



Research Article

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SYMPTOMATIC MANAGEMENT OF FUNCTIONAL DYSPESPIA: EVALUATION OF EFFICACY AND SAFETY OF PUDIN HARA PEARLS AND PUDIN HARA LIQUID

JLN Sastry *, SD Pandey, Anurag Vats, Sasibhushan Vedula, Sunil Kumar
Head, Healthcare Research Dabur Research and Development Centre, 22, Site IV, Sahibabad, Ghaziabad,
Uttar Pradesh, India

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***Corresponding author**

E-mail: j.sastry@mail.dabur

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ABSTRACT

Treatment of functional dyspepsia has been a preferential niche for natural remedies. Pudina Hara Pearls and Pudina Hara Liquid comprise extracts of *Mentha* sp. which are used traditionally to provide relief in symptoms of dyspepsia. Objective of the current study was to assess the efficacy and safety of Pudina Hara Pearls and Pudina Hara Liquid in symptomatic management of functional dyspepsia. 79 patients with functional dyspepsia were administered either Pudina Hara Pearls (1cap/tid) or Pudina Hara Liquid (10 drops/tid) after meals for 5 days or resolution of symptoms, whichever was earlier. Efficacy was assessed from baseline on basis of improvement in symptoms such as acid regurgitation, heart burn, stomach pain, upper abdominal bloating, nausea and the Investigator's and the patient's global evaluation of therapeutic response. Safety was assessed on basis of development of adverse events and changes in hematological and biochemical profiles. Pudina Hara Pearls and Pudina Hara Liquid produced significant improvement in symptoms of functional dyspepsia. Though there were no statistically significant differences in comparative efficacy of study products, Pudina Hara Pearls were better on symptoms like acid regurgitation, upper abdominal bloating and nausea; and Pudina Hara Liquid was better in relieving feeling of acidity, loss of appetite and vomiting. No adverse events were reported with any of the study products. Results concluded Pudina Hara Pearls and Pudina Hara Liquid are effective in the management of symptoms functional dyspepsia and can be used safely.

Keywords: Pudina Hara, Functional Dyspepsia, Indigestion, Symptomatic.

INTRODUCTION

Dyspepsia is a syndrome consisting of epigastric pain, burning, fullness, discomfort, early satiety, nausea, vomiting and belching¹. An organic cause like gastro-duodenal ulcer, gastro-esophageal reflux disease, and gastric cancer is found in 40% of patients with dyspeptic symptoms². In others, dyspepsia is considered to be idiopathic and termed as Non-ulcer Dyspepsia or Functional Dyspepsia. Patients with dyspepsia have reduced health-related quality of life because their symptoms, particularly abdominal pain and indigestion, cause emotional distress, problems with food and drink, and impaired vitality^{4,5}. Ayurveda recognizes this condition is one of the major digestive disorders like Amlapitta or Vidagdhajirna that result due to dysfunction of Jatharagni, or the *Agni* situated in upper part of digestive system and identifies etiological factors like indulgence of incompatible foods, irregular food habits and seasonal variations for it.^{6,7}

Treatment of functional dyspepsia remains problematic. Historically, the H₂-receptor antagonists have been tried but the results are disappointing. The use of Cisapride and itopride is now severely restricted due to side effects and failed Phase III trials. Proton pump inhibitors have shown modest efficacy. *Helicobacter pylori* eradication has shown some minor benefits⁸. As treatment of functional dyspepsia with conventional medication remains unsatisfactory, herbal remedies have been tried in small studies and the results have been promising^{9,10}. Pudina Hara Pearls and Pudina Hara Liquid (Mfd: Dabur India Limited) are Ayurvedic formulations intended to be used in indigestion that comprise extract of Pudina (*Mentha* sp). There have been references to Pudina as a medicinal herb for gastrointestinal upsets since ancient times¹¹. The current study evaluated the efficacy and safety of Pudina Hara Pearls and Pudina

Hara Liquid in patients with functional dyspepsia in terms of improvement in symptoms.

MATERIAL & METHODS

Study Product

Each 180 mg of Pudina Hara Pearls comprises of *Mentha* oil (*Mentha piperata*, Aerial part, Oil.) - 0.174 ml and Spearmint Oil (*Mentha spicata*, Aerial part, Ol.) - 0.034 ml along with excipients, preservatives and colors.

