Original Research Article

Evaluation of efficacy and safety of Ayucid capsule in subjects suffering from chronic symptomatic gastroesophageal reflux disease

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Abstract

Objectives: The objective of the study was to assess the efficacy and safety of Ayucid capsule and Omeprazole 20 mg in patients suffering from chronic symptomatic gastroesophageal reflux disease (GERD).

Materials and Methods: It was an open-label, randomized, comparative, multicenter, prospective clinical study. Subjects in Ayucid group were advised to consume two Ayucid capsules twice daily orally before meals, and subjects in Omeprazole group were advised to consume one Omeprazole (20 mg) capsule orally before lunch for 28 days. All *P* values were reported based on two-sided significance test, and all the statistical tests were interpreted at 5% level of significance.

Results: A total of 63 subjects (33 in Ayucid group and 30 in Omeprazole group) completed the study. At the end of the study, the number of cases of heartburn and symptom of heartburn and severity scores of acid regurgitation, dysphasia, and nausea reduced significantly ($P < 0.05$) in both the study groups. Significant relief in symptoms such as epigastric pain, loss of appetite, bloating of stomach, constipation, and gaseous distension was observed in both the groups. Majority of subjects showed significant ($P < 0.05$) reduction in GERD health-related quality of life subscores and improvement in overall efficacy in both the groups. No posttreatment significant ($P > 0.05$) changes were observed in safety laboratory parameters and vitals. Of the reported adverse events in the two groups, none were found to be related to the study drugs.

Conclusion: Ayucid capsule is equally effective or noninferior to that of Omeprazole capsule in relieving the GERD symptoms.

Keywords: Ayucid capsule, gastroesophageal reflux disease, health-related quality of life subscore, Omeprazole capsule

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition in which retrograde movement (reflux) of gastric contents occurs into esophagus, which can provoke symptoms such as heartburn and nausea that impair the quality of life (QOL) of a person.[1,2] GERD is probably one of the most prevalent diseases over the world.[3] Limited data are available on the prevalence of GERD in India, but few studies have reported an approximate prevalence of 10%–20% in Europe and USA and of <5% in Asia.[1]

Pharmacological treatment options of GERD are directed toward neutralization or suppression of gastric acidity.[3,4] Medications such as antacids (aluminum and magnesium hydroxide), mucoprotective agents (sucralfate, alginic acid), prokinetics (metoclopramide, cisapride, mosapride), H2-antagonists (cimetidine, ranitidine, famotidine), and proton pump inhibitors (pantoprazole, rabeprazole) are indicated in the management of GERD symptoms.[3,5,6] Surgical treatment options are indicated in case of failure of optimal pharmacological management.[5] Although these treatment options are effective in the management of GERD, most of these possess various side effects, need longer duration, and are expensive.[7-9] Thus, physicians and patient tend to explore alternative treatment methods such as *Ayurveda*.[7-9]

Keeping in mind the basic concepts of *Ayurveda*, Welex Laboratories Pvt. Ltd. has developed Ayucid capsule for the management of chronic symptomatic GERD. Ayucid capsule is a combination of 13 herbal ingredients. Most of the ingredients of Ayucid capsule help neutralize excess acidity, reduce inflammation, prevent heartburn and heal ulcers, and decrease flatulence, nausea, and vomiting. Furthermore, few ingredients of Ayucid capsule possess carminative, antispasmodic, digestive, and appetizer properties.[10-14]

Looking at the various activities of the ingredients present in Ayucid capsule, a hypothesis was postulated that Ayucid capsule may be helpful in the management of GERD. Hence, to test this hypothesis, a clinical study was conducted.

MATERIALS AND METHODS

Study design

It was an open-label, prospective, multicenter, interventional clinical study. The study protocol and related documents were reviewed and approved by the Institutional Ethics Committees of PDEA's College of Ayurveda and Research Centre, Sector 25, Pradhikaran, Nigdi, Pune - 411 044; KVTR Ayurvedic College, Boradi, Taluka Shirpur, District-Dhule - 425 428, and Ayurved Sanshodhan Vibhag, Ayurved Seva Sangh Hospital, Ganeshwadi, Panchvati, Nashik - 422 003, India, on August 11, 2017; July 31, 2017; and July 26, 2017, respectively. The CTRI registration number of the study is CTRI/2018/01/011260 dated January 11, 2018. The study was conducted in accordance with GCP Guidelines, issued by the Department of AYUSH in March 2013.

