A Clinical Trial of Multi Herbal Preparation (EZCol®) Syrup for Constipation in Pakistani Population

Abstract

Background: Constipation is an intestinal syndrome that can be created alone or in the context of another disease in patients. There are several treatment available to cure the constipation but use of stimulant laxative in chronic and acute constipation is more safe and useful in any age patient. In this cross sectional study we clinically observed the efficacy of multi herbal extract (Cassia senna, Rheum palmatum and Cuscuta reflexa) in constipation. We have used local company syrup (EZCol® syrup) Punjab Pakistan. This syrup contained multi herbs and senna leaves extract is main constituent of this syrup. The active constituents of senna leaves are sennosides which considered treating constipation. Sennosides increasing the transfer rate of materials from the large intestine, we aimed to assure the effect of senna leaves extract along with other herbal extract (Rheum palmatum and Cuscuta reflexa) for the treatment of constipation.

Materials and Methods: In this study, 35 patients were observed after taking the syrup (dose of 500 mg daily for 3 days). A questionnaire (ROUTE2-003) was developed and distributed to the patients after prescription of EZCol® syrup. The study was approved form ethical committee of Rashid Lateef Medical College and Arif Memorial Teaching Hospital, Lahore Pakistan.

Results: Treatment was continued for 3 days and data was compiled and result shown significant cure in constipation. Maximum patients felt relief from constipation just within 3 days. Some patients felt abdominal cramp, vomiting and diarrhea in third day. Moreover no further significant complications were found in patients.

Conclusion: Senna extract is a safe, well-tolerated herbal supplement that does not have significant drug interactions and it seems that this drug can be used as an appropriate treatment for constipation in patients.

Keywords: Chronic constipation, defecation, Laxative, Senna, Syrup

Introduction:

Chronic constipation has been reported in 15% to 25% of the general population (1, 2). It affects patients of all ages and both sexes, and different cultures and ethnicities. It is more commonly reported in women, elderly patients, residents of chronic care facilities and patients with concurrent psychiatric illnesses. Constipation decreases patients' quality of life (QoL); its impact on QoL is comparable with patients suffering from asthma, rheumatoid arthritis and psoriatic arthritis (3-5). Constipation is an intestinal syndrome, which can be developed alone or as a background disease (6). It is estimated that constipation imposes about $ 6.9 milliard cost annually to countries (7). Intestinal movement problems are also common in patients admitted in the intensive care unit (ICU). In studies conducted on constipation, the prevalence of constipation varies between 15% and 83% (8). Several factors such as splenic hypoperfusion caused by shock, electrolyte disorders, and particularly hypocalcemia and hypomagnesemia, some of the drugs mainly used in ICU, such as opiates, can cause constipation (9). Previous studies have shown a significant relationship between constipation, organ dysfunction, and prolonged admission time in ICU and failure to separate from mechanical ventilation (10, 11). To treat constipation, there are various drug groups such as osmotic, volumetric, and stimulating laxatives, and they have different mechanism of action and complications. Stimulating laxatives such as bisacodyl and senalin apply their effect by changing the transfer of electrolytes through intestinal mucosa (7, 12). Their effects appear in the form of oral prescription between 6 and 12 h and if used rectally, it appears about 20 min later (13, 14). Stimulating laxatives may be associated with side effects such as salt overload, hypokalemia, and protein-losing entropy. Bisacodyl is used for many years as the first-line laxative around the world, and clinical experience suggests that this drug can be very effective in treating constipation (15, 16).

Senna is a stimulating laxative, which acts locally in the large intestine and increases the intestinal movement and decreases the intestinal transit time and rises the watery feces portion (17-19). In addition to the drugs produced so far, Route2 Health company in Pakistan has produced a laxative with the brand of EZ Col syrup by combining three substances of the Cassia senna, Rheum palmatum and Cuscuta reflexa respectively. It is expected that the side effects of

this drug, including abdominal cramps, to be reduced by adding two herbal substances to the senna.

The ingredients of the senna leaf are anthraquinones, including dianthrone glycosides, mainly sinusoids A and B, along with sinusoids C and D. Anthraquinone glycosides are absorbed in the gastrointestinal tract and glycons released during metabolism and secretion into the large intestine lead to increased peristaltic intestinal movement (20).

