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

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Authors' contributions

This work was carried out in collaboration among all authors. Author YM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors UF, HY and MG managed the analyses of the study. Authors HU, HR, HAS, MM and RKM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Constipation is one of the symptoms of intestinal syndrome which would be happened along with some other 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 of any age patients. 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). This syrup contains multi herbs and senna leaves extract is main ingredient of this syrup. The active constituents of enna leaves are Sennosides which considered as an effective treatment for constipation. Sennosides increase 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.

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Materials and Methods: In this study, 35 patients were observed after taking the syrup (dose 15 mL 2 time/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 diarrhea at third day. Moreover no further significant complications were found in patients.
Conclusion: Senna is an FDA-approved over-the-counter (OTC) laxative. Senna leaves extract is a safe, effective and well-tolerated herbal supplement for the treatment of constipation having no significant adverse effect.

Keywords: Chronic constipation; defecation; laxative; senna; syrup.

1. INTRODUCTION

Chronic constipation has been reported in 15% to 25% of the general population [1,2]. It affects patients of all ages and both sex. 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]. Intestinal movements problems are also common in patients admitted in the intensive care unit (ICU). In previous studies conducted on constipation, the prevalence of constipation varies between 15% and 83% [7]. 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 [8]. Previous studies have shown a significant relationship between constipation, organ dysfunction, and prolonged admission time in ICU and failure to separate from mechanical ventilation [9,10]. 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 [11,12]. 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 [13,14].

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 [15-17]. In addition to the drugs produced so far, Route 2 Health Company in Pakistan has produced a laxative with the brand of EZCol syrup by combining three substances such as 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 with senna.

The ingredients of the senna leaves are anthraquinones 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 [18].

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 hospitalization, 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 herbal product and no study has been conducted so far, we decided to check its efficacy of above syrup in constipation patients.

2. MATERIALS AND METHODS

The present study was a cross sectional clinical trial conducted on patients who visited Arif Memorial Teaching Hospital, Lahore Pakistan. Purposive sampling was done and all patients

Fig. 1. Flow diagram of a clinical trial

who reported with have constipation were included. Patients with alarm features such as weight loss and gastrointestinal bleeding were excluded. A questionnaire (ROUTE2-003) 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) were treated with EZCol syrup. The effects of EZCol syrup 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. ROUTE2-003 questionnaire was developed to collect information. Consent were taken from all patients. Adverse effects of EZCol syrup

(nausea, vomiting, headache and abdominal pain) were also evaluated.

2.1 Materials Used in the Study

EZCol *is a multi-herbal syrup*
Contains:
Cassia senna ext.
Rheum palmatum ext.
Cuscuta reflexa ext.

2.2 Inclusion and Exclusion Criteria

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

1. Age less than 55 years.
2. Symptom related with constipation.
3. Patients not taking any medicine for constipation.

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

1. Having irritable bowel syndrome.
2. Already talking medicines.
3. Gastrointestinal bleeding
4. With electrolyte imbalance.
5. Has a history of diabetic neuropathy
6. 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.
7. 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.
8. Known human immunodeficiency virus (HIV) or Hepatitis B/C (HBV/HCV) infection
9. Pregnant, breast-feeding, or lactating women.

2.3 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.

2.4 Survey Instrument

A questionnaire used to assess the treatment outcomes or cure after the use of EZCol syrup. The questionnaire contains three sections. The first section contain 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 comprises of the information about the adverse effect after the exposure to 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.

3. RESULTS

The purpose of this study was to evaluate the clinical efficiency of this combination for the treatment of constipation and its complications. 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 fibrous food.

3.1 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 submitted questionnaire to project administrator. Signs of constipation complications were 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 increased number of bowel movement per day (not mentioned in table). 100% patients get relieve of sensation of incomplete evacuation. 87.5% patients evacuated soft stool after 3 days. Out of 35 patients 20 (%) patients reported about watery stool at 3rd day.

3.2 Adverse Effect

In our trial there were no specified symptoms of adverse effect reported. 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 and 1 patient (2.8%) had nausea.

4. 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 (dose 15 mL 2 time/daily for 3 days). 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 observed till 3rd after end of the treatment. The results of the study indicated there was significant change on feces consistency. 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

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

Sr. No.	Symptoms	Before treatment n (%)	After 3 days 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)

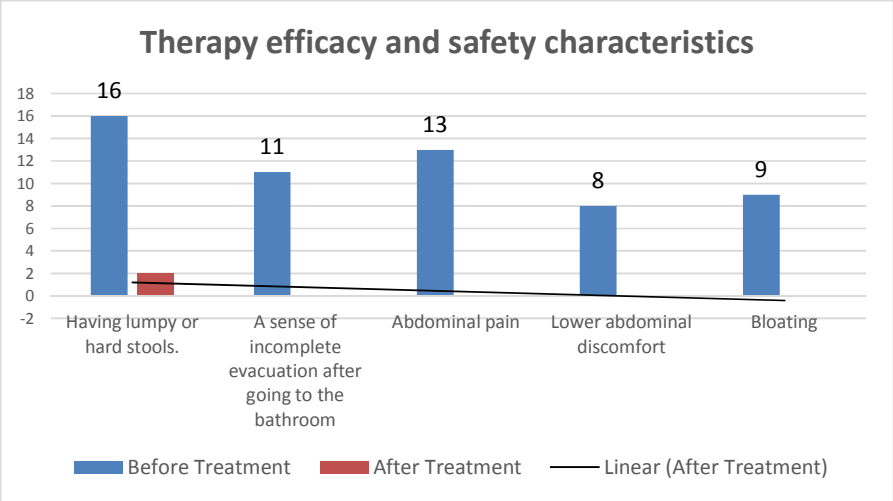

Fig. 2. Therapy efficacy and safety characteristics

accelerated the transmission time to the large intestine. This study also showed that sinusoids drugs have an effect on the colon movement and secretion. In our study treatment was continued for 3 days 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.

5. CONCLUSION

Senna is an FDA-approved over-the-counter (OTC) laxative. Our study revealed that EZCol syrup which contains multiple herbal extract (mainly senna leaves extract) is safe, efficient and well-tolerated herbal syrup for the treatment of constipation that does not have significant adverse effect.

DISCLAIMER

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.

CONSENT AND ETHICAL APPROVAL

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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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