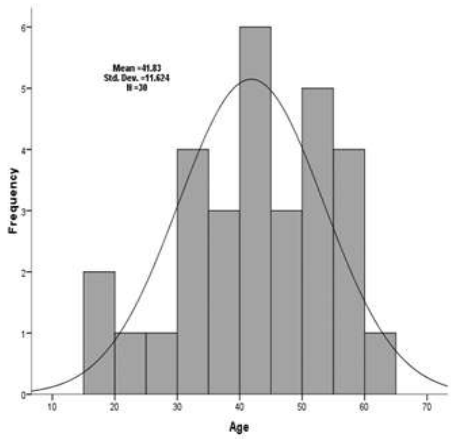

Figure 2 : Age Distribution of The Participant Patients

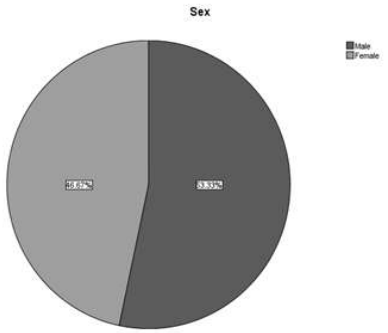

Figure 3 : Sex Distribution of Participant Patients

In case of acute 2, 11 and 5 patients showed mild, moderate ad good effects while in case of chronic 1, 7 and 4 patients out of 30 showed mild, moderate and good results respectively. The efficacy results of laxisen capsule are presented in the form of Fig4.

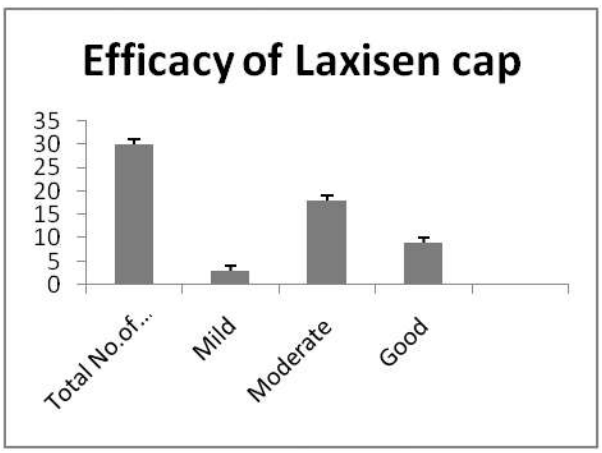

Figure 4 : Efficacy Results of Laxisen Capsule

Most of the patients included in the study were observed for following symptoms on screening visit. The hard and lumpy stool, straining during defecation and sensation of the incomplete evacuation of the bowl. Some of the patients also presented other associated complaints i.e. headache, abdominal blotting, nausea, flatulence, acidity, low back ache and stress. Thirty patients completed the study and no patient was presented with significant changes in the normal physiological signs like blood pressure, pulse rate, respiratory rate and body temperature. All of the 30 evaluable patients did not show any side effects or adverse effects and no one of the study patients was withdrawn from or dropped out of the study because of adverse effects. The mean weekly frequency of bowl movements in the study participants was 9.95 for acute constipation while 9.23 for chronic constipation. During the follow up visits significant increase in frequency of the bowl movements was observed for acute patients and was reported to be 18.20 and for chronic constipation it was noted on last follow up visit and it was observed to be 17.07. The data for the change in frequency of the bowel movements showed significant increase for both acute and chronic constipation. Assessment of changes in stool form was done on "Bristol Stool Form Scale" and was evaluated as a mean weekly score ranging from 1 to 7. There was significant increase in mean weekly score of stool form on each follow up visit for almost all the study participants.

DISCUSSION

The data of the clinical trial conducted for the evaluation of safety and efficacy of the polyherbal formulation Laxisen confirm its beneficial effects. Laxisen significantly increased the bowel movements frequency in the patients with acute as well as chronic constipation. From the data it can be inferred that the polyherbal formulation is equally effective in both acute and chronic constipation. After the non-laxative period of seven days the increase in the mean frequency of the bowel movements was not clinically and statistically significant instead a slight increase from the baseline value. A statistically significant improvement for straining and difficulty during defecation and sensation of incomplete evacuation was observed. The mean score of straining during defecation on the last follow up visit and the difference between the screening day values (day 0) and the last follow up visit was clinically significant. The difference between the mean values of straining during defecation and anorectal blockade on the screening day visit and the mean values after the non-laxative period of one week was also clinically significant. Clinically significant decrease in the time spent on toilet for bowel evacuation was observed after the last follow up visit i.e. 1st – 2nd

follow up for acute patients while 1st – 6th for chronic constipation. Although the mean average time spent on toilet for bowel evacuation after the non-laxative period slightly increased in comparison with the mean values obtained on last follow up visit. Still a decrease was observed in the mean values compared with the baseline values. High standard deviation was observed in the clinical study data. Small sample size and the efficacy response variability might be a possible reason for high standard deviation. Improvement in the mean score of clinical manifestations of other associated symptoms like flatulence, acidity, blotting and belching was statistically significant in the study participants at all follow up visits. 30% of the patients showed good results, 60% showed moderate results while 10 % were presented with mild effects. No side effects were observed in the study patients. All the patients were monitored for non-laxative period of seven days after the last follow up visit. Improvements in the symptoms of constipation of the study participants were observed from mild to good and all the participants were observed for the relapse of the symptoms during the non-laxative period. None of the study participants showed any relapse of the symptoms. The study drug showed significant result as compared to previous clinical studies on Cassia senna. This is attributed the synergistic effect of the herbs like Terminalia chebula, operculina turpethum, Convolvulus scammonia, Rosa damascena, Ficus hispida and Vitis vinifera that are added in order to increase the laxative properties of Cassia senna. In the present clinical trial significant improvement in the bowel movement frequency and stool form was observed. The study drug was used in capsule [26] form and the patients were observed for side effects as well as adverse effects. No side effects or adverse effects were reported by the study participants. The study participants showed good tolerability (100%) to the study drug. No statistically significant changes in the normal physiological functions of the study participants were observed which confirm that the study drug is a safe and effective formulation for the management of constipation. All of the ingredients formulated in the study drug have laxative and purgative properties. Although the exact mechanism of action could not be understood from the clinical trial, probably the synergistic effect of the ingredients constitutes it a balanced formulation for the management of constipation. Cassia senna alone is supposed to be a habit forming laxative agent [27], while Laxisen did not show any habit-forming effect. This clinical trial was conducted to obtain the efficacy assessment on the study drug Laxisen, therefore, an open label and pilot study was conducted on small sample size. To ensure and endorse the above findings, double blind randomized controlled comparative clinical studies on larger sample size are suggested.

CONCLUSION

From the above data and its statistical analysis it can be concluded that the polyherbal formulation Laxisen is effective laxative formulation in the treatment of both acute and chronic constipation. 1-2 weeks of treatment for acute constipation and 1-6 weeks of treatment for chronic constipation with Laxisen showed significant results. All patients were given a non-laxative period of one week and it was observed that the drug also prevented the relapse of most of the symptoms of constipation for one week. Safety of the study was evaluated by monitoring the participants for any side effects or adverse effects and they did not show any side effects or adverse effects. From above study findings it was found that Laxisen is safe and effective polyherbal laxative formulation for the treatment of constipation.

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Conflicts of interest

We declare that we have no conflict of interest.

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