Given the high prevalence of constipation in patients admitted to the ICU and high complications and costs imposed on the health-care system of countries like Pakistan, its treatment is considered to be an important issue and it can reduce the complications such as prolonged admission and mortality, as a result, the health system costs are reduced. In this studies Senna extract and other two herbal extract efficacy was determined. As EZCol® syrup drug is a domestic product and no study has been conducted so far, we decided to check its efficacy of above syrup in constipation patients

Material and Method

The present study was a cross sectional clinical trial conducted on patients who came Arif Memorial Teaching Hospital, Lahore Pakistan. Purposive sampling was done and all patients who reported to have constipation were included. Patients with alarm features such as weight loss and gastrointestinal bleeding were excluded. A questionnaire was developed including questions on general information, constipation symptoms and stool form. Before starting, all stages of the study and the possible complications were explained to the participants or their companions, and written informed consent was obtained. The present study was approved by the Medical Ethics Committee of Rashid Lateef Medical College and Arif Memorial Teaching Hospital, Lahore Pakistan. This study was conducted at local hospitals for a period of seven days 6-11-2019 to 9-11-2019.

This cross sectional study included 35 patients less than age 55 years (median age: 29 years, range 5 - 55) who were treated with for EZCol® syrup The effects of EZCol® syrup was evaluated at 3rd day after intake (frequency of feces excretion during the day, feces consistency score, vital signs and adverse effects). In one child with age of 5 year the feces condition or form was monitored and shown in figure 1. ROUTE2-003 questionnaire was developed to collect

information. Adverse effects of EZCol® syrup (nausea, vomiting, headache and abdominal pain) were also evaluated. The data were analyzed with Microsoft excel.

Comment [U1]: Missing statistical test and level of significance.

Materials used in the study

EZCol is a multi-herbal syrup

contains:

Cassia senna ext.

Rheum palmatum ext.

Cuscuta reflexa ext.

Inclusion and exclusion criteria

The following inclusion criteria were used for the selection of patients.

1. Age less than55 years.
2. Constipation symptoms.
3. Patients don't take any medicine.

The following exclusion criteria were used for the selection of patients:

1. Have an indwelling bladder catheter in place.
2. Patients having irritable bowel syndrome.
3. Patients already talking medicines.
4. Gastrointestinal bleeding
5. Patients with electrolyte imbalance.
6. Has a history of diabetic neuropathy
7. Has a history of bariatric surgery for treatment of obesity; surgery to remove a segment of the GI tract; or surgery of the abdomen, pelvic or retroperitoneal area during the 6 months prior to Screening; or appendectomy or cholecystectomy 3 months prior to screening; or other major surgery 1 month prior to Screening
8. Has a history of cancer with last date of proven disease activity/presence of malignancy within 5 years, except for adequately treated basal cell carcinoma of the skin, cervical dysplasia, or carcinoma in situ of the skin or the cervix
9. Known human immunodeficiency virus (HIV) or Hepatitis B/C (HBV/HCV) infection

10. Pregnant, breast-feeding, or lactating woman

Sampling and sample size

The sample size was estimated by using Krejcie and Morgan's sample size calculator (Krejcie RV and Morgan DW, 1970). A suitability sampling technique was used to recruit a sample of 35 participants from residents of Pakistan.

Survey instrument

The survey questionnaire used to assess the treatment outcomes or cure after the use of EZCol® syrup. The questionnaire contains three sections. The first section contained of items related to sign and symptoms before cure. The second section contains treatment outcomes after the exposure of EZCol® syrup. The last portion of questionnaire contains the information about the adverse effect after the exposure of EZCol® syrup. Questionnaire was in local and English language and was designed by assistant professor Rashid Lateef Medical College and Arif Memorial Teaching Hospital, Lahore Pakistan. Patients were examined during 3 days of treatment and the variables were evaluated. Patients in study were followed up daily for 3 days during the trial, and the variables studied in the research were checked and recorded. The measured variables included demographic characteristics (age by year and gender), frequency of feces excretion during the day, feces consistency score, vital signs and adverse effects

Ethical standard

This study was endorsed by Ethics Committee of Rashid Lateef Medical College and Arif Memorial Teaching Hospital, Lahore Pakistan and was carried in acquiescence with the Helsinki Declaration. The need for informed consent was renounced because of the study design.

Comment [U2]: To verify: It is necessary to obtain the patient's consent for thes type of treatment even if this medication is commonly used.

Results

Out of 35 patients with age between 5 and 55 years, 20 (57.1 %) were males. Significantly, higher number of females reported greater severity of constipation as compared to males. Patients were inquired about the special food that they used for relieve their constipation. About 80% (n=28) patients reported using a combination of fibre and purgatives. Patients reported using fibres, purgatives and home remedies.

Comment [U3]: A laxative usually has prescription indications such as: age and dose. I can't find these data in the text and the child is very young.

Comment [U4]: The n is small, could incorporate more cases and compare types of diets and types of laxatives used, by to compare the results. Because by observing the results of a single product, is not a research project.

