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A Comparative Study of L-Glutamine And Azulene Combination As An Add on Therapy To Standard Treatment in H.Pylori Infected Gastritis And Peptic Ulcer Disease

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Abstract :
***Aim**: To evaluate the efficacy of L-Glutamine and Azulene combination in the eradication of H.Pylori infected gastritis and Peptic ulcer disease compared to standard treatment.*
***Methodology**: Patients attending MGE department with gastritis or peptic ulcer disease caused by H.Pylori were selected and randomized into two groups (30 each). Control and test groups received standard triple regimen (C.Amoxicillin 1gm BD, T.Metronidazole 600mg BD and C.Omeprazole 20mg BD) for 2 weeks followed by omeprazole for two weeks. Glutamine 0.67g and azulene 2.01g combination was added to test group for 4 weeks along with the standard treatment. H. pylori eradication was assessed four weeks after therapy using endoscopy and rapid urease test. 2-weeks follow-up done.*
***Results**: The symptoms decreased by 80% in test group and 46.7% in control group (p=0.024). Eradication rate by RUT in test group is 83.3% and 56.6% in control group (p=0.024). Endoscopic grading showed significant improvement from grade 3 to grade 1 in the test group compared to control group (p=0.003).*
***Conclusion**:Combination of L-glutamine and azulene along with triple regimen showed higher eradication rate of H. pylori compared to the standard triple regimen.*
***Keywords:**Azulene, Gastritis, Helicobacter pylori, L-Glutamine, Rapid urease test.*

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I. Introduction

Gastritis and Peptic ulcer disease are the multifactorial disorders of the gastrointestinal tract affecting more than fifty percent of the world population[1]. Gastritis is a condition in which the stomach mucosa is inflamed and peptic ulcer is defined as a break in the mucosal surface with appropriate depth (>5 mm in size) at endoscopy or histological evidence of involvement of gastric submucosa[2]. Any compromise to the gastroduodenal mucosal integrity by noxious agents causes gastritis and peptic ulcer disease[3]. Infection with Helicobacter pylori plays the pivotal role in pathogenesis of gastritis, peptic ulcer disease [4].When peptic ulcer disease is not treated adequately, it can lead to complications like gastric outlet obstruction, perforation, penetration and bleeding. In long term, chronic gastritis can progress to atrophic gastritis, MALT (mucosal associated lymphoid tissue) lymphoma and gastric carcinoma[5]. H. pylori is identified as group 1 carcinogen by the WHO because it significantly increases the risk of gastric cancer[6]The triple regimen consisting of two antibiotics (either of Amoxicillin, Clarithromycin, Tetracycline and Metronidazole) and proton pump inhibitor (Omeprazole, Lansoprazole or Pantoprazole) are employed in the treatment of H. pylori infection has changed chronic gastritis and peptic ulcer from a chronic recurrent disease to a curable entity[7].With this standard treatment the eradication rate is 70% and most of the patient takes proton pump inhibitors for longer duration for the symptomatic relief of abdominal pain which leads to unphysiological acid suppression[8].

The standard triple regimen targets only at the aggressive factor such as H.pylori bacteria. Therefore, the drug that enhances the mucosal defence mechanism and stimulating gastric epithelial regeneration and restitution activity should be added for effective treatment.L-Glutamine is a non-essential amino acid. It has a major role in ammonia detoxification, acts as fuel for rapidly proliferating cells like lymphocytes, monocytes, fibroblasts. Fibroblasts has a major role in wound healing and strengthen the mucosal integrity. Glutamine is known to have a role in the biosynthesis of certain muco-proteins which stimulate mucin synthesis. It also stimulates HSP 70 whose induction protects cells against cytotoxic mediators[9].Azulene, an extract of the flower German Chemomile has anti inflammatory, anti histamine and anti oxidant activity. It also stimulates reepithelialization[10].Studies about L-Glutamine and azulene combination in the treatment of gastritis and peptic ulcer disease have shown good results.

