An Open-Label, Interventional, Single-Center, Prospective Clinical Study to Evaluate the Efficacy and Safety of “AHPL/AYTAB/1514” in Patients Suffering from Halitosis

Abstract

Objectives: The main objective of the study was to assess the efficacy and safety of AHPL/AYTAB/1514 tablet in patients suffering from halitosis. Methodology: Fifty four patients were recruited in the study. Patients were advised to take maximum two tablets or at least one tablet four times a day (depending on tolerability of the drug) orally for 60 days. Patients were called for follow-up on day 15, 30, 45, 60, and 75. Data describing quantitative measures were expressed as mean ± standard deviation comparison of variables representing categorical data were performed using Chi-square test, Student’s t-test, or Wilcoxon Sign Rank test. Results: At the end of the treatment, significant reduction in halitosis, gingivitis index, and dental plaque index was observed. Even after stoppage of treatment for 15 days after 60 days of treatment, there was no relapse in halitosis. Few patients experienced sore throat, cough, and common cold during the study, which were resolved with the treatment of AHPL/AYTAB/1514 tablet. No significant change in vital parameters and most of the safety laboratory parameters were observed. No staining on tooth was observed in any patient. Almost all patients showed excellent improvement as per global evaluation done by the physician and patient. Almost all patients showed excellent tolerability to the study drug. Few patients showed mild AE, which were resolved without stoppage of study drug. Conclusion: The study provides good evidence in support of the efficacy and safety of the AHPL/AYTAB/1514 tablet in halitosis.

Keywords: AHPL/AYTAB/1514 tablet, dental plaque, gingivitis, halitosis

Introduction

It has been estimated that 8%-50% of people in the developed world perceive halitosis (oral bad odor).[1-3] Furthermore, it is revealed that the prevalence of halitosis range to around 50% in the USA, 27.5% in China, and 22% in France.[4]

The origin of halitosis may be related to the systemic (15%) and oral conditions (85%).[5,6] Oral causes include dentition (deep carious lesions, food impaction, and putrefaction), periodontal infections (gingivitis, periodontitis, etc.), microorganisms (Fusobacterium species etc.), teeth deposition with plaque, coated tongue, and many others.[7] The systemic causes include diseases such as liver problems, gastrointestinal tract problems, respiratory diseases, and uremia.[8] Halitosis due to oral causes can be preventable by daily brushing, flossing, and maintaining oral hygiene. Regular use of antimicrobial agents in the form of toothpastes, oral mouth fresheners and mouthwashes are useful in the management of halitosis.[2] Most of these medications are considered to be helpful in decreasing the bacterial count, increasing mouth freshness and maintaining the pH of the oral cavity.[6] Although these conventional approaches are effective in masking the bad breath, they can cause several side effects.[9,10] Mouthwash considered unpleasant, and it can give rise to a burning sensation of the oral mucosa if used too frequently. Mouth lozenges, brushing, and flossing are not very effective in reducing oral malodor. Thus, after long-term trial of conventional medicines, people generally approach to alternative treatment options such as herbal or Ayurveda therapies.[9,11]

Keeping in mind the basic concept of Ayurveda, Ari Healthcare Pvt. Ltd., has developed “AHPL/AYTAB/1514” tablet for effective management of...
halitosis. “AHPL/AYTAB/1514” tablet is a unique combination of Haridra (Curcuma longa),[12‑15] Pippali (Piper longum)[16‑19] and Putiha (Mentha arvensis).[20,21] A hypothesis was postulated that “AHPL/AYTAB/1514” tablet will be helpful in the management of halitosis. Hence, to test this hypothesis, a clinical study to evaluate the efficacy and safety of “AHPL/AYTAB/1514” in patients suffering from halitosis was planned.

Methodology

The study was an open-label, interventional, single-center, and prospective clinical study. Ethics committee of Maharashtra Cosmopolitan Education Society, at M. A. Rangoonwala College of Dental Sciences and Research Centre, 2390-B, KB Hidayatullah Road, Azam Campus, Pune-1, approved the study. The study was conducted in accordance with good clinical practices guidelines (issued by AYUSH in 2013). The clinical trials registry- India (CTRI) registration no. is CTRI/2015/07/006058 [Registered on: 31/07/2015].