Primary and secondary objectives

The primary objective of the study was to evaluate the efficacy of Ayucid capsule and Omeprazole 20 mg in patients suffering from chronic symptomatic GERD without esophageal erosion by assessing changes in resolution of heartburn. The secondary objectives of the study were to evaluate the efficacy of Ayucid capsule and Omeprazole 20 mg by assessing symptoms of GERD, including acid regurgitation, dysphagia, epigastric pain, and nausea, the requirement of rescue medication (antacid), the QOL on GERD health-related QOL (GERD-HRQL) questionnaire, and the global assessment for overall change assessed by the patient and the investigator at the end of the study. The other secondary objectives were to assess the safety and tolerability of study drugs by assessing adverse events (AEs) and adverse drug reaction and laboratory parameters at the end of the study.

Sample size

Anticipating 25% dropouts, we enrolled 75 subjects to get 60 evaluable cases at the end of the study. The sample size calculation was based on the assumption that a sample size of 60 evaluable cases (i.e., 30 subjects in each group) would provide an 80% power to estimate the improvement in GERD symptoms at 5% level of significance.

Subject selection

Subjects of either sex in the age group of 18–60 years (both years inclusive) having a history of heartburn ≥12 months and <5 years were included in the study. Subjects with GERD questionnaire score ≥8 and current episodes of moderate-to-severe heartburn on at least four occasions in the last 7 days before screening were included in the study. Subjects who were known case of organic diseases such as gastric ulcer, duodenal ulcer, and gastric cancer; subjects who have underwent abdominal surgeries 12 months before the study; subjects with a history of significant cardiovascular event <12 weeks before recruitment; and subjects with an anticipated need for concomitant medication with anticholinergic, promotility agents, prostaglandin analogs, sucralfate, nonsteroidal

anti-inflammatory drugs, or salicylates other than low-dose aspirin (#165 mg/day for cardiovascular prophylaxis) were excluded from the study. Subjects with severe or chronic hepatic or renal diseases; any active malignancies; chronic or contagious infectious disease such as active tuberculosis, hepatitis B or C, or HIV; active metabolic or gastrointestinal diseases that may interfere with nutrient absorption, metabolism, or excretion, excluding diabetes; and chronic alcoholics and habitual tobacco chewers; pregnant and lactating females were also excluded from the study.

Study drug

Ayucid capsule in an Ayurvedic proprietary medicine supplied by sponsor of the study, i.e., Welex Laboratories Pvt. Ltd. Omeprazole 20 mg capsules were procured from the market. Ayucid capsule contains 13 ingredients as mentioned in Table 1.

Study procedure

On screening visit, written informed consent was obtained from the subjects. Subject's physical and systemic examinations and *Prakruti* evaluation were done. Subject's clinical symptoms, digestion-related symptoms, and GERD questionnaire score were noted. On the next day morning, subject's blood sample was collected on empty stomach for laboratory tests, i.e., complete blood count, erythrocyte sedimentation rate, hemoglobin %, fasting blood sugar level, liver function tests, lipid profile, renal function tests, and HIV I and II. Furthermore, subject's urine routine and microscopic examination and urine pregnancy test (only if the subject was female of fertile age) were done. Subject's chest X-ray posteroanterior view and electrocardiogram (ECG) were done.

A washout period of 3 days was advised. During the washout period and till the end of the trial, subjects were advised to refrain from any Ayurvedic, allopathic, nutraceutical, hormonal, *Unani*, *Siddha*, herbal, and homeopathic medications indicated for GERD or heartburn. In case of severe heartburn, subjects were allowed to take tablet Gelusil (aluminum hydroxide and magnesium hydroxide).

Table 1: Composition of Ayucid capsule (each capsule contains)

Ingredient	Scientific name	Quantity (mg)
Lajwanti extract	*Mimosa pudica*	40
Shatavari extract	*Asparagus racemosus*	40
Amla extract	*Emblica officinalis*	40
Yashtimadhu extract	*Glycyrrhiza glabra*	40
Dhaiful extract	*Woodfordia fruticosa*	40
Pitpapra extract	*Fumaria parviflora*	30
Saunf extract	*Pimpinella anisum*	30
Kapur kachri	*Hedychium spicatum*	30
Nishot	*Operculina turpethum*	30
Harde extract	*Terminalia chebula*	30
Utpal	*Nymphaea nouchali*	30
Khus	*Vetiveria zizanioides*	30
Giloy extract	*Tinospora cordifolia*	30

Hard gelatin capsules shells-IP. Permitted colors are used in capsule shell. IP: Indian pharmacopeia

On baseline visit, subjects were recruited in the study if he/she met all the eligibility criteria. As per the computer-generated randomization list, all recruited subjects were randomized to one of the two study groups, i.e., Group-A: Ayucid capsules and Group-B: Omeprazole (20 mg) capsules. On baseline visit, one diary card was given to the subject to record requirement of rescue medicines, occurrence, and severity of heartburn. At baseline visit and at every follow-up visit, subjects were asked for occurrence of any AEs. Subjects underwent general and systemic examinations. Subject's clinical symptoms, digestion-related symptoms, and GERD questionnaire score were noted. Subject's QOL was evaluated on GERD-HRQL questionnaire.