Studies done in china showed higher eradication of H pylori induced gastritis and peptic ulcer disease by treating with L –Glutamine and azulene along with standard triple regimen. There are no studies to know the efficacy of l-glutamine and azulene as an add on therapy to H pylori infection in South India.
Therefore, the present study was done to compare the efficacy of L- glutamine and azulene combination as an add on therapy to standard triple regimen with standard triple regimen alone.

II. Methodology

2.1. Study Procedure

This was a randomized, open label, prospective, parallel group two arm comparative study was done at Institute of Pharmacology and Department of Medical Gastroenterology, Rajiv Gandhi Government General hospital, Madras Medical College, Chennai. The study was carried as per ICH, GCP guidelines, Declaration of Helsinki and after obtaining approval from the Institutional Ethics Committee, Madras Medical College, Chennai. Patients were explained about the study procedure and purpose of the study. Information sheet and informed consent forms written in the regional language were provided to each patient. Patients were enrolled in the study after signing the consent form. The study was carried out from June 2015 to March 2016 for 6 weeks (4 weeks study period and 2 weeks follow up period) for each patient. Adult patients with gastritis and peptic ulcer disease with H. pylori positive by Rapid Urease Test were the study population. Total number of patients were 60 patients and 30 patients in each group (control and study groups).

2.2 Eligibility Criteria:
Inclusion Criteria:

- Age: 18-60 years.
- Sex - Both genders.
- Patients with dyspeptic symptoms, confirmed diagnosis of gastritis and peptic ulcer by endoscopy
- Patients with rapid urease test positive for H. pylori.
- Patients willing to give written informed consent.

Exclusion Criteria

- Pregnant and lactating women.
- Patients with intestinal obstruction, ulcer perforation.
- History of proton pump inhibitor intake in the last two weeks.
- Participation in another clinical study in the last three months.
- Patients with any chronic systemic illness.
- Patients with history of allergy to medications – amoxicillin, metronidazole, omeprazole.

1.3 Treatment Plan
30 patients in the control group received triple regimen (C.Amoxicillin 1 g BD, T.Metronidazole 400 mg TDS and C.Omeprazole 20 mg OD) for 2 weeks. 30 patients in the study group received triple regimen for 2 weeks with L-Glutamine 663.30mg and azulene 2.01 mg three times a day for 4 weeks.
2.4. Laboratory Investigations

- Random Blood Sugar, Urea, Creatinine
- SGOT, SGPT
- Systolic and diastolic blood pressure
- Endoscopy
- Rapid Urease Test.

2.5 Adverse Events :
Adverse event if any, reported by the patient or observed by the physician during the study was recorded.

2.6 Statistical Analysis

The obtained data was analysed using SPSS statistics version 21. The mean age distribution was analysed using student paired t test. The sex distribution was analysed by chi- square test. The analysis of subjective symptoms and rapid urease test were done by chi – square test. The endoscopic grading was done using Wilcoxon signed rank test.The blood pressure and biochemical investigations were analyzed using student's paired t-test whereas the difference between the Control and Study group were analyzed using students independent t-test.

III. Results

116 patients were screened and 60 patients were enrolled in this study who fulfilled the eligibility criteria. All the enrolled patients completed the study.There were no drop outs.

Table 1: H.Pylori Eradication (Rapid Urease Test)

Groups	0 Weeks		4 Weeks		P value
	Positive	Negative	Positive	Negative	
Control	30 (100%)	0	13 (43.3%)	17 (56.6%)	< 0.001
Study	30 (100%)	0	5 (16.6%)	25 (83.3%)	<0.001
p value	0.024				

Table 1 shows the rapid urease test result of both study groups at the baseline and end of 4 weeks. Study group has better eradication rate of 83.3% than the control group 56.6% at the end of 4 weeks. Statistical analysis within the groups showed a significant negativity at the end of 4 weeks ($p<0.001$). statistical analysis between the groups showed a significant difference ($p = 0.024$) at the end of 4 weeks

H.*Pylori* Eradication (Rapid Urease Test)

