

**RETROSPECTIVE PROSPECTIVE OPEN LABEL OBSERVATIONAL STUDY TO
EVALUATE THE EFFICACY AND ADVERSE DRUG REACTIONS IN PATIENTS
TAKING CONSTAC CHURN FOR LONG TERM IN CONSTIPATION****¹*Dr. Ashwin Porwal, ²Dr. Deepak Kulkarni and ³Dr. Paresh Gandhi**¹Consultant Colorectal Surgeon, Healing Hands clinic.²General Surgeon, Healing Hands Clinic.³General Surgeon, Healing Hands Clinic.4th floor, Millennium Star Extension, Above KFC, Adjacent to Ruby Hall Clinic,
Dhole Patil Road, Pune, Maharashtra, India***Corresponding Author: Dr. Ashwin Porwal**

Founder, Consultant Colorectal Surgeon, Healing Hands clinic.

Article Received on 27/04/2018

Article Revised on 17/05/2018

Article Accepted on 07/06/2018

ABSTRACT

Ayurveda practiced in India from thousands of years. Chronic constipation is global issue and more found in old age group. Use of polyherbal formulation in constipation is common and used by >80% population. Long term efficacy and safety concern issues raised in this study by identifying adverse drug reactions. Oral use of constac advised for 180 days to 1200 participants, of which 948 completed the study. Symptoms were analyzed using longos ODS Score system. It was found that use of constac after 120 days giving nearly constant and good results in participants till day 180. Non serious adverse events were also noted and but due to polyherbal origin unable to establish the exact causality with ADRs.

INTRODUCTION

In Indian traditional medicine Ayurveda is the most powerful, dominating therapy and a reliable option available for the various disease treatments including constipation. It is practiced in India from thousands of years.^[1] Around the world, it is the most common gastrointestinal complaint resulting in over two million reported cases annually (Luscombe, 1999). It was found that its prevalence is more in elderly and with increase in age it increases.^[2] Comparatively more frequently observed in females 26 % as compared to men 16 % in age group of 65 years. Similarly in more elder group 84 years ratio was 34 and 26%.^[3,4]

The American College of Gastroenterology Chronic Constipation Task Force defined chronic constipation as "unsatisfactory defecation characterized by infrequent stool, difficult stool passage or both at least for previous 3 months". Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stool, prolonged time to stool or need for manual manoeuvres to pass stool".^[5] Lists of symptoms as per Rome IV criteria for diagnosis of CC include hard stool, straining, feeling of incomplete evacuation and anorectal blockage, manual evacuation, and infrequent bowel movement. Presence of any two of these symptoms for a long duration (with onset at least 6 months ago and currently symptomatic for a minimum of a 3-month period) in the absence of greater than 25% of stools being loose without treatment with laxative

suggests a diagnosis of chronic constipation (CC).^[6] As per Bristol stool scale in an Asian context, even type III stool is also considered to denote constipation.^[7,8] With careful history taking of patients reveals the causes that include as insufficient dietary roughage, lack of exercise, suppression of defecatory urges arising at inconvenient moments, inadequate time for full defecation and prolong travel, sometimes unable to understand having constipation and neglect the symptoms. In all the population with constipation most cases come as primary or idiopathic and other cases found secondary to medications or diseases. Primary causes are intrinsic problems of colonic or anorectal function, whereas secondary causes are related to organic disease, systemic disease or medications.^[9] WHO report says more than 80% of world population is dependent on herbal medicine. In Ayurveda wide range of approaches are there which is accepted by more than 80% population using herbs, minerals, various detoxifying regimes and their combinations.^[10] These combinations may include multiple drugs in a single formulation. In this study focusing on constipation, constac an ayurvedic polyherbal formulation for constipation was used and patients who were taking it for >3 months, followed up for caused adverse drug reaction. Various publications which already raise concern about the safety of Ayurveda medicines.^[11,12,13] As Ayurveda already captured a global attention for the treatment of chronic, non infectious diseases but compared to old age practices major changes observed for its use, change in

environment, increasing use of insecticides, adulteration of herbs, concomitant use of herbs with drugs of other system of medicines, new manufacturing techniques, lack of proper regulations in pharmaceutical industry, and easy availability of combinations of herbs over the counter. With huge demand of using this safety also a major concern comes out. A National Pharmacovigilance Program in Ayurveda, Siddha and Unani (ASU) drugs has been initiated by Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy (AYUSH); Ministry of Health and Family Welfare, Government of India.^[14] The main aims of this program is to collect data pertaining to the occurrence of ADR and to identify and quantify the risk associated with the use of drugs or formulation. The primary aim of this study was to find efficacy, number of ADRs and their percentage caused by constac powder used for the treatment of constipation for longer period. The secondary objective of this study was to see the effect of taking follow ups to find ADRs. In India reporting of adverse event taking ayurveda medicine is not practiced as found in modern medicine. With this keeping in mind this study was designed planned and executed.