Each 1ml (20 drops approx) of Pudina Hara Liquid comprises Pudina Satva (*Mentha piperata*, Aerial part, Ol.) - 0.0337 ml along with excipients, preservatives and colors.

Study Design

The trial was a 5 days open label, prospective and comparative study conducted at Dhanwantri Ayurvedic Hospital, Chandigarh, India. The study was approved by the institutional ethics committee of Dhanwantri Hospital on 09.03.2006. All procedures followed were in accordance with ICH-GCP Guidelines. Subjects that entered the study had voluntarily given a written informed consent. The study was retrospectively submitted to the CTRI vide REF/2016/04/011092.

Patient Enrollment

Patients attending the Dept. of Kayachikitsa (medicine), Dhanwantri Hospital, Chandigarh, were screened for enrolment as per the inclusion/exclusion criteria. Male and Female subjects between 12 - 60 years of age suffering from functional dyspepsia *i.e.* indigestion and its related signs and symptoms such as fullness, bloating, nausea, gassy discomfort,

loss of appetite, spasm and pain in the chest or abdomen for at least on two occasions in the preceding week and were having normal hepatic and renal functions (LFT & RFT) were included. Subjects with persistent dyspepsia, vomiting, severe epigastric pain, unintentional weight loss, iron deficiency anemia, gastrointestinal bleeding, dysphasia, odynophagia, previous gastric surgery, epigastric mass, suspicious barium meal, peptic ulcer and NSAID use. Organic deformity or malignancy of the GI tract, significant systemic and psychological condition (s) which may hamper the study proceedings, conditions requiring immediate surgical intervention, known hypersensitivity to study product or its ingredient (s), concomitant medications known to adversely interact with study products or their ingredients, alcohol or drug abuse, pregnancy, lactation and females planning to conceive in near future were excluded from the study.

Study Protocol

Detailed subject history, including the intensity and frequency of symptoms, previous treatment and physical examination were recorded at baseline. Thereafter, subjects were assigned to receive either Pudina Hara Pearls 1 capsule or Pudina Hara Liquid 10 drops, orally three times a day after meals for 5 days or resolution of symptoms, whichever was earlier according to computer generated randomization.

End Points

Therapeutic: 5 days of intervention with study products or resolution of symptoms whichever was earlier.

Clinical: Reduction in the symptom(s), if any, associated with indigestion and its related problems.

PARAMETERS OF ASSESSMENT

Improvement in the following parameters was assessed from baseline to study completion: -

Improvement in Subjective Symptoms of dyspepsia¹²

1. Acid regurgitation
2. Heartburn
3. Feeling of acidity
4. Loss of appetite
5. Stomach
6. Upper abdominal bloating
7. Upper abdominal dull ache
8. Stomach pain before meals
9. Stomach pain when anxious
10. Vomiting
11. Nausea
12. Belching,
13. Fullness of stomach
14. Flatulence
15. Intensity of Pain

Symptoms no. 1-12 were assessed on a five-point scale where, 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe. Symptoms no. 13-14 were assessed over a 4-point scale: 0=Null, 1=present, does not cause trouble in work at all; 2=present, sometimes cause trouble in work, 3=Present and due the symptom unable to do work.

Symptom no.15 was assessed on a 0-10-point scale on VAS, where 0 = absent/never, 10 = extremely severe constant.2. For global evaluations, Patients' & Investigators were asked to

encircle the degree of control on a scale of 0-100%, where 0 = no relief, 100 = best relief one could get.3. Safety was assessed on basis of clinically significant changes in hematological & biochemical parameters (CBC, ESR, LFT, RFT and RBS).

Follow up

Evaluation of therapeutic response was carried out daily for 5 days on basis of improvement in subjective symptoms, the ADR/AE profile and the global efficacy assessments. Hematological and biochemical profiles (CBC, ESR, LFT, RFT and RBS) were assessed at baseline and day 5. For global assessment, patients were given a daily diary with instructions to fill the diary every day. It was collected from patients on day 5.