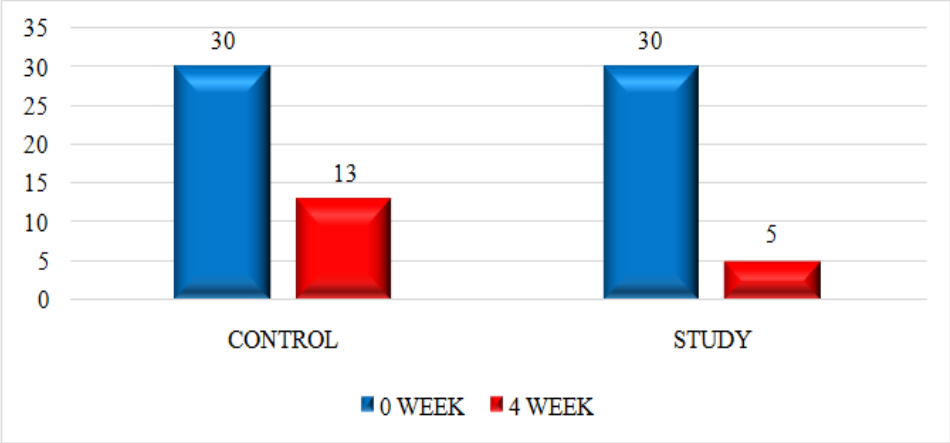

Fig 1

Table 2 : Endoscopic Grading

	0 weeks		4 weeks		P value
	Control	Study	Control	Study	
Grade 1	0	0	14	25	
Grade 2	0	0	14	5	
Grade 3	12	14	2	0	
Grade 4	18	16	0	0	<0.001
P value	0.605		0.003		

Table 2 shows the number of patients with endoscopy grading from 1 to 4 in both the groups at the baseline and at 4 weeks, both groups showed significant ($p< 0.001$) improvement in endoscopic grading at 4 weeks. Statistical analysis between the groups showed a significant difference at the end of 4 weeks ($p = 0.003$)

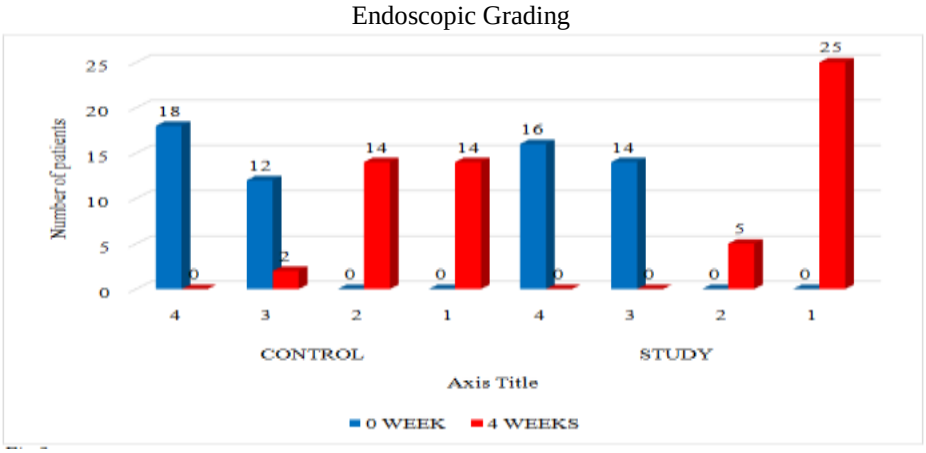

Fig 2

Table 3 : Pattern Of Subjective Symptoms

	0 week		4 weeks		P value
Groups	Abdominal Pain	Dyspepsia	Abdominal Pain	Dyspepsia	
Control	21 (70%)	9 (30%)	13 (43.3%)	3 (10%)	<0.0001
Study	23(76.7%)	7 (23%)	4 (13.3%)	2 (6.6%)	<0.0001