At baseline visit and at every follow-up visit (except the last follow-up visit), subjects were provided either with Ayucid capsules or Omeprazole (20 mg) capsules. Subjects from Group-A were advised to consume two Ayucid capsules twice daily orally before meals and subjects from Group-B were advised to consume one Omeprazole (20 mg) capsule orally before lunch for 28 days. Subjects were advised to continue their concomitant medications other than the medications indicated for GERD or heartburn. On each study visit, drug compliance was assessed by investigator. Subjects were advised to continue diet and exercise regimen (which they were already following) during the entire study. Subjects were called for follow-up visits on day 7, day 14, day 21, and day 28.

On day 28, global evaluation for overall change was done by the investigator and subject. Laboratory investigations and ECG were done. Tolerability of trial drugs was assessed by investigator and the subject. All the subjects were asked to stop trial medication and take advice of investigator for further treatment.

Statistical analysis

Statistics was performed using statistical software SPSS 10.0 (SPSS Inc., Chicago) by a qualified statistician. Data describing quantitative measures were expressed as mean ± standard deviation or standard error or the mean with range. Qualitative variables were presented as counts and percentage. Comparison of variables representing categorical data was performed using Chi-square test. All *P* values were reported based on two-sided significance test, and all the statistical tests were interpreted at least up to 5% level of significance.

RESULTS

A total of 87 subjects were screened. There were 12 screen failures as they did not meet the inclusion/exclusion criteria. Of these subjects, 75 subjects were randomized into two groups. There were 12 dropouts from the study, which were due to reasons other than occurrence of AEs. A total of 63 subjects (33 in Ayucid and 30 in Omeprazole group) were considered as completers.

Of the 33 subjects in Ayucid group, there were 15 males and 18 females. Of the 30 subjects in Omeprazole group, there were 11 males and 19 females. The average age of subjects in the Ayucid group was 45.70 ± 9.41 years while in the Omeprazole group was 39.73 ± 9.02 years.

At the end of the study, complete resolution of heartburn was observed in 14 (42.42%) and 17 (56.66%) of subjects of Ayucid group and Omeprazole group, respectively. The difference between both the groups was statistically insignificant ($P > 0.05$). The details are given in Table 2.

The mean score of severity of heartburn in Ayucid group at baseline visit was 2.33 ± 0.54 which reduced significantly ($P \leq 0.05$) to 1.25 ± 0.88, 1.17 ± 0.71, 0.79 ± 0.73, and 0.58 ± 0.50 on day 7, 14, 21, and 28, respectively. The mean score of severity of heartburn in Omeprazole group at baseline visit was 2.17 ± 0.59 which reduced significantly ($P \leq 0.05$) to 0.92 ± 0.86, 0.72 ± 0.68, 0.52 ± 0.51, and 0.43 ± 0.50 on day 7, 14, 21, and 28, respectively. The difference between both the groups was statistically insignificant ($P > 0.05$).

The mean score of severity of acid regurgitation in Ayucid group at baseline visit was 1.76 ± 0.87 which reduced significantly ($P \leq 0.05$) to 1.03 ± 0.86, 0.76 ± 0.74, 0.62 ± 0.56, and 0.39 ± 0.50 on day 7, 14, 21, and 28, respectively. The mean score of severity of acid regurgitation in Omeprazole group at baseline visit was 1.80 ± 0.80 which reduced significantly ($P \leq 0.05$) to 0.80 ± 0.76, 0.56 ± 0.58, 0.48 ± 0.51, and 0.23 ± 0.43 on day 7, 14, 21, and 28, respectively. The difference between both the groups was statistically insignificant ($P > 0.05$).

The mean score of severity of dysphagia in Ayucid group at baseline visit was 0.97 ± 1.02, which reduced significantly ($P \leq 0.05$) to 0.66 ± 0.90, 0.34 ± 0.67, 0.24 ± 0.44, and 0.09 ± 0.29 on day 7, 14, 21, and 28, respectively. The mean score of severity of dysphagia in Omeprazole group at baseline visit was 1.03 ± 0.85 which reduced significantly ($P \leq 0.05$) to 0.48 ± 0.71, 0.20 ± 0.41, 0.10 ± 0.30, and 0.03 ± 0.18 on day 7, 14, 21, and 28, respectively. The difference between both the groups was statistically insignificant ($P > 0.05$).