AIM AND OBJECTIVE

1. To see the efficacy, find number of ADRs and their percentage caused by constac powder used for long term in the treatment of constipation
2. To see the effect of taking follow ups to find out unreported ADRs caused Constac

Study Drug

It is a polyherbal formulation which contains:

1. Hirada (Fruit) *Terminalia chebula*
2. Behada (Fruit) *Terminalia bellirica*
3. Amala (Fruit) *Embelica officinalis*
4. Isabgol (Husk) *Plantago ovate*
5. Balhirada (Fruit) *Terminalia chebula*
6. Sonamukhi (Leaves) *Cassia senna*
7. Mulethi (Root) *Glycyrrhiza glabra*
8. Ajwain (Seed) *Ptychotis ajowan*
9. Badishep (Fruit) *Foeniculum Vulgare*
10. Elaichi (Fruit) *Elettaria Cardamomum*
11. Erand Tail (Oil) *Ricinus communis*
12. Narikel lavan (Processed salt with coconut)
13. Permitted preservative and excipient.

Drug Dose: 1-4 teaspoon (4.2-8.4 grams) using from > 3months.

Usage Directions: Directly on tongue followed by water.

Ethics committee approval and regulatory compliance

This study was conducted after getting approval from independent ethics committee and conducted as per schedule Y of drug and cosmetics rule 1945, ICMR national ethical guidelines for biomedical and Health research involving human participants. Every participant selected was informed and consent obtained before

enrollment and initiation of the study. All information provided by the participant was studied and confidentiality was maintained.

Study Design

1. A retrospective Prospective, observational, open label, single centre, non comparative.

Inclusion Criteria

1. Patients visited and taking constac powder for >3months as suggested by qualified physician
2. Following instruction and giving feedback for the given treatment.

Exclusion Criteria

1. Vulnerable person who is unable to understood the change in constipation condition symptoms or adverse events after taking treatment.
2. Taking other formulation for constipation along with given treatment.

Study Plan

Study is been conducted in Healing hands clinic, a leading proctology clinic and centre of excellence for training in proctology. Patients identified who has been taking constac for the constipation from >3 months retrospectively with the help of registration logs and diagnosis. Voluntarily written informed consent of all the participants were taken before enrolling into the study. Total 1200 patients were identified and of which 948 patients were included as per inclusion criteria in the study. Participants were follow up using telecom and interviewed for constipation using longos ODS Score system and enquired for any adverse drug reaction experience in next day30, 60, 120, and 180. Patients specifically asked to give information on efficacy and adverse drug reaction caused after taking constac powder. All the adverse events specifically noted as experienced by the individual taking constac for treatment of constipation

Participant

Patient visiting to healing hands clinic for the constipation treatment.

RESULTS

Total n=984 patients interviewed using telecom at day 30, 60, 120, &180 of which n=612 (62.19%) were female and n= 372 (37.80%) were male. Participants responses for changes in mean score of chronic constipation were noted as per longos ODS Score system from day 30 to 180 in which defecation frequency per week mean (SD) score were improved from 7.02(0.24) to 7.05(0.26), straining intensity score were varies between 0.14(0.34) to 0.18(0.14), extension of time in defecation mean (SD) score were improved from 0.63(0.45) to 0.31(0.46), sensation of incomplete evacuation mean(SD) score were improved from 0.42(0.50) to 0.10 (0.31), recto/peritoneal pain/discomfort mean (SD) score were reduced from

0.44(0.58) to 0.16 (0.36), activity reduction per week mean(SD) score were improved 1.07 (1.13) to 0.39 (0.88) and digitations mean (SD) score were reduced from 0.52 (0.71) to 0.07 (0.34). All the symptoms show a good improvement which does not show too much variation from day 120 to 180. This indicates that at some point it shows constant results irrespective of increase in duration in consumption of constac. After taking constac as suggested by physician, patient was contacted for the adverse events experienced by the individuals and noted.

