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Is *Chios mastic* gum effective in the treatment of functional dyspepsia? A prospective randomised double-blind placebo controlled trial

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ABSTRACT

Background: Herbal remedies are increasingly popular for the treatment of functional dyspepsia. *Chios mastic* gum is a resinous exudate from the stem of *Pistacia lentiscus* var. *chia*. It is a traditional natural remedy used throughout the eastern Mediterranean.

The aim of this study was to assess the efficacy of *Chios mastic* gum in patients with functional dyspepsia. *Methods:* One hundred and forty eight patients fulfilling Rome II criteria for functional dyspepsia were randomly assigned to receive either *Chios mastic* gum 350 mg three times daily or placebo. After 3 weeks of treatment the change from baseline in the severity of symptoms of functional dyspepsia was assessed using the Hong Kong index of dyspepsia. Patients' global assessment of efficacy was also evaluated. *Results:* The symptom score after treatment was significantly lower in the *Chios mastic* gum than in the placebo group ((14.78 ± 1.78) vs (19.96 ± 1.83)) ($p < 0.05$). There was a marked improvement of symptoms in 40% of patients receiving placebo and in 77% of patients receiving *Chios mastic* gum ($p < 0.02$). Individual symptoms that showed significant improvement with *Chios mastic* gum were: stomach pain in general, stomach pain when anxious, dull ache in the upper abdomen and heartburn (<0.05 for all four symptoms). *Conclusion: Chios mastic* gum significantly improves symptoms in patients with functional dyspepsia compared to placebo.

1. Introduction

Dyspepsia is a very common problem that affects large numbers of individuals worldwide especially in the Westernised world. Patients with dyspepsia problems are treated both by primary care physicians as well as gastroenterologists in the different health care systems. Dyspepsia in the absence of an identifiable structural lesion in the upper gastrointestinal system is referred to as functional dyspepsia (Talley et al., 1999).

Treatment of functional dyspepsia remains problematic. Historically the H_2-receptor antagonists have been tried in dyspepsia but the results were generally disappointing (Talley et al., 1986; Kato et al., 2005; Ashizawa et al., 2006,). At about the same time prokinetics were also used in functional dyspepsia. Mosapride showed a small improvement in symptoms in a small trial (Wu et al., 2006). Cisapride, a related compound has shown superiority over placebo in meta-analyses but its use is now severely restricted due to cardiac side effects (Veldhuyzen van Zanten et al., 2001). Itopride a newer D2-receptor antagonist has shown some promising results in one large and two smaller trials (Amarapurkar and Rane, 2004; Zhu et al., 2005; Holtmann et al., 2006) but it has failed Phase III trials (Talley et al., 2008). As for proton pump inhibitors recent meta-analyses have shown efficacy but the effect was modest (Moayyedi et al., 2004; Van Zanten et al., 2006). *Helicobacter pylori* eradication has shown some minor benefit in recent trial and meta-analyses (Moayyedi et al., 2003; Di Mario et al., 2005; Ang et al., 2006). As for alosetron, whose use is restricted in some countries due to side effects it has shown benefit in functional dyspepsia (Talley et al., 2001).

As treatment of functional dyspepsia with conventional medication remains unsatisfactory, herbal remedies such as iberogast (Melzer et al., 2004a,b; Von Arnim et al., 2007), and artichoke leaf extract (Holtmann et al., 2003; Meier and Brignoli, 2005) have been tried in small studies for the treatment of this condition. The results have been promising and results from bigger trials are awaited.

Chios mastic gum is a resinous exudate which is derived from the stem of the bush *Pistacia lentiscus* var. *chia*. *Chios mastic* gum is usually sold as a chewing gum. It is also used in cooking and

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cosmetics. There have been references to Chios mastic gum as a medicinal product for gastrointestinal upsets since ancient times (Kaliora et al., 2007). It is still widely used as a remedy for these in many parts of the Mediterranean basin and the Middle East (Triantafyllou et al., 2007).

Although *Chios mastic* gum is traditionally used in dyspepsia like symptoms no properly designed trial has ever been conducted to test its efficacy. Our aim was to evaluate the efficacy on *Chios mastic* gum in patients with functional dyspepsia in terms of improvement of the perception of symptoms.

2. Materials and methods

The trial was a 3-week double-blind randomised placebo controlled study designed to investigate the effects of *Chios mastic* gum on functional dyspepsia symptoms.

The study was conducted in Chios District General Hospital Skyliitsion, Chios, Greece.

The study was approved by the local ethics committee (Reference no. MGCGH0031/05) and the Greek Medicines Agency (Reference no CGH266/05 B). All procedures followed were in accordance with the Declaration of Helsinki (1975, amended 2000) on experimentation on human subjects. Patients that entered the study had previously given written informed consent.