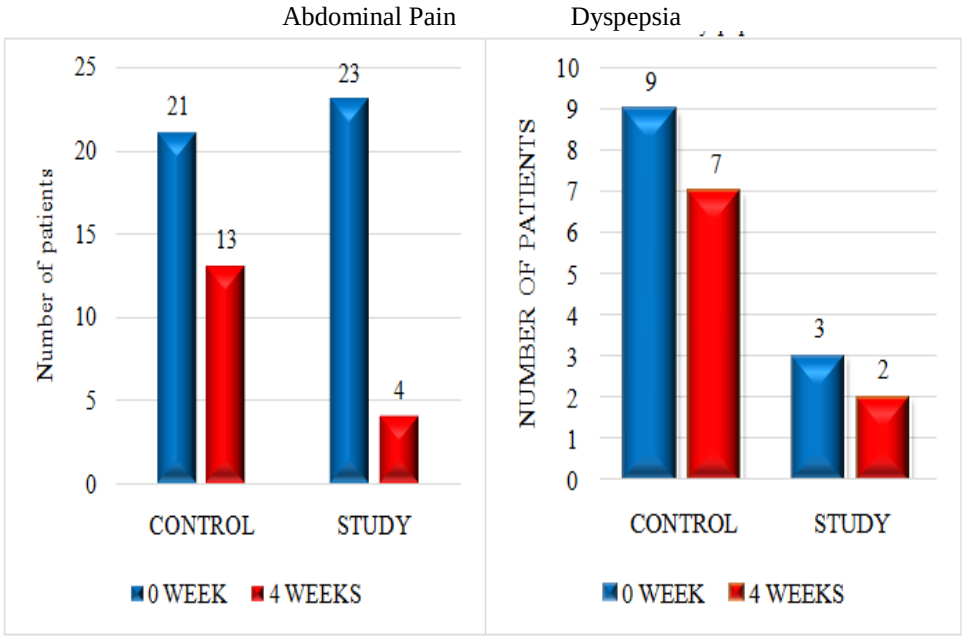

Fig 3A & 3B

Table 3 and figure 3A & 3B shows the pattern of subjective symptoms in both the groups at baseline and at 4 weeks.Both abdominal pain and dyspepsia improved in both the groups

Table 4: Adverse Drug Reactions Monitoring

Adverse Drug Reaction	Control Group	Study Group
Nausea	3 (10%)	2 (6.7%)
Metallic taste	5 (16.7%)	4 (13.3%)
Flatulence	3 (10%)	1 (3.33%)
Diarrhea	5 (16.7%).	2 (6.7%)

Adverse drug reactions were less in study group on comparing with the control group.

Rapid urease test kit showing positive result (red) at 0 week and negative result (yellow) at 4 weeks

Fig 4

Endoscopic appearance of the patient at 0 week and 4 weeks.