Longo's ODS score system

Study Days	Defection Frequency per week mean (SD)	Straining Intensity mean (SD)	Extension of time in defecation mean(SD)	Sensation of incomplete of evacuation mean(SD)	Recto/Perineal pain/Discomfort mean(SD)	Activity reduction per week mean(SD)	Digitations mean(SD)
Day 30	7.02(0.24)	0.14(0.34)	0.63(0.45)	0.42(0.50)	0.44(0.58)	1.07 (1.13)	0.52(0.71)
Day 60	7.05(0.26)	0.20 (0.15)	0.40(0.51)	0.10 (0.31)	0.14(0.35)	0.37(0.87)	0.10(0.37)
Day 120	7.08(0.29)	0.21 (0.16)	0.34(0.48)	0.11(0.32)	0.20 (0.38)	0.40 (0.90)	0.09 (0.36)
Day 180	7.05 (0.26)	0.18 (0.14)	0.31 (0.46)	0.10 (0.31)	0.16(0.36)	0.39 (0.88)	0.07 (0.34)

*p<0.05, significant by student 't' test as compared to baseline (Day 30)

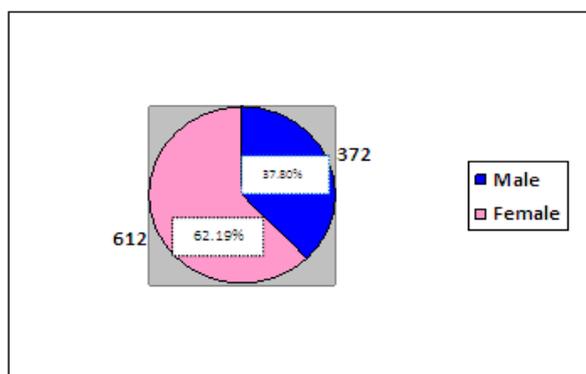


Figure 1: Sex Ratio and Percentage.

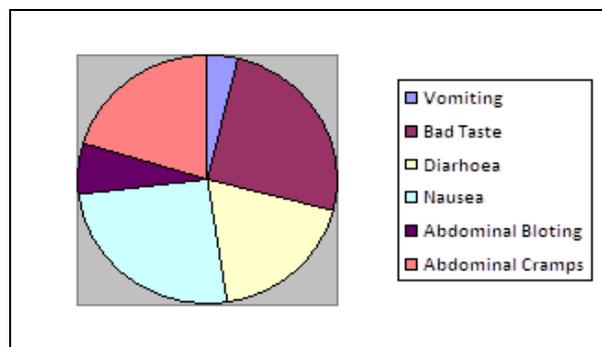


Figure 3: Overall distribution of Adverse Events of Constac.

List of adverse events

Sr. No	Adverse event	Percentage
1	Bad taste	1.24
2	Diarrhea	5.93
3	Nausea	1.70
4	Abdominal Bloating	5.15
5	Abdominal Cramps	4.24

Adverse events reported as per telecom from total population n=10(1.01%) vomited in 1st attempt, n=63(6.40%) patients complaining of bad taste, n= 47 (4.7%) patients complaining of having diarrhea, n=64 (6.5%)patients complaining for nausea, n=17 (1.72%)patients complaining with abdominal bloating, n=51 (5.18%) patients complaining of abdominal cramps. All the adverse events found to be non serious and easily managed by advising the symptomatic treatment.

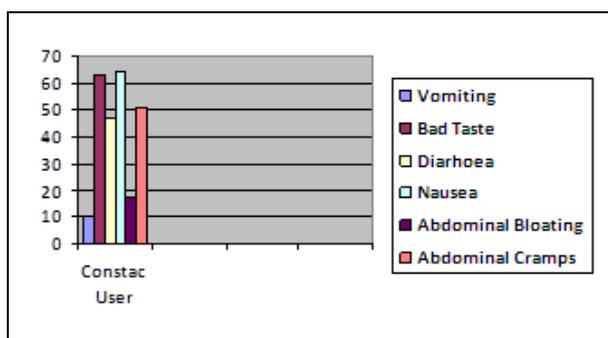


Figure 2: ADRs with Constac Powder

DISCUSSION

In case in ayurvedic medicine which many a times available as polyherbal formulation, it is very difficult to establish causal relationship between formulation and adverse drug reaction. In the beginning of 2006 idea on a pharmacovigilance program for traditional medicine came into existence. To give the evidence of medicine pharmacovigilance is the best possible way.^[17] It's scope includes Patient care and safety when using Ayurvedic medicines and related interventions. With this keeping in mind study aimed to investigate constac powder clinically for constipation and its effect on bowel movement, well being. As constac already been in market from >2 years and established as safe and

