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RESEARCH ARTICLE

Gastroplex® As An Investigational Medicinal Product In Treatment Of Acute And Chronic Gastritis: Single Centre, Randomized, Double Blind, Clinical Study.

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Introduction: Gastritis is a condition with variable clinical manifestations and no known cure. An NSAID-based treatment for Helicobacter pylori infection has been associated with negative side effects conventionally. Studies have been done on the potential of investigational medicinal products (IMPs) to cure gastritis. In this study, the efficacy of the IMPs was compared against placebos in the treatment of gastritis.
Methods: A randomised, double-blind, placebo-controlled investigation was conducted in the region of Maharashtra, India. In addition to standard medication, patients were administered either investigational medicinal products (IMPs) or placebos. The primary and secondary outcomes were assessed using the Gastrointestinal Quality of Life Index (GIQLI) and the Visual Analogue Scale Severity Scale for Pain (VAS), respectively. Measurements were taken at the initial assessment and subsequently on a weekly basis for a duration of four weeks. The sample that was intended-to-treat (ITT) was analysed using a two-way repeated measures ANOVA.
Results: There were 60 participants in the analysis. By the conclusion of week four, the Gastroplex®-treated participants had significantly less pain than the placebo group (p-value = 0.003). With a significant effect size, the GIQLI score likewise favored IMPs over placebos (p-value = 0.002). There were no negative consequences noted.
Conclusion: Gastroplex® demonstrated better efficacy compared to placebo in lowering pain and raising GIQLI scores in participants with acute and chronic gastritis. The therapy was also safe and well-tolerated.
Trial registration: CTRI/2023/01/049226

Keywords: Gastritis, Gastroplex®, randomized controlled trials, *Helicobacter pylori*, placebo.

INTRODUCTION

Gastritis, a typical illness marked more by histological traits than by specific clinical manifestations or symptoms, is an inflammation of the stomach mucosa. The classification of gastritis depends on the time course (acute or chronic), histological characteristics, anatomical distribution, and underlying pathogenic mechanisms[1]. While Helicobacter pylori (H. pylori) infection is the most common cause of gastritis globally, acute gastritis can become a chronic illness if left untreated[1]. It has been reported that a large percentage[2] of persons with functional dyspepsia or non-erosive gastroesophageal reflux who are not infected with H. pylori also have gastritis[3].

Non-infectious gastritis causes include but not limited to, use of Nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, alcohol, or tobacco and autoimmune processes. The corpus and fundus of

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the stomach are the main areas damaged by chronic atrophic gastritis caused by autoimmune gastritis, which also causes significant atrophy of the parietal and chief cells[1]. In addition, gastroenteritis has been linked to infections with Mycobacterium avium intracellular, Herpes simplex, and Cytomegalovirus[3,4].

Gastritis may also develop as a result of acid reflux. Less frequently, gastritis may arise from conditions such as collagenous gastritis, sarcoidosis, eosinophilic gastritis, and lymphocytic gastritis[5].

Antibiotics are typically used to treat H. pylori-associated gastritis, causing the polymorphonuclear infiltration and chronic inflammatory infiltrate to fade and progressively repair the stomach mucosa[1,6]. The likelihood that H. pylori treatment alone will not completely cure mucosal atrophy and metaplastic changes emphasises the importance of customised treatments for various types of gastritis based on their specific aetiologies[7–9]. Depending on the underlying reason, various methods of treatment are used for gastritis. While autoimmune metaplastic atrophic gastritis may need vitamin supplementation, H. pylori gastritis frequently responds to treatment. For autoimmune enteropathy, immunomodulatory treatment may be used, and dietary changes may be helpful for eosinophilic gastritis[10,11].