Statistical Analysis

Statistical Analysis was carried out on SAS and included both descriptive and inferential tests Intensity of pain was analyzed using repeated measures ANOVA. Pair-wise comparisons between the groups were performed only in case of statistical significance ($p < 0.05$).

RESULTS & DISCUSSION

90 subjects were recruited in study and 79 subjects completed the trial There were 11 subjects who did not complete the study, which includes lost to follow-up and withdrawal consent however no subject dropped out because of safety reasons. Of these, 43 were treated with Pudina Hara Pearls and 36 with Pudina Hara Liquid. A relatively high proportion of subjects in this study were women - 72.10% and 58.33%, respectively in Pudina Hara Pearls and Pudina Hara Liquid groups. The mean age was 32.97±1.92 and 34.31±10.99 years, respectively in the groups.

Effect on subjective symptoms: Pudina Hara Pearls and Pudina Hara Liquid were effective in reducing subjective symptoms of functional dyspepsia. Overall, a significant improvement in symptoms was observed visit 2 onwards to study completion and subjects reported 61.96 % and 51.04% improvement in symptoms from baseline at study completion (Table 1).

Both the study products were effective from day 1 in relieving acid regurgitation and heart burn. A significant reduction in these conditions was observed from day 2 onwards to study completion. Significant relief in feeling of acidity was observed earlier with Pudina Hara Liquid (day 2 onwards) than with Pudina Hara Pearls (day 4 onwards).

Significant improvement in appetite in subjects in both the study groups was observed at study completion. Stomach pain and upper abdominal dull ache showed significant reduction from day 3 onwards and in both the treatment arms. Subjects in both the groups showed significant reduction day 2 onwards in intensity of pain. Response, though little, was also observed in stomach pain before meals and stomach pain when anxious in both the groups.

Subjects in both the groups showed significant improvement in nausea day 2 onwards. Pudina Hara Liquid was found more effective reducing in vomiting. In case of belching, both the study products were equally effective. Both the study products were effective in relieving fullness of stomach, flatulence and upper abdominal bloating. Significant improvement in all the three symptoms was found to be earlier with Pudina Hara Pearls (Table 2).

Subject's & Physician's Global Evaluation: Global evaluations by patients' and Investigator showed improvement ($p < 0.05$) in the both the treated group results from day 2 onwards to study completion in both the groups.

Individually, all the subjective symptoms improved in the treatment groups in comparison to the baseline. There were, however, no statistical differences between the overall effects of therapies. None of the patients discontinued treatment because of adverse events. All safety parameters were within the normal limits at the end of the trial.

Treatment of functional dyspepsia has recently been a preferential niche for natural remedies. Due to the paucity of effective conventional medication for the treatment of functional disorders of the alimentary tract, natural remedies and herbal preparations have been tested for these conditions during the past few years^{8,9}. Herbal products seem to be effective and safe in non-ulcer dyspepsia due to their carminative, stomachic and

antispasmodic properties¹⁰. For indigestion spices as food additives have been used widely since ancient time. Apart from enhancing the taste and flavor of food spices have been widely believed to exert digestive stimulant action. A few medicinal properties of spices such as tonic, carminative, stomachic and antispasmodic have long been recognized. These attributes, largely empirical, nevertheless efficacious, have earned them pharmacological application in the indigenous system of medicine as digestive stimulant and to relieve digestive disorders. Spices such as ajowain, cumin, ginger, mint, hing, garlic, fennel, coriander and pepper are the usual ingredients of digestive stimulant as both commercial and home remedies. *Pudinah*, an ingredient of both Pudin Hara Pearls and Pudin Hara Liquid, possesses anti-spasmodic, anti-emetic, digestive¹⁰ and anti-oxidant^{13,14} properties which may have contributed to the overall effect of drug in relieving symptoms of dyspepsia.

