ORIGINAL ARTICLE

TO COMPARE THE SAFETY AND EFFICACY OF THREE DIFFERENT, PROTON PUMP INHIBITORS OMEPRAZOLE, ESOMEPRAZOLE AND RABEPRAZOLE IN A TRIPLE DRUG REGIMEN IN PATIENTS WITH PEPTIC ULCER DISEASE IN THE ERADICATION OF H. PYLORI INFECTION

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ABSTRACT: Peptic ulcer disease continues to be issue especially due to its high prevalence in the developing world. Helicobacter pylori (H. pylori) infection associated duodenal ulcers should undergo eradication therapy. There are many regimens offered for H. pylori eradication which include triple, quadruple, or sequential therapy regimens. In our study we planned to see whether these differences in pharmacokinetic properties show any difference in the efficacy and safety parameters between treatment with omeprazole rabeprazole and esomeprazole in the triple drug regimen for eradication of H.pylori infection in peptic ulcer patients in our hospital Osmania General Hospital / Osmania Medical College, Hyderabad. **MATERIALS AND METHODS:** A total number of 45 patients were enrolled in the study. Patients with either sex suffering from peptic ulcer defined as ulcer crater of >2.5mm in size by endoscopy. Study Design: It was a randomized double blind, parallel and comparative study. **CONCLUSION:** Two weeks after triple drug treatment, H.pylori was negative in 66.7%, 73% and 80% and Rapid urease test was negative in 53%, 60% and 66% in group A, B and C respectively. Endoscopy findings showed significant reduction in size and healing of ulcers in group A, B and C. There was improvement in signs and symptoms by 53 to 80%, after 2 weeks. Hence after therapy with triple drug regimen H.pylori eradication was 66-80% and healing of ulcers was 83–100% which was higher in Rabeprazole group. At 6 weeks, there was complete relief of signs and symptoms. At the follow up of 10 weeks there was no ulcer recurrence. No adverse effects were noted in all the groups. In conclusion, Triple drug regimen had shown to eradicate H.pylori infection in the treatment of Peptic ulcer. There was healing of ulcers in all the groups which was highly significant. There was no recurrence of peptic ulcer with these regimens in all the groups. However Rabeprazole group patients became asymptomatic rapidly than other groups with better H.pylori eradication.
KEYWORDS: Helicobacter pylori, Peptic ulcer disease, Proton-pump inhibitors.

INTRODUCTION: The discovery of Helicobacter Pylori (H.pylori) by Warren and Marshall from Perth, Australia in 1980's made a paradigm shift in the understanding of pathogenesis of many common and uncommon gastrointestinal disease processes as well as therapy of H. Pylori related diseases.[1,2] In the past most peptic ulcers were considered idiopathic, but since the historic discovery it became clear that most ulcers result from infection with H.pylori or the use of non-steroid anti-inflammatory drugs (NSAIDS) or both.[3] H.pylori infection has a worldwide distribution

and is usually associated with chronic gastritis, peptic ulcer, gastric cancer and mucosal associated lymphoid tissue (MALT) lymphoma.[4] It has been found that 0.4 to 1% of uninfected adults acquire H.plyori each year and the incidence of H.pylori infection tends to increase with age.[5, 6] Mostly H.pylori infected individuals are asymptomatic, approximately 16% of them develop peptic ulcer disease, and 1-2% of them can develop a major ulcer related complication each year.[7] The risk of peptic ulcer in a person during life time infected with H.pylori ranges from 3% in United States to 25% in Japan.[8] H.pylori is recognized to be the main aetiological factor in pathogenesis of duodenal ulcer and non -autoimmune gastritis. Approximately 95% of the patients with duodenal ulcer and 50% of the patients with non-ulcer dyspepsia are colonized with H.pylori. Several studies have shown that eradication of H.pylori cures duodenal ulcers and prevent relapse.