Single or combination of homeopathy medicines exhibit beneficiary role in the treatment of a wide range of gastric disorders[12]. *Carica Papaya* has suggested the ability to neutralize stomach acidity, thereby protecting stomach against gastric ulcer[13,14]. Gastroplex®, a multi-substance combination drug, has been evaluated for its therapeutic efficacy in the Indian population as part of research on the treatment of gastritis. The components of Gastroplex® include *Carica Papaya* Q[14], *Hydrastis Canadensis* Q[15], *Belladonna* Q[16], *Iris Versicolor* Q[16], *Lycopodium Clavatum*[17], *Pulsatilla Nigricans* Q[18], *Anacardium Orientale* Q[19], *Nux Vomica* Q[20], *Robinia Pseudacacia* Q[21], *Colocynth* Q[22], *Caram Carvi*[23], and Palatable Syrup Base. Because of the range of causing variables and treatment techniques related to gastritis, ongoing research and clinical investigations are still required to increase our understanding and improve therapy strategies for this difficult gastrointestinal condition.

MATERIALS AND METHODS

Trial Design

A randomised, double-blind, placebo-controlled clinical trial was done over a set length of time to collect data from Indian patients with acute and chronic gastritis[24]. Patients who met the inclusion criteria were randomly assigned to either Gastroplex® Syrup or a placebo. The researchers gathered data on a variety of characteristics, including symptom severity, adverse events, and patient-reported outcomes. This study was approved by independent ethics committee and registered at the clinical trial registry of India (CTRI/2023 /01/049226).

Participants

The study, which was conducted at a single study centre, included about 60 evaluable participants with acute and chronic gastritis. Subjects had to fulfil particular inclusion requirements in order to be eligible to participate. These requirements included being male or non-pregnant and non-lactating female between the ages of 18 and 70, having symptoms such as abdominal pain, epigastric burning, nausea and vomiting, and early satiety suggestive of acute or chronic gastritis, and being willing and able to provide written informed consent. Additionally, participants had to be able to follow the dosage requirements for the research medicine and finish the testing schedule.

However, there were several exclusion standards that would bar participants from taking part in the study. These requirements included being pregnant or nursing, having a body mass index greater than 35 kg/m2, having a history of an allergic reaction to the investigational medicine's active ingredient or excipients, or having a history of a gastric ulcer, duodenal ulcer, gastric carcinoma, Zollinger-Ellison syndrome, or esophageal varix[25]. Other exclusion criteria included factors such as active drug or alcohol abuse, a history of drug or alcohol addiction or abuse within the previous year, major surgery to the gastrointestinal tract, liver, or kidney within three months of study entry, a history of allergic asthma, organ or tissue transplant, psychiatric disorders including eating disorders, autoimmune disorders, and clinically significant disorders affecting various bodily systems.

One study centre was engaged in the investigation, which involved about 60 individuals with acute and chronic gastritis. Specific inclusion and exclusion criteria had to be met by participants, who were then disqualified if any of the exclusion criteria were met.

By minimising any confounding factors, these criteria made sure that the study population was acceptable for the study's goals.

Primary Objective

The primary goal of this study was to examine the efficacy of Gastroplex® Syrup in Indian patients with acute and chronic gastritis. The efficacy assessment involved monitoring the severity of symptoms such

as abdominal pain, bloating, nausea, and indigestion after treatment with Gastroplex® Syrup. Data on symptom improvement were collected using validated grading systems, patient diaries, and frequent assessments.

Secondary Objective

In order to determine whether Gastroplex® Syrup is safe and well-tolerated by Indian patients with both acute and chronic gastritis, the study's secondary goal examined these factors. As part of the safety assessment, patients' adverse events and side effects that occurred during the study were tracked and recorded. In addition, the researchers obtained information on the syrup's acceptability, which involved gauging patient adherence to the regimen, acceptance of it, and general contentment with it.

Sample size

A sample size of 60 patients per arm was established using statistical calculations, with a power of 90% and a significance threshold of 0.05[26]. The estimate employed a power analysis of two independent proportions (Null Case) and took into account a group difference of 20%. The two-sided Z test with pooled variance was used as the test statistics[27].

Treatment procedures

An investigational medicinal product (IMP) was given to trial participants for a total of 12 weeks. Based on the study's eligibility requirements, participants were chosen and then randomised in a 2:1 ratio to one of two treatment groups, with the first group getting Gastroplex® syrup and the second group receiving a placebo syrup.

Randomization

A randomization schedule created by R Studio was used to choose the sequence of treatment assignments for each patient, guaranteeing a balanced distribution[28,29]. The study practitioner or a designated person administered the research medications in a double-blind fashion. The process was determined with Gastroplex®'s existing dosage.