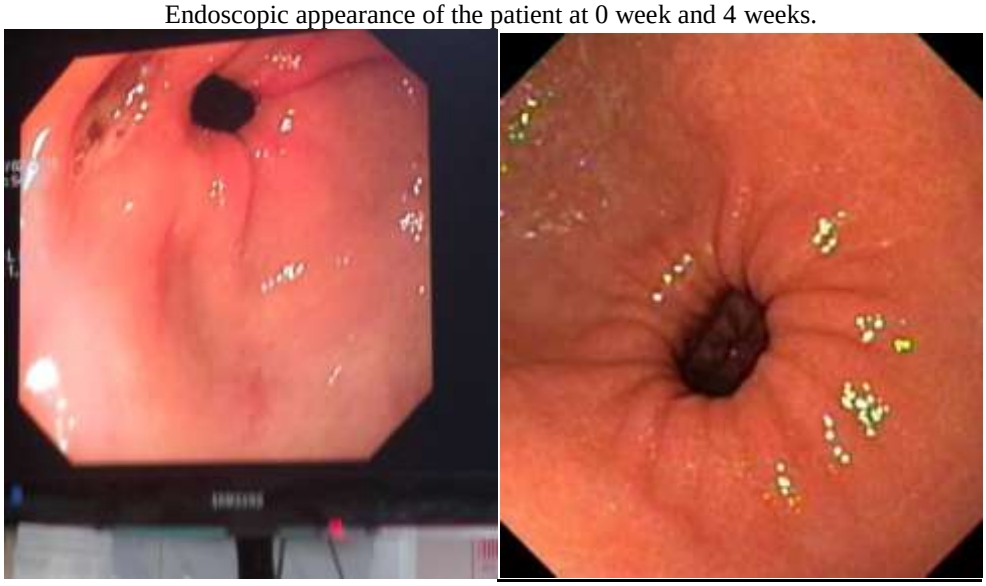

Fig 5

IV. Discussion

The therapeutic efficacy of L-Glutamine and azulene combination with standard triple regimen in the eradication of Helicobacter pylori of Peptic ulcer disease was assessed in this study.Along with antibiotics, newer agents that enhance the gastric mucosal defence mechanisms (such as mucus and bicarbonate secretion), to overcome oxidative stress, stimulate gastric cellular regeneration and restitution and modulate immune system are added in this study.L –Glutamine is an important nutrient for gastric mucosal cells and primary metabolic fuel for fibroblasts, which plays an important role in healing. It also acts as a cofactor for the formation of purine and pyrimidine; components of DNA and RNA which is important for rapidly proliferating cells like gastrointestinal epithelial cells. Thereby, Glutamine strengthens the mucosal integrity and speeds up mucosal repair and healing by promoting restitution and regeneration of epithelial cells. It increases the level of secretory Ig A and strengthens the common mucosal immune system in GIT.L-glutamine helps in the clearance of ammonia by enhancing the urea cycle.

Oxidative stress, an imbalance between free radical generation and scavenging system also have a role in pathogenesis of gastritis and peptic ulcer disease. L-glutamine increases the endogenous level of anti-oxidant by enhancing the synthesis of glutathione to counter act the oxidative stress[9].Azulene possesses antihistaminic, anti-inflammatory and antioxidant properties which helps in the healing of gastritis and peptic ulcer. It can also block the aggregation of H. pylori in the gastric mucosa[10].In this study, the symptoms were decreased by 80% in

study group and 53.33% in control group. This shows, there was significant improvement of subjective symptoms in patients who received L-glutamine and azulene along with standard therapy when compared to the patients who had standard therapy alone with p value 0.024.The endoscopic grading showed statistically significant improvement from grade 4 to grade 1 in the study group compared to the control group with p value of 0.003.

Rapid urease test helps in the detection of H.pylori clearance from the gastric mucosa. Combination therapy with L-Glutamine and azulene in study group showed 83.3% eradication rate, compared to 56.6% in the control group with significant p value of 0.024. This is consistent with previous study done by Zhao- Gui-ying, where H pylori clearance is 87.50% with test group (triple regimen + l-glutamine and azulene) and 60.26% with control group (triple regimen alone). The ulcer healing in test and control groups were 92.50% and 67.95% respectively[11].

The incidence of adverse effects were 30% in the study group and 53.3% in the control group. Metallic taste was the commonest adverse event.The number of adverse events observed were less in patients receiving l-glutamine and azulene combination as add on therapy compared to patients receiving standard treatment alone. All the Adverse Drug Reactions were categorized as possible under WHO causality assessment scale. According to the Modified Hartwig and Siegel severity assessment scale all the reactions reported was mild. This shows that l-glutamine and azulene did not increase the occurrence of adverse events.As evidenced by earlier studies, this study has also showed that addition of l-glutamine and azulene to standard triple regimen significantly improved the treatment outcome.

V. Conclusion

From our study, we conclude that, in addition to antibiotics and anti-secretory agents, drugs that enhance the natural defence mechanism in the submucosal region, having anti-oxidant property and causing direct healing of inflammation and ulcer gives the better result.L-glutamine and azulene as add on therapy to standard triple regimen for H.pylori is effective in improving the healing of gastritis and peptic ulcer disease.

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