2.1. Assignment

Patients visiting the Gastroenterology, Internal Medicine and Abdominal Surgery clinics at the Outpatients Department were recruited. Subjects were consecutively enrolled.

Males and females 18–75 years of age were eligible for the trial if they were found to satisfy Rome II criteria for functional dyspepsia (Talley et al., 1999). Functional dyspepsia was diagnosed if recurrent upper abdominal pain or discomfort were present. Discomfort was characterised by the presence of one or more of the following symptoms. Bloating, nausea, vomiting, belching and loss of appetite. These could be associated with gastro-esophageal reflux symptoms i.e. acid regurgitation and heartburn. Patients whose main (more than once a week) or only complain was gastro-esophageal reflux were excluded from the trial. Symptoms had to be present for at least 12 weeks in the previous 9 months.

Patients underwent a physical examination, routine laboratory tests, upper gastrointestinal endoscopy and *Helicobacter pylori* testing. Patients harbouring a *Helicobacer pylori* infection were excluded. Upper gastrointestinal endoscopy had to be performed within the last 2 months before entering the study. Patients with a hiatal hernia were allowed to enter the study but not patients who were found to have gastritis or duodenitis, on endoscopy.

Patients that were using medication that could alter gastric function notably narcotics, tricyclic antidepressants and calcium channel blockers were not eligible for the study. A washout period of 4 weeks was imposed on the use of prokinetics and proton pump inhibitors.

2.2. Masking

The randomisation was generated using Proc random (SAS version 6.9). Patients were enrolled at the Dyspepsia clinic of the Gastroenterology Department. Medication was delivered to the hospital in blocks of twelve. Central pharmacy assigned participants to their groups. Patients received one capsule three times a day for 3 weeks. The study medication was packaged identically for the two study groups and was identifiable only by a randomisation number. Patients who met the inclusion and exclusion criteria were assigned a randomisation number and were treated with the correspondingly identified study medication. Participants, researchers that conducted the study and those who assessed the outcomes were blinded to group assignment.

2.3. Participant flow

After the diagnosis of functional dyspepsia was established, patients were asked to enter the study. Between two and nine days after completion of the test battery, the disease specific questionnaire was administered to determine patients' baseline status. At that point they were randomised to receive either placebo or pure *Chios mastic* gum 350 mg three times daily for 3 weeks. Pure *Chios mastic* gum was dispensed in capsule form with no flavourings added to the natural product. Placebo capsules were identical in size and filled with lactose. Patients were asked to take tablets before meals. Quality control of the mastic gum was assured by the Mastic Gum Growers Cooperative. Composition of *Chios mastic* gum can be found in Appendix A. A reference sample from the same batch was stored by the sponsor. Mastic gum was first mechanically separated from impurities and finally, purity was checked by fractional distillation.

2.4. Analysis

We used the validated Hong Kong index of Dyspepsia (HKID) (Hu et al., 2002), to assess symptoms at baseline and at the end of treatment. The HKID was administered by an investigator in a face to face interview. It measures the following twelve dyspepsia symptoms on a five point scale each (0 for absent, 1 for mild, 2 for moderate, 3 for severe and 4 for very severe). Stomach pain in general, bloating of the upper abdomen, dull ache of the upper abdomen, stomach pain before meals, stomach pain when anxious, vomiting, nausea, belching, acid regurgitation, heartburn, acidity in the stomach, loss of appetite. A summary score of 0–48 represents the severity of the dyspeptic symptoms.

Patients' global assessment of efficacy was also evaluated at the end of the 3 weeks' trial period. The first specific question used was: "Did you see any improvement of your symptoms while on the trial medication?" Then a second question was asked: "On this five point scale which answer would more accurately describe your symptoms' improvement?" Symptom-free, marked improvement, moderate improvement, no change and deterioration. A positive response to treatment was pre-specified as improvement of at least two points in the five point Likert scale.

2.5. Follow up

At the end of the study patients returned their medication and capsules were counted. Patients taking more than 75% of the capsules were thought to be compliant. At the end of the study a physical examination was performed as well as routine laboratory tests including full blood count, liver and renal function tests and measurement of blood glucose, cholesterol, triglycerides and uric acid.

One month after study completion patients returned to the clinic and an inquiry on side effects and adverse events was then made.

The change in the summary HKID score relative to the baseline was evaluated as a primary outcome. The patients' global assessment of efficacy at the end of the study was a second primary outcome.

2.6. Statistical analysis

An intention to treat analysis was conducted on all patients randomised to therapy who received at least one dose of study medication.