Table 2: Assessment of resolution of heartburn symptom in two groups

Study group	Visits			
	Day 7	Day 14	Day 21	Day 28
Ayucid capsule (%)	6 (18.18)	5 (15.15)	11 (33.33)	14 (42.42)
Omeprazole capsule (%)	9 (30)	10 (33.33)	10 (33.33)	17 (56.66)
P value between groups	>0.05	>0.05	>0.05	>0.05

The mean score of severity of epigastric pain in Ayucid group at baseline visit was 0.97 ± 1.02 which reduced significantly ($P \leq 0.05$) to 0.59 ± 0.87, 0.48 ± 0.63, 0.24 ± 0.44, and 0.21 ± 0.42 on day 7, 14, 21, and 28, respectively. The mean score of severity of epigastric pain in Omeprazole group at baseline visit was 0.87 ± 0.82 which reduced insignificantly ($P > 0.05$) to 0.80 ± 0.82 on day 7 and reduced significantly ($P \leq 0.05$) to 0.20 ± 0.41, 0.29 ± 0.46, and 0.17 ± 0.38 on day 14, 21, and 28, respectively. However, the difference between both the groups was statistically insignificant ($P > 0.05$).

The mean score of severity of nausea in Ayucid group at baseline visit was 1.06 ± 0.61which reduced significantly ($P \leq 0.05$) to 0.72 ± 0.81, 0.41 ± 0.57, 0.34 ± 0.48, and 0.36 ± 0.55 on day 7, 14, 21, and 28, respectively. The mean score of severity of nausea in Omeprazole group at baseline visit was 1.07 ± 0.83 which reduced significantly ($P \leq 0.05$) to 0.64 ± 0.86, 0.28 ± 0.52, 0.14 ± 0.36, and 0.13 ± 0.35 on day 7, 14, 21, and 28, respectively. The difference between both the groups was statistically insignificant ($P > 0.05$).

The mean appetite score in Ayucid group at baseline visit was 5.12 ± 1.34 which improved significantly ($P \leq 0.05$) to 5.50 ± 1.18, 6.57 ± 1.32, 7 ± 1.52, and 7.20 ± 1.55 on day 7, 14, 21, and 28, respectively. The mean appetite score in Omeprazole group at baseline visit was 4.73 ± 1.39 which improved significantly ($P \leq 0.05$) to 5.72 ± 1.54, 6.06 ± 1.54, 6.93 ± 2.14, and 7.75 ± 2.27on day 7, 14, 21, and 28, respectively. The difference between both the groups was statistically insignificant ($P > 0.05$).

The mean total GERD-HRQOL score in Ayucid group was 26.48 ± 16.60 which reduced significantly to 10.93 ± 11.29 and 5 ± 5.26 on day 14 and 28, respectively. The mean total GERD-HRQOL score at baseline visit in Omeprazole group was found to be 27.10 ± 18.44 which reduced to 8.84 ± 11.19 and 4.18 ± 4.35 on day 14 and 28, respectively. The details are given in Table 3.

Significant improvement in other digestion-related symptoms such as bloating of stomach, constipation, and gaseous distension was observed in both the

groups. If compared between the groups, the difference was statistically insignificant. The details are given in Table 4.

At the end of the study, as per the global assessment for overall change done by the physician and subject, 29 (87.88%) and 22 (73.33%) subjects showed very much-to-much improvement in Ayucid capsule group and Omeprazole capsule group, respectively. Two (6.45%) and 5 (18.52%) subjects reported minimal improvement in Ayucid group and Omeprazole capsule group, respectively.

No significant change in any of the laboratory parameters was observed at the end of the study. There was no significant change in any of the vital parameters which was observed at the end of the study.

A total of 39 AEs (26 in Ayucid and 13 in Omeprazole group) were reported. Among 26 AEs of Ayucid group, 20 AEs were not related to the study drug, while six AEs were possibly related to the study drug. Among 13 AEs of Omeprazole group, 11 AEs were reported as unrelated to the study drug, while one AE each was reported as possible and probably related to the study drug. No treatment or procedure or interruption of study drug was required in both groups to resolve these episodes.