In addition there is histological resolution of chronic active gastritis after eradication of H.pylori.[9]

Prevalence is low in developed countries and relatively high in developing countries where the infection occurs early in life and is often associated with low socio-economic status.[10] It has been appreciated that H.pylori infection is the cause of gastritis. There is a wide variation (58-94%) in the prevalence of H.pylori infection in gastric ulceration.[11] Gastric cancer is the second most frequent cause of cancer – related deaths. Prospective studies have shown that H.pylori confers 3-6 fold increased risk of gastric cancer and muscosa associated with MALT, especially if the infection is asymptomatic long standing or acquired in childhood.[11] 72 to 98% of the patients with gastric MALT lymphoma are infected with H.pylori. Furthermore eradication of H.pylori alone induces regression of gastric malt lymphoma in 70-80% of cases.[8] H.pylori has been classified as a type 1, definite carcinogen since1994, mainly on the basis of large sero-epidemiologic case control studies. WHO added H.pylori to its list of known carcinogens which become important reason for eradicating H.pylori infection.[11] The National institute of Health consensus conference in 1994 concluded that all patients with peptic ulcer disease whether on first presentation or on recurrence and also those on maintenance therapy for a confirmed ulcer should be cured of their infection using an anti-secretory drug combined with anti H.pylori antibiotics. Patients with a history of complicated or refractory ulcer disease who are H.pylori positive should also be treated for the infection. Eradication of H.pylori drastically lowers the recurrence of H.pylori associated peptic ulcers. The Indian consensus statement also supports the same view.[12] Therapeutic strategies previously aimed at controlling intragastric PH to maintain long term remission of peptic ulcer. At present it has been targeted to eradicate H.pylori in order to prevent recurrences in peptic ulcer disease.

According to recent international guidelines the clinical goals for rapid ulcer healing and prevention of relapse can be accomplished by combination therapy consisting of an antisecretory drug, Proton pump inhibitor or Ranitidine and 2 antimicrobial agents preferable amoxicillin, clarithromycin or metronidazole. When applying such multi drug regimens, possible synergy between the agents suggest that pharmacokinetic considerations might help to improve H.pylori eradication rates which should be above 85 to 90% on an intention to treat basis.[13] Proton pump inhibitors in triple drug therapy was first introduced in 1993.[14] omeprazole is the first available PPI that has been used for nearly 2 decades. More recently, other members of the PPI family including pantoprazole, Lansoprazole, rabeprazole and esomeprazole are available. They mainly differ from

omeprazole in their individual pharmacokinetic properties. Proton pump inhibitors (PPI) have both direct and indirect effect on H.pylori eradication. They increases the permeability of gastric juice by decreasing it viscosity and reduce the degradation of acid labile antibiotics in the stomach by increasing intragastric PH. The results of clinical trials of H.pylori eradication regimens have been widely variable and considerable debate has ensued with regard to most effective and acceptable antimicrobial regimens, particularly in developing countries.

In our study we planned to see whether these differences in pharmacokinetic properties show any difference in the efficacy and safety parameters between treatment with omeprazole rabeprazole and esomeprazole in the triple drug regimen for eradication of H.pylori infection in peptic ulcer patients in our hospital Osmania General Hospital / Osmania Medical College, Hyderabad.

OBJECTIVE OF THE STUDY: To compare the safety and efficacy of three different Proton pump inhibitors, Omeprazole, Esomeparazole and Rabeprazole in a triple drug regimen in patients with peptic ulcer disease in the eradication of H.pylori infection.