Blinding and allocation

The study's administration of the investigational medicinal products (IMPs), including their dosage and administration, was done using a double-blind procedure. Serially numbered,
sealed envelopes were used for the allocation of treatments. Over the course of four weeks, subjects were told to ingest the syrup in the following amounts: three teaspoons (or 15 ml), six teaspoons (or 30 ml), twice daily after meals. If a subject missed a dose, they were encouraged to take the next dose at their usual dosing time, provided that it happened within 8 hours of the scheduled time. Syrup from the Gastroplex® brand was given to Treatment Group A, while syrup from the placebo brand was given to Treatment Group B. Throughout the 4-week period, both groups maintained the same dose schedule.

Scheduling

Screening, in-treatment, and post-treatment assessments made up the three primary stages of the study plan for each subject. The informed consent form could be signed up to 28 days prior to the delivery of the investigational medicinal product (IMP), and that marks the beginning of the subject's involvement in the study. Within 28 days of the baseline/Day 1 visit, the screening assessments were completed.

All subjects had to show up for certain study sessions, which included screening, baseline/day 1, week 2, and week 4 (the completion of treatment), during the course of the study. At various points throughout the study, these visits allowed for the gathering of vital data.

Statistical analysis

The statistical analysis plan (SAP) used to compare the efficacy of Gastroplex® in treating acute and chronic gastritis symptoms to a placebo is given in this summary. By comparing the percentage of patients in each group who reported an improvement in their symptoms, the study used a set of hypotheses to investigate this claim. Data evaluation techniques included statistical tests, confidence intervals, and analytic techniques.

The study includes two sample proportion tests comparing the null hypothesis (H_0: $P1 \geq P2$) with the alternative hypothesis (H_a: $P1 < P2$), where P1 denotes the proportion of patients in the Gastroplex® group who have improved and P2 denotes the proportion in the placebo group. The difference in the proportions was computed using a one-tailed hypothesis and a 95% confidence range.

A rating scale was used to evaluate subjective factors such as abdominal pain, epigastric burning, motion sickness, and early satiety. These factors were assessed both before and after therapy using the Ranked ANCOVA method[30]. R Studio 4.2.3[31] was used to conduct the statistical analysis. The sample that was intended-to-treat (ITT) was analysed using a two-way repeated measures ANOVA.

Outcome measures

Primary outcome; the Gastrointestinal Quality of Life Index (GIQLI)[32] and changes in pain levels as measured by the Visual Analogue Scale (VAS) at the end of week 4 compared to baseline were the main efficacy objectives. To calculate treatment effects, an

analysis of variance (ANOVA) model, least-square means, and 95% confidence intervals were utilised. The Shapiro-Wilks test[33] and the Levenes test[34] were used, respectively, to examine the assumptions of normality and homogeneity of variances. The hypothesis of superiority over placebo was supported if the two-sided p-values for the primary efficacy endpoints were less than 5%. The parametric analysis was additionally validated by Wilcoxon rank sum tests.

Secondary outcome: The safety population and the Full Analysis Set (FAS) population were the two populations taken into consideration for the analysis. The number and percentage of patients who experienced adverse events (AEs) following the study drug's initial dose were compiled. The severity grade, relationship grade, and MedDRA Primary System Organ Class[35] and Preferred Terms were used to categorise AEs. Treatment provided a comprehensive summary of vital signs and physical exams.

The statistical analysis strategy ultimately offered a thorough method for assessing the effectiveness and safety of Gastroplex® in improving the symptoms of both acute and chronic gastritis as compared to placebo.

RESULTS AND DISCUSSIONS

Demographics

A total of 62 participants were screened for this clinical investigation, which was carried out in Mumbai, Maharashtra, and 60 of the eligible subjects were enrolled. Two participants (3.2%), who were already receiving therapy from modern medicine, were not randomly assigned. The investigation was carried out at a single research facility in India between March 4 and April 23, 2023.