Table 1: Effect of Treatment on Subjective Symptoms of Dyspepsia (with % Improvement)

Treatment Group	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
Pudin Hara Pearl	11.41±6.45	11.41±6.69 (0)	9.00±5.98* (21.12)	07.41±6.06* (35.06)	05.69±5.91* (50.13)	04.34±5.08* (61.95)
Pudin Hara Liquid	11.50±5.68	11.16±5.75 (2.96)	8.91±4.96* (22.52)	07.80±5.31* (32.17)	05.88±4.55* (48.87)	5.63±5.37* (51.04)

*= significant, $p < 0.05$

Table 2: Individual score symptom influenced by the treatment - Pudin Hara Pearls (1 cap/tid for 5 d)

Symptom	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
Acid Regurgitation	1.27±1.18	1.20±1.16 (5.51)	0.81±0.98*(3 6.22)	0.62±0.78* (51.18)	0.46±0.70* (63.78)	0.27±0.54* (78.74)
Heartburn	1.23±0.99	1.13±1.01 (8.13)	0.93±1.07* (24.39)	0.83±0.97* (32.52)	0.67±0.94* (45.53)	0.44±0.66* (64.23)
Feeling of Acidity	0.97±1.01	1.06±0.98 (9.28)	0.93±1.00 (4.12)	0.76±0.97 (21.65)	0.55±0.93* (43.30)	0.44±0.76* (54.64)
Loss of Appetite	1.34±1.28	1.20±1.16 (10.45)	0.97±1.12* (27.61)	0.93±1.16* (30.60)	0.83±1.11* (38.06)	1.72±1.07* (46.27)
Stomach Pain	1.16±1.17	1.23±1.23 (6.03)	1.00±1.13 (13.79)	0.83±0.97* (28.45)	0.53±0.73* (54.31)	0.39±0.58* (66.38)
Upper Abdominal Bloating	1.20±1.03	1.20±0.91 (0.00)	0.74±0.75* (38.33)	0.67±0.94* (44.17)	0.44±0.66* (63.33)	0.30±0.59* (75.00)
Upper Abdominal Dull Ache	0.95±0.97	1.02±0.93 (3.59)	0.90±0.86 (2.56)	0.65±0.65* (15.38)	0.53±0.66* (21.54)	0.37±0.65* (29.74)
Stomach Pain when Anxious	1.39±0.69	1.58±0.85 (13.67)	1.39±0.76 (0.00)	1.34±0.61 (3.60)	1.32±0.71 (5.04)	1.23±0.61* (11.51)
Stomach Pain before Meals	0.39±0.69	0.58±0.85 (48.72)	0.39±0.76 (0.00)	0.34±0.61 (12.82)	0.32±0.71 (17.95)	0.23±0.61 (41.0)
Vomiting	0.37±1.64	0.39±0.79 (5.41)	0.34±0.71 (8.11)	0.27±0.62 (27.03)	0.23±0.52 (37.84)	0.18±0.50 (51.35)
Nausea	1.06±0.96	0.97±1.01 (8.49)	0.67±0.94* (36.79)	0.48±0.73* (54.72)	0.32±0.68* (69.81)	0.32±0.71* (69.81)
Belching	1.04±1.02	0.95±0.95 (8.65)	0.93±0.91 (10.58)	0.69±0.86* (33.65)	0.53±0.76* (49.04)	0.48±0.66* (53.85)
Fullness of Stomach	2.69±1.12	2.60±1.19 (3.35)	2.34±1.17* (13.01)	2.04±1.11* (24.16)	1.79±1.10* (33.46)	1.67±0.91* (37.92)
Flatulence	2.69±1.18	2.55±1.25 (5.20)	2.34±1.17* (13.01)	2.09±1.19* (22.30)	1.81±0.93* (32.71)	1.69±0.86* (37.17)
Intensity of pain	4.00±2.39	3.68±2.24 (8.00)	3.31±2.15* (17.25)	2.71±2.05* (32.25)	2.26±2.00* (43.50)	1.84±2.12* (54.00)

*= significant, $p < 0.05$

Table 3: Individual symptom score influenced by the treatment - Pudina Hara Liquid (10 drops/ tid for 5d)