Peptic ulcers are excavated defects in the Gastrointestinal mucosa that result when epithelial cells succumb to the caustic effects of acid and pepsin in the lumen.[15] Ulcerations arise when caustic effects of aggressive factors like acid, pepsin, bile overwhelm the defensive factors of the gastrointestinal mucosa which include mucus and bicarbonate secretion, prostaglandins, blood flow and the process of restitution and regeneration after cellular injury.[16] Ulcer is an abnormal event defined histologically as necrotic mucosal defect that extend through the muscularis mucosae and into the submucosa or deeper layers. The term peptic ulcer disease is commonly used to refer to ulcerations of the stomach, duodenum or both, but peptic ulcers can develop in any portion of the gastrointestinal tract that is exposed to acid and pepsin in sufficient concentration and duration.[15] Peptic ulcer disease is now approached as an infectious disease in which elimination of causative agent cures the condition.[8] Over 99% of peptic ulcers are caused by infection with the bacterium. Helicobacter pylori or by the use of non-steroid anti-inflammatory drugs.[16] Helicobacter pylori (H.pylori) was isolated from the mucosal biopsies of patients with chronic active gastritis by Marshall and Warren in 1983.[17,18] It may attach to gastric epithelium but under normal circumstances does not appear to invade cells.[19]

Transmission: three routes of infection have been postulated.[20] Feco-oral route, Oro-oral route, Gastro-oral route. Upto 60% of peptic ulcers are associated with H.pylori infection. This infection may lead to impaired production of stomatostatin by D cells, and in time, decreased inhibition of gastrin production, reduced duodenal bicarbonate production.[21]

Diagnostic Tests: H.pylori infection can be diagnosed by 1. Non-invasive methods 2. By endoscopic biopsy of the gastric mucosa.

Tests for detection of H.pylori

Test	Sensitivity / specificity %	comments
(Invasive endoscopy / Biopsy required)		
1. Rapid urease	80 – 95 / 95 – 100	simple; false negative with recent use of PPI, antibiotics or birmuth compounds.
2. Histopathology	80 – 90 / > 95%	requires pathology, processing and staining provides histologic information.
3. Culture	-/-	time consuming, expensive allows determination of antibiotic susceptibility
Non invasive		
1. Serology	> 80 / > 90	inexpensive, convenient, not useful for early follow up.
2. Urea breath test	> 90 / >90	Simple, rapid useful for early followup.

Table 1

Pharmacokinetic properties of Omeprazole, Esomeprazole and Rabeprazole are shown in table 2.

PPI's	Bio availability (%)	Plasma half life t½ (hrs)	t max (hrs)	c max ug/l	AUC Ug/1/h	First pass metabolism
Omeprazole 20mg	25 – 40	0.5 – 1.2	1-6	4.47	3.47	Extensive
Esomeprazole 40mg	89	1.2	0.5-2	5.39	5.59	Less
Rabeprazole 20mg	52	0.6-1.	3 – 5	4.06	8.09	Extensive

Table 2

The future of eradication therapy for H.pylori lies in understanding of the mechanism of resistance and restricting its development, decreasing the world wide pool of infection by developing safe and efficient vaccines, by targeting H.pylori in the stomach using sensitizers with laser and developing rapid eradication strategies.[11] Vaccination offers the possibility of treating patients with established H.pylori infection. It seem that the naturally infected stomach does not mount an effective secretory IgA response to the infection. Vaccination reverses this and an effective mucosal immune response to one of the surface proteins of H.pylori lead to both prevention of infection as well as cure of ongoing infection.[18]

MATERIALS AND METHODS: The present clinical study was conducted in patients with endoscopically proven peptic ulcer at Department of Gastroenterology and Department of Pharmacology in Osmania General Hospital / OMC, Hyderabad.

Sample Size: A total number of 45 patients were enrolled in the study.
Study Population: Patients with either sex suffering from peptic ulcer defined as ulcer crater of > 2.5mm in size by endoscopy.
Study Design: It was a randomized double blind, parallel and comparative study. The total number of patients were divided into three groups randomly, with 15 patients in each group.

INCLUSION CRITERIA:

1. Patients aged between 20 – 70 years of either sex.
2. Endoscopically proven peptic ulcer with a size of > 2.5mm in size and with evidence of H.pylori infection by histopathology and rapid urease test.

EXCLUSION CRITERIA:

1. Patients on antiulcer drugs preceding 4 weeks except antacids.
2. Patients on NSAIDS and corticosteroids.
3. Patients with co-existing gastric carcinoma, pyloric