The mean age of the subjects ranged from 19 to 63 years, with a mean of 41.7 years. 34 (56.7 %) of the subjects were females and 26 (43.3 %) of the subjects were males. And 15 (25%) of the female subjects had child bearing potential. The mean BMI of the subjects ranged from 17.7 to 34.7 kg/m^2 years, with a mean of 27.7 kg/m^2. The mean height of the subjects ranged from 1.5 to 1.7 m, with a mean of 1.6 m. The mean weight of the subjects ranged from 49.5 to 100 kg, with a mean of 71.1 kg. All subjects in the study were of Indian origin.

Gastroplex® and a placebo were the two treatment groups formed from the recruited participants. All 40 (100%) of the participants in the Gastroplex® group who were enrolled in the research completed it. In the same manner, all 20 participants (100%) in the Placebo group finished the experiment. There were not any expulsions from the study. Table 1, 2 and 3 summarises the design and Figure B elaborately says about the consort work flow.

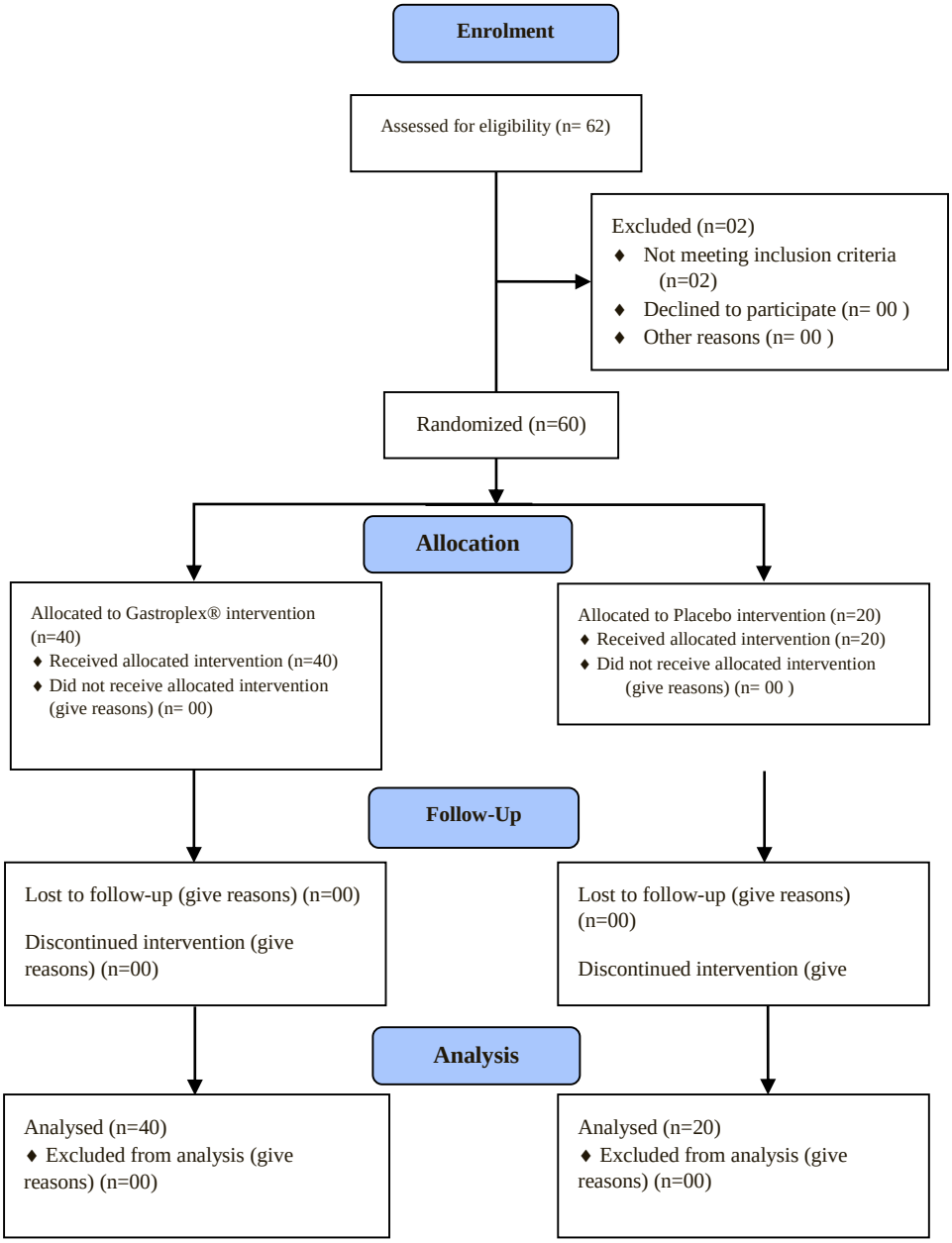

Figure B: Patient flowchart.