Table 3: Assessment of gastroesophageal reflux disease health-related quality of life score (mean±standard deviation)

Study group	Symptom*	Study visit		
		Baseline	Day 14 ($P \leq 0.05$)	Day 28 ($P \leq 0.05$)
Ayucid capsule	TH	10.58±7.38	4.24±4.85	1.87±2.67
	TR	10.58±7.38	4.24±4.85	1.87±2.67
	TG	26.48±16.60	10.93±11.29	5±5.26
Omeprazole capsule	TH	11.47±7.93	3.60±4.98	1.79±2.35
	TR	11.47±7.93	3.60±4.98	1.79±2.35
	TG	27.10±18.44	8.84±11.19	4.18±4.35
P value between both groups			>0.05	>0.05

Symptoms=TH: Total heartburn, TR: Total regurgitation, GERD: Gastroesophageal reflux disease, HRQOL: Health-related quality of life, TG: Total GERD-HRQOL score

Table 4: Assessment of other digestion-related symptoms

Study group	Symptom*	Study visit		
		Baseline	Day 14 ($P \leq 0.05$)	Day 28 ($P \leq 0.05$)
Ayucid capsule (%)	B	21 (63.63)	13 (39.39)	12 (36.36)
	C	18 (54.54)	9 (27.27)	8 (24.24)
	G	29 (87.87)	19 (57.57)	15 (45.45)
Omeprazole capsule (%)	B	17 (56.66)	13 (43.33)	9 (30)
	C	15 (50)	7 (23.33)	7 (23.33)
	G	25 (83.33)	12 (40)	10 (33.33)
P value between both groups			>0.05	>0.05

*Symptoms=B: Bloating of stomach, C: Constipation, G: Gaseous distension

DISCUSSION

In the present clinical study, 63.33% patients had *Pitta-Vata* and *Vata-Pitta Prakruti*. This is in line with the Ayurvedic principles that *Pitta*-predominant persons usually suffer from *Pitta Dosha*-related disorders. Twenty eight-day treatment with Ayucid capsule showed complete resolution of heartburn in 42.42% patients, while 56.66% patients showed complete resolution of heart \burn in Omeprazole group. However, the difference between the groups was statistically insignificant. Severity of heartburn was also reduced significantly in both the groups, and the difference between the groups was statistically insignificant. These results indicate therapeutic effect of "Ayucid capsule" in resolving heartburn effectively in patients with GERD.

The mean severity scores of acid regurgitation, dysphasia, and nausea reduced significantly in both the groups; and the difference between the groups was statistically insignificant. Ayucid capsule was as effective as Omeprazole in relieving symptoms of GERD.

Symptoms such as epigastric pain and appetite were relieved significantly in both the groups. When compared between the groups, the difference was statistically insignificant. It was observed that only one subject in Ayucid capsule group required the use of rescue medication only once during the study period.

In both the study groups, significant reduction in all the three subscores of GERD-HRQL was observed at the end of the study, and the difference between the groups was statistically insignificant.

Significant improvement in digestion-related symptoms such as bloating of stomach, constipation, and gaseous distension was observed in both the groups. The difference between the groups was statistically insignificant. Majority of the patients of both the groups reported improvement as per the assessment of overall change by the physician and by the patient.

Ayucid capsule is a combination of 13 standardized herbal extracts. These ingredients have been individually tested and found to have *Pitta Shamaka* (pacifying) property. These ingredients help neutralize excess acidity, reduce inflammation, and prevent heartburn and heal ulcers.[10-14] The ingredients also help in relieving flatulence, nausea, and vomiting. It was observed from the results of the present clinical study that the synergistic effect of the standardized herbal extracts in the formulation contributed

to the overall effect in the management of heartburn and other symptoms of GERD.[10-14]

A total of 39 AEs (26 in Ayucid and 13 in Omeprazole group) were reported. No treatment or procedure or interruption of study drug was required in both groups to resolve these episodes. The mean values of most of the laboratory parameters were within normal limits both at baseline visit and at the end of the study. No significant changes in any of the vital parameters (viz., heart rate, respiratory rate, body temperature, and blood pressure) were observed during and at the end of the trial in both the groups.

Taken together, these observations demonstrate that Ayucid capsule is safe and effective to be used in patients suffering from chronic symptomatic GERD without esophageal erosion.

CONCLUSION

Four weeks of treatment with Ayucid capsule showed significant improvement in symptoms of GERD, including heartburn, acid regurgitation, nausea, and epigastric pain. Ayucid capsule proved to be equally effective or noninferior to that of Omeprazole capsule in relieving the GERD symptoms. Hence, it can be concluded that Ayucid capsule can be a safe and effective alternative in the management of chronic symptomatic GERD.

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Conflicts of interest

There are no conflicts of interest.

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