Study objectives

The primary objective was to evaluate the efficacy of “AHPL/AYTAB/1514” on halitosis using bad breath analyzer scale (as 0 = no halitosis, 1 = mild halitosis, 2 = moderate halitosis, and 3 = severe halitosis) and on organoleptic assessment scale (as 0 = no appreciable odor, 1 = barely noticeable odor, 2 = slight but clearly noticeable odor, 3 = moderate odor, 4 = strong odor, and 5 = extremely foul odor). The secondary objectives were to evaluate efficacy of “AHPL/AYTAB/1514” by assessing Gingivitis on Loe and Silness gingival index, dental plaque on Turesky modification of Quigley Hein index, intensity of sore throat and cough on a 4 points scale, acceptability of trial drug, incidence and severity of infections during the study period, quality of life on the World Health Organization quality of life (WHOQOL)-BREF (questionnaire) and acceptability of trial drug (1. Taste of drug on grade 0 = acceptable, 1 = tolerable, 2 = unacceptable; 2. Burning sensation in mouth on grade 0 = absent, 1 = present; 3. Dryness of mouth on grade: 0 = absent, 1 = present). Furthermore, the secondary objectives were to assess overall treatment satisfaction by patient and physician on global assessment scale for overall improvement and assessment of drug compliance. The other secondary objectives were to evaluate the safety of “AHPL/AYTAB/1514” by assessing the tolerability of study drug, changes in laboratory parameters and by assessing the adverse events.

Sample size

The sample size was based on the primary efficacy parameter that was mean % reduction in bad breath from baseline (analyzed using bad breath analyzer) value.[22] The sample size calculation was based on the assumption that a total 54 patients would be enrolled, to get 40 completers. These 40 patients provided 80% power.

Subject selection

Male and female patients between 18 and 54 years of age suffering from moderate-to-severe halitosis attending out-patient department at study center, voluntarily signed an informed consent form and willing to follow the study procedures were selected for the study. Patients who had a destructive periodontal disease or who had undergone a periodontal surgery in the past 3 months from screening visit; patients with severe gingival inflammation and severe periodontitis were excluded from the study. Patients who were using antibiotic, antimicrobial, analgesic medications, mouthwash, mouth fresheners (lozenges/tablets), or desensitizing toothpaste during the previous 1 month from screening visit, having dependency or failure to keep abstinence for antioxidant agents, vitamins, anti-inflammatory drugs, hormones, Ayurvedic/herbal/homeopathic/naturopathy medications, medicated/sensitive toothpastes or having known hypersensitivity to any ingredient of the study drug were excluded from the study. Patients with a history of dentine hypersensitivity, having a removable orthodontic device, the presence of fixed dental appliance, large or defective restorations, and cracked enamel were excluded from the study. Patients with any medically compromised conditions contraindicating the oral examination, preexisting systemic disease necessitating long-term medications, and having genetic, endocriinal disorders, significant abnormal laboratory parameters, and pregnant and lactating women were excluded from the study.

Investigational drug

The investigational product, i.e., AHPL/AYTAB/1514 tablet was manufactured by the Sponsor, i.e., Ari Healthcare Pvt. Ltd following GMP. The composition of the drug is given in Table 1.

Study procedure

On screening visit (day -7), written informed consent was obtained from patients. Patient’s demographic data and Dosha Prakriti Parikshan was noted. Patient’s general, systemic, and oral examinations were done. On screening visit (day -7) and on every visit, patient’s assessment for halitosis was made using Bad Breath Analyzer[22] and on organoleptic assessment scale[23] the assessment of gingivitis,[24] dental plaque[25] and sore throat and cough (if any) was done.[26] On screening visit, on day 30 and 60, assessment of quality of life of subject was done on WHOQL– BREF (questionnaire).[27]

Table 1: Composition of AHPL/AYTAB/1514 tablet

| Ingredients       | Botanical name       | Quantity (mg) |
|-------------------|----------------------|---------------|
| Haridra extract   | Curcuma longa        | 50            |
| Pippali extract   | Piper longum         | 2.5           |
| Putiha extract    | Mentha arvensis      | 2.5           |

Each film coated tablet contains
On screening visit, if Loe and Silness gingival index score was <2 and Turesky modification of Quirley Hein index score was <4 then the patient was considered for further evaluation as per the inclusion and exclusion criteria. Patient’s X-ray chest (posteroanterior view) and electrocardiogram (ECG) were done. All the patients were advised to undergo laboratory investigations such as complete blood count (CBC), Hb%, erythrocyte sedimentation rate (ESR), renal function test (serum uric acid and serum creatinine), liver function tests (LFTs) (serum glutamic-pyruvic transaminase, Sr Bilirubin levels, Sr Alkaline phosphatase), lipid profile, and fasting blood sugar. Urine pregnancy test of all female patients of reproductive age was done. A washout period of 7 days was advised. During washout period and whole study period, all the patients were advised to refrain from antioxidant agents, vitamins, anti-inflammatory drugs, antibiotics, antimicrobial drugs, hormones, herbal/Ayurvedic/homoeopathic medications, medicated/sensitive tooth pastes. All the patients were advised and trained by the investigator to maintain their oral hygiene. They were advised to continue the diet and exercise regimen, which they were already following. All patients were advised to visit study site for follow-up visits, namely, baseline visit (on day 0), visit-1 (on day 15), visit-2 (on day 30), visit-3 (on day 45), visit-4 (on day 60), and visit-5 (on day 75).

On baseline visit (day 0), patient was recruited in the study, if he/she met all the inclusion criteria. On baseline visit and every follow-up visit, patients were asked for the occurrence of any adverse event during the washout period. On day 0, 15, 30, and day 45 visits, all the patients were provided 15 mono cartons each containing 10 “AHPL/AYTAB/1514” tablets (total 150 tablets, i.e., 120 tablets for 15 days and 24 tablets for next 3 days, if follow-up visit was delayed by maximum 3 days). All the patients were advised to take 2 (AHPL/AYTAB/1514) tablets 4 times (i.e., 2 tablets after breakfast, 2 tablets after lunch, 2 tablets after evening tea time/snacks and 2 tablets after dinner) a day orally for 60 days. During the study, the drug dosage was adjusted from minimum 1 tablet twice a day to maximum 2 tablets 4 times a day as per the patient’s tolerance. All study patients were advised to keep the tablets on the tongue and suck on the tablet till it dissolves completely in the mouth. On day 0, 15, 30, and day 45 visits, a dose chart was given to patients to keep a daily record of the use of study drug.

On day 60, treatment tolerability was assessed by investigator and patient. From day 60 onward until day 75, all study patients were advised not to use the study drug and come to follow-up on day 75 (last study visit) to observe any relapse or recurrence of halitosis. On day 60, all the patients were advised to undergo laboratory investigations. Patient’s ECG was done. On day 60 and day 75, patient’s global evaluation for overall improvement and investigator’s global evaluation for overall improvement were done. [28]

### Results

A total of 54 patients suffering from moderate to severe halitosis were screened. Six out of 54 patients did not meet the inclusion/exclusion criteria, hence were not included in the study. Out of 6 patients who did not meet inclusion/exclusion criteria, 2 patients had a history of diabetes and 4 patients had severe periodontitis. Out of 48 recruited patients, 47 patients completed the study, while 1 subject dropped out prematurely. The reason for dropout was the withdrawal of consent due to personal reason. Out of 47 patients who completed the trial, 28 (59.60%) were males, whereas 19 (40.40%) were females. The mean age of patients was 34.23 ± 8.83 years, mean weight was 64.11 ± 12.32 kg and mean height was 163.62 ± 11.89 cm. No significant change from baseline to end of therapy values in any of the vital signs (pulse rate, body temperature, respiratory rate, systolic and diastolic blood pressure, and body weight) was observed in all the study patients.

At the beginning of the trial as per bad breath analyzer, out of 47 patients, moderate halitosis was observed in 18 (38.3%) cases, and mild halitosis was observed in 29 (61.70%) cases. As the study progressed, gradual reduction in halitosis was observed. On day 60, 17 patients (94.44%) out of 18 from moderate halitosis group and 25 (86.20%) out of 29 cases from mild halitosis group registered improvement in halitosis. When compared to the baseline visit, the difference was statistically significant. On day 75, one case from mild halitosis group showed improvement in halitosis and shifted to no halitosis group. No recurrence/relapse in halitosis was observed in any of the cases at the end of the study. When compared with the baseline visit, the difference was statistically significant [Table 2 and Graph 1].

As per organoleptic assessment scale, at the beginning of the trial, out of 47 patients, 36 (76.6%) patients had slight, but clearly noticeable odor and 11 (23.4%) patients had a barely noticeable odor. On visit 4, 2 (4.3%) patients had a slight but clearly noticeable odor, 6 (12.7%) patients had a barely noticeable odor, and 39 (83.0%) patients had no appreciable odor. When compared with the baseline visit, 94.44% of cases showed a decrease in slight but clearly noticeable odor, and the difference was statistically significant. On visit 5, 41 (87.2%) patients showed no appreciable odor when compared with the day 60 visit, two patients were shifted from barely noticeable odor to no appreciable odor group.
There was no change in slight but clearly noticeable odor group, suggesting no recurrence/relapse in halitosis on day 75 [Table 3 and Graph 2].

According to the Loe and Silness gingival index for gingivitis, 20 (42.6%) patients had moderate inflammation, and 27 (57.4%) patients had mild gingival inflammation on baseline visit. No patient had normal gingiva at the beginning of the trial. Inflammation decreased with the regular treatment with tablet AHPL/AYTAB/1514, and 1 (2.1%) subject had normal gingiva on day 60. On day 60, 18 (90%) out of 20 patients showed a decrease in gingivitis from moderate-to-mild intensity. When compared, the differences were statistically significant. One (2.1%) patient shifted from normal gingiva group to mild inflammation group, the difference was statistically insignificant. On day 75, 1 (2.1%) patient had moderate inflammation, 44 (93.6%) patients had mild inflammation and 2 (4.3%) patients had normal gingiva. When compared with the day 60 visit, no patient had recurrence or relapse in gingivitis [Table 4 and Graph 3].

On baseline visit, out of 47 patients, 3 (6.4%) patients had a continuous band of plaque, 43 (91.5%) patients had isolated flecks of plaque and 1 (2.1%) patient had no plaque as per Turesky modification of Quigley Hein index score. On visit 4, 8 (17.0%) patients had no plaque. When compared from day 45 to day 60, there was worsening of plaque condition in 2 out of 3 patients in a continuous band of plaque group. Seven (16.28%) out of 43 patients from isolated flecks of plaque group had shown improvement in plaque. When compared from day 45 to day 60, there was worsening of plaque condition in 1 patient from no plaque group. When compared from the baseline value, the difference was statistically significant in no plaque group. On visit 5, 11 (23.4%) patients had no plaque. When compared from day 60 to day 75, there was an improvement in plaque condition in 1 out of 3 patients in a continuous band of plaque group, 2 out of 36 patients in isolated flecks of plaque group. Furthermore, 2 more patients were added to no plaque group on day 75 as compared to day 60. The difference was statistically significant [Table 5 and Graph 4].

At the beginning of the trial, 46 (97.9%) cases did not have a sore throat or a cough, whereas 1 patient had a mild sore throat and cough. On day 15, all 100% of cases did not have a cough which was not a significant change from baseline. On day 30, 46 (97.9%) cases did not have a cough, and 1 (2.1%) patient had a mild cough. The difference was not significant from baseline. On day 45, day 60 and day 75, all 100.0% cases did not have a cough or a sore throat, which was not significant (P > 0.05) change from baseline.

No patient reported unacceptability of taste of study drug. Initially, only 1 patient reported burning sensation and dryness of mouth after usage of study drug, but patient did not stop usage of study drug, and the problem was resolved without any additional management. No patient felt burning sensation and dryness of mouth with the use of study indicating excellent tolerability.
According to global evaluation for overall improvement done by physician and patient, the excellent improvement was observed in 44 (95.7%) patients and good improvement was observed in 2 (4.3%) patients. Furthermore, on day 75, no relapse or recurrence of halitosis was observed in 45 (97.8%) patients. Improvement in halitosis was observed in 1 (2.2%) patient on day 75.

Excellent tolerability was observed in 41 (89.1%) patients and good tolerability was observed in 5 (10.9%) patients.
No statistically significant ($P > 0.05$) difference was observed between baseline and day 60 lab values of CBC, Hb%, ESR, serum uric acid, serum creatinine, and LFTs. Statistically significant ($P < 0.05$) reduction in mean serum triglyceride level was observed from baseline value (129.17 ± 42.18) to day 60 value (109.87 ± 33.89). No post treatment significant ($P > 0.05$) changes in ECG of any patient were observed.

Four domains including physical health, psychological, social relationships and environment were assessed in the measurement of quality of life of study patients. Statistically insignificant increase in mean scores of physical and psychological health was observed on day 60 while the statistically significant improvement in mean score of social relationship and environment was observed on day 30 and 60.

Discussion

The present study was conducted to assess the efficacy and safety of AHPL/AYTAB/1514 tablet in patients suffering from halitosis. At the end of the treatment period (60 days), the statistically significant improvement was observed in halitosis, gingivitis, and plaque index. After treatment with study drug, there were no statistically significant changes in body weight and all the vital parameters.

Few patients had seasonal mild sore throat and mild cough (during the study period), which were resolved with the study drug treatment. The patient did not require additional treatment other than study drug, indicating benefits of study drug on symptoms such as a sore throat and cough.

It was also observed that after 2 months consumption of AHPL/AYTAB/1514 tablet, no staining on the tooth was observed in any subject. Furthermore, those who already had stained teeth initially did not show an increase in the stains post treatment.

It was observed from the data that not a single subject reported unacceptability of taste of study drug. Few patients reported burning sensation and dryness of mouth after usage of study drug, strong taste of menthol and burning sensation in the chest, but they resolved without any additional treatment, and the study drug was continued. Cough, common cold, constipation and bleeding per rectum during the trial were adverse events reported by patients, those were not related to the study drug. Only two patients developed mild mouth ulcers on the 2nd and 3rd day of treatment due to study drug as per the investigator. Investigator advised dietary changes to the patients, and the problems were resolved completely.

No statistically significant difference between baseline and day 60 was observed in lab values except triglycerides level, which reduced significantly post treatment. Ingredients of AHPL/AYTAB/1514’ tablet, i.e., C. longa and P. longum possess anti-hyperlipidemic activity.[29] The synergistic action of these ingredients could have helped bring down serum triglyceride level in patients.

On the assessment of quality of life of patients, it was observed that no statistically significant change in physical and psychological health of patients occurred post treatment. Statistically significant improvement in social relationship on day 60 was observed. On day 30 and day 60 of treatment statistically significant improvement in environmental score was observed. AHPL/AYTAB/1514’ tablet effectively reduced halitosis and plaque. The significant reduction in halitosis has helped patients interact socially well.

The study showed that AHPL/AYTAB/1514’ tablet is very safe and effective in alleviating halitosis, plaque and gingivitis. AHPL/AYTAB/1514 tablet is a unique combination of Haridra (C. longa), Pippali (P. longum) and Putiha (M. arvensis). C. longa possesses anti-inflammatory and antibacterial activities.[12-15] P. longum also possesses anti-inflammatory, anti-microbial, anti-oxidant and adaptogenic properties.[16-19] Putiha is helpful to alleviate halitosis and gingivitis. Putiha is also used as a mouth and throat antiseptic and mouth freshener.[20,21] Thus, the synergistic action of ingredients of AHPL/AYTAB/1514 tablet could have helped in alleviating halitosis, gingivitis, and plaque.

Randomized, multicenter, active comparator, clinical study with large sample size is recommended to further validate the claims.

Conclusion

AHPL/AYTAB/1514 tablet is safe and effective in alleviating halitosis, gingivitis, and plaque. Even after stoppage of treatment for 15 days after 60 days of treatment, there was no relapse in halitosis. AHPL/AYTAB/1514 tablet is also effective in treating sore throat, cough, and the common cold. Furthermore, AHPL/AYTAB/1514 tablet may help in improving quality of life.

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Conflicts of interest
There are no conflicts of interest.

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