efficacious on constipation. But this study was planned and executed to see long term efficacy, rare or new or unknown adverse drug reaction which were initially not observed, recognized or reported after taking constac an Ayurvedic polyherbal formulation for > 6months in constipation. The difficult part was the identification of patients as per planed study. It was planed and done by means of taking follow up and enquiry on efficacy and all adverse drug reaction experienced by the individuals. Ingredients in this formulation already proved there efficacy since many years and published in ayurveda literatures. This formulation proved their collective action in constipation. With allopathic medicine view it is difficult to find exact mechanism of action. Established polyherbal added in this formulation giving the balanced results in case of chronic constipation.

CONCLUSION

Long term use of constac in chronic constipation is safe. In this study participants were surprised when they were asked for the adverse events. Participants were taking it as ayurvedic formulation and thinking of no side effects (adverse events), which was found to be false in this study. It was very difficult to find and confirm that side effect was caused by which content in this formulation. This study was a good success to find the long term effect of this formulation but in case reporting of adverse events need of further studies is the requirement of time.

REFERENCES

1. National Centre for Complementary and Alternative Medicine. Available from: <http://www.nccam.nih.gov/health/ayurveda/introduction.htm#intro>.
2. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol*, 2004; 99: 750–9.
3. Harari D. Constipation. In: Halter JB, Ouslander JG, Tinetti ME et al. (eds). *Hazzard's Geriatric Medicine and Gerontology*. 6th edn, McGraw-Hill Companies: New York, USA, 2009; 1103–22.
4. Harris LA. Prevalence and ramifications of chronic constipation. *Manag Care Interface*, 2005; 18: 23–30.
5. Brandt LJ, Schoenfeld P, Prather CM, et al. An evidence-based approach to the management of chronic constipation in North America. *Am J Gastroenterol*, 2005; 100 (Suppl 1): S5–22.
6. Drossman DA, Hasler WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. *Gastroenterology*, 2016; 150(6): 1257–1261. doi: 10.1053/j.gastro.2016.03.035.
7. Gwee KA, Ghoshal UC, Gonlachanvit S, et al. Primary care management of chronic constipation in Asia: the ANMA chronic constipation tool. *J Neurogastroenterol Motil*. 2013;19:149
8. Gwee K A, Bak Y T, Ghoshal U C, et al. Asian consensus on irritable bowel syndrome. *J Gastroenterol Hepatol*, 2010; 25: 1189.
9. Andrews CN, Storr M. The pathophysiology of chronic constipation. *Canadian Journal of Gastroenterology and Hepatology*, 2011; 25(Suppl B): 16B-21B.
10. Gogtay NJ, Bhatt HA, Dalvi SS, Kshirsagar NA. The use and safety of non-allopathic Indian medicines. *Drug Saf*, 2002; 25: 1005-19.
11. Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, et al. Heavy metal content of Ayurvedic herbal medicine products. *JAMA*, 2004; 292: 2868-73.
12. Kales SN, Saper RB. Ayurvedic lead poisoning: An under-recognized, international problem. *Indian J Med Sci*, 2009; 63: 379-81.
13. Parab S, Kulkarni R, Thatte U. Heavy metals in 'herbal' medicines. *Indian J Gastroenterol*, 2003; 22: 111-2.
14. National Pharmacovigilance Protocol for Ayurveda. Siddha and Unani (ASU) Drugs. New Delhi: Dept of AYUSH, Ministry of Health and Family Welfare, GOI, 2008.
15. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*, 1981; 30: 239-45.
16. Ligthelm RJ, Borzi V, Gumprecht J, Kawamori R, Wenying Y, Valensi P. Importance of observational studies in clinical practice. *Clin Ther*, 2007; 29: 1284-92.
17. Mukherjee PK. Quality Control of Herbal Drugs - An Approach to Evaluation of Botanicals, New Delhi: Business Horizons, 2002; 604–8.