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Treatment response at 3rd day

In this study, we administered EZCol® syrup to patients with constipation symptoms and collected information. Out of 35 patients 57.1% were male and mean age of the patients was 29± 11. All patients had submitted questionnaire to project administrator. Sign and symptoms of constipation was observed and not down before treatment and mentioned in table 1. Treatment time line was decided 3 days and most of patients were cured after 3 day. Bloating was 100% cured after 3rd day of treatment. 90.2% patients had increased number of bowel movement per day. 100% patients had relief of sensation of incomplete evacuation. Out of 35 patients 20 (%) patients reported about watery stoll at 3rd day.

Adverse Effect.

In our trials there were no specified symptoms of adverse effect. Subjects did not report specific symptoms including gastrointestinal upset, nausea and diarrhea. Regarding the complications observed during the 3rd day of treatment, 2 patients (5.7%) had vomiting and 5 patients had abdominal cramps (14.2%) and 1 patient (2.8%) had nausea. As strict principles were undertaken, only few cases of adverse events were reported as shown in table 3.

Table 1 Patient profile and characteristics	
Characteristic	**n (%)**
Age in years (Average)	
Mean ±SD	**29±11**
Range	**5-55**
Gender	
Male	20 (57.14)
Female	15 (42.85)
Type of disease	Constipation
Duration of treatment	3 days

Table 2 Therapy efficacy and safety characteristics

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Sr.	**Symptoms**	**Before treatment**	**After 3 days**

No.		n (%)	n (%)
1	**Having soft stool**	16 (45.7)	14 (87.5)
2	**A sense of complete evacuation after going to the bathroom**	11 (31.4)	11 (100)
3	**Frequency of faeces excretion**	13 (37.14)	13 (100)
4	**Lower abdominal discomfort**	08 (22.85)	08 (100)
5	**Bloating**	09 (25.71)	09 (100)

Fig. 1 Therapy efficacy and safety characteristics

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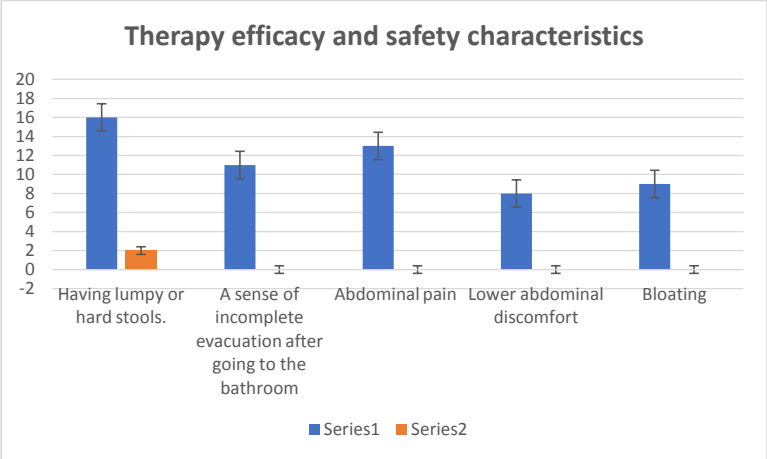

Discussion

The present trial was designed to determine the efficacy and safety of EZCol® syrup (Cassia senna, Rheum palmatum and Cuscuta reflexa) for constipation treatment (doses one tea spoonful 2 times a day). Patients were followed-up for 3 days after end of the treatment period. The assessment of primary and key secondary end points was done for patients who completed the first 3 days of treatment period. Incidence of Adverse Events (AEs) was reported till 3rd after end of the treatment. This study was conducted to check the effects of EZCol® syrup on constipation in patients. The results of the study indicated no significant change on feces consistency. On the

other hand, the mean frequency of excretion during the 2nd day of treatment was significantly higher.

In a study conducted by Pachlo et al., bisacodyl and sinusoids A and B, which are the active ingredient of senalin, were prescribed to mice. The results of this study showed that both bisacodyl and sinusoids A and B treatments similarly stimulated loose feces during 24 h and accelerated the transmission time to the large intestine, although the duration of transmission was longer for bisacodyl. This study also showed that sinusoids drugs have an effect on the colon movement and secretion. In a study conducted by Sitadini et al., three regimens of polyethylene glycol along with bisacodyl, sinusoid along with magnesium sulfate, and sinusoid along with polyethylene glycol were examined. The results of this study showed that the drug regimen containing the sinusoid resulted in a better intestinal cleansing, better mucosal coating, and colonic secretion compared to bisacodyl drug regimen. However, in our study, senna gives significant relief from constipation and low level abdominal cramp was reported by patients.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Comment [U7]: Please, complete the reference data 7.

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