Efficacy evaluation

The VAS scale was used in the study as a measurement instrument that tries to measure a characteristic or attitude that was believed to range across a continuum of values and cannot easily be directly measured. Table 1 give the analysis of all the changes' according to VAS.

At week two of research comparing Gastroplex® with placebo, the LS mean difference in pain scores was 0.281. A p-value of 0.198 revealed that this difference was not statistically significant, though. Indicating a significant difference in pain scores between the therapies at week 4, the LS mean difference was 1.25 and the p-value of 0.04. The present analysis used 'intention-to-treat' statistics, which shows improvement in pain levels according to the VAS scores tabulated in Table 1. This involves the inclusion of all participants initially assigned to each group in the analysis, regardless of their adherence to the study protocol in completing the intervention.

Nasopharyngitis was the most common infection symptom, with low frequencies (2.5%) in the treatment arm and higher 4.3% in the placebo group. Generalized pain was noted by one (2.5%) subject in treatment arm and two (10%) subjects in placebo. Gastroplex® was well tolerated and was comparable with placebo which was confirmed by the fewer incidences of adverse events and good compliance.

CONCLUSION

In this single-centre clinical study, 60 patients completed their participation. The study was divided into two groups: 40 patients were assigned to the Gastroplex® group (Treatment Group A) and 20 to the Placebo group (Treatment Group B). All

participants were included in the Full Analysis Set (FAS) and safety analysis. The two treatment groups were comparable in terms of baseline characteristics. The average age of participants was 41.7 years. The Body Mass Index (BMI) of participants varied, with an average of 27.7 kg/m². Participants' height and weight also showed a range, with average values of 1.6 meters and 71.1 kg, respectively.

CONFLICT OF INTEREST

The one of the author SR is the owner of the company which manufactures this product. However, the study was conducted by independent CRO and SR has no role in conduct, data analysis and interpretation of the results.

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Figure Captions

Figure A: Patient flowchart.

Tables

Table 1: Summary of subject demographic characteristics at baseline: continuous variables (FAS population)

	Gastroplex® (n=40)	Placebo (n=20)	All (n=60)
Age (Years)			
N	40	20	60
Mean (SD)	41.4 (11.1)	42.2 (10.9)	41.7 (11)
Height (in m)			
N	40	20	60
Mean (SD)	1.6(0.1)	1.6 (0.1)	1.6 (0.1)
Weight (in kg)			
N	40	20	60
Mean(SD)	74 (11.6)	65.4 (9.4)	71.1 (11.6)
BMI (Kg/m²)			
N	40	20	60
Mean(SD)	28.3 (3.8)	26.4 (3.9)	27.7 (3.9)

		Gastroplex® (N=40)		Placebo (N=20)		All (N=60)	
Variable	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Gender	**Female**	22	55	12	60	34	56.67
	Male	18	45	8	40	26	43.33

Table 2: Analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 2 as compared to Baseline.

Gastroplex®					Placebo				Absolute Change from Baseline				
Visit	N	Mean	SD	Mean Percent Change#	N	Mean	SD	Mean Percent Change#	Mean	SD	LS Mean	95% CI	p-Value*
Baseline	40	3.1	2.4	0	20	3.9	2.3	0	1	1.27	0.281	(-0.96, 0.40)	0.655
Week 2	40	2.3	2.1	-10	20	2.3	2.1	-8.13					
Week 4	40	1.6	2.1	-19	20	3.3	3	-6.88	1	2.08	1.25	(0.208, 2.303)	0.04

*: Using ANOVA[36]
N = Number of subjects with non-missing values
CI – Confidence Interval[38]
 # Positive values for percentage change indicate worsening of pain and negative values indicate improvement of pain

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