Symptom	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
Acid Regurgitation	1.38±1.15	1.27±1.25 (7.97)	1.00±1.01* (27.54)	0.83±1.02* (39.86)	0.66±0.95* (52.17)	0.58±0.96* (57.97)
Heartburn	1.38±1.15	0.36±1.19 (73.91)	0.88±1.11* (36.23)	0.88±1.08* (36.23)	0.72±1.11* (47.83)	0.61±1.04* (55.80)
Feeling of Acidity	1.11±0.88	1.16±0.91 (4.50)	0.83±0.84* (25.23)	0.66±0.92* (40.54)	0.47±0.69* (57.66)	0.41±0.60* (63.06)
Loss of Appetite	1.19±1.21	1.16±1.25 (2.52)	1.00±1.06 (15.97)	1.05±1.09 (11.46)	0.83±1.05* (30.25)	1.72±0.97* (39.50)
Stomach Pain	1.27±1.05	1.36±1.09 (7.09)	1.08±0.90 (14.96)	0.80±0.85* (37.01)	0.55±0.77* (56.69)	0.63±1.01* (50.39)
Upper Abdominal Bloating	1.16±1.08	1.02±1.02 (12.07)	1.05±1.06* (9.48)	0.80±1.03* (31.03)	0.69±0.92* (40.52)	0.72±1.11* (37.93)
Upper Abdominal Dull Ache	0.88±0.91	0.91±0.93 (1.60)	0.80±0.95 (4.26)	0.77±0.89* (5.85)	0.55±0.65* (17.55)	0.52±0.81* (19.15)
Stomach Pain when Anxious	1.44±0.65	1.47±0.73 (2.08)	1.36±0.63 (5.56)	1.30±0.52 (9.72)	1.19±0.52 (17.36)	1.25±0.69 (13.19)
Stomach Pain before Meals	0.44±0.65	0.47±0.73 (6.82)	0.36±0.63 (18.18)	0.30±0.52 (31.82)	0.19±0.52 (56.82)	0.25±0.69 (41.03)
Vomiting	0.25±0.50	0.22±0.48 (12.00)	0.11±0.31* (56.00)	0.16±0.56* (36.00)	0.02±0.16* (92.00)	0.05±0.23* (80.00)
Nausea	0.86±0.93	0.88±0.97 (2.33)	0.58±0.80* (32.56)	0.50±0.81* (41.86)	0.44±0.80* (48.84)	0.44±0.73* (48.84)
Belching	1.19±1.19	1.02±1.13 (14.29)	0.88±1.00 (26.05)	0.80±1.09 (32.77)	0.52±0.97* (56.30)	0.55±0.99* (53.78)
Fullness of Stomach	2.55±0.96	2.50±1.08 (1.96)	2.47±1.15 (3.14)	2.27±1.13 (10.98)	2.02±0.97* (20.78)	1.91±1.02* (25.10)
Flatulence	2.61±0.93	2.38±1.07 (8.81)	2.36±1.07 (9.58)	2.25±1.02* (13.79)	1.86±0.79* (28.74)	1.80±0.70* (31.03)
Intensity of pain	4.64±2.33	4.25±2.50 (8.41)	3.77±2.66* (18.75)	2.93±2.59* (36.85)	2.51±2.51* (45.91)	1.96±2.76* (57.76)

*= significant, $p < 0.05$

Table 4: Global Evaluation of Symptoms Therapeutic Response (with % Improvement)

Treatment Group	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
Pudina Hara Pearl	11.41±6.45	11.41±6.69 (0)	9.00±5.98* (21.12)	07.41±6.06* (35.06)	05.69±5.91* (50.13)	04.34±5.08* (61.95)
Pudina Hara Liquid	11.50±5.68	11.16±5.75 (2.96)	8.91±4.96* (22.52)	07.80±5.31* (32.17)	05.88±4.55* (48.87)	5.63±5.37* (51.04)

*= significant, $p < 0.05$

CONCLUSION

Pudina Hara Pearls and Pudina Hara Liquid were significant in reducing symptoms of functional dyspepsia such as acid regurgitation, heartburn, feeling of acidity, stomach pain and upper abdominal bloating etc. Though there were no statistically significant differences in comparative efficacy of study products on symptoms of dyspepsia, Pudina Hara Pearls were better on acid regurgitation, heart burn, upper abdominal bloating and stomach pain and Pudina Hara Liquid was better in relieving feeling of acidity, intensity of stomach pain and vomiting. No adverse events were reported during the course of study in any of the study subjects. It could be concluded that both Pudina Hara Pearls and Pudina Hara Liquid were effective in the management of functional dyspepsia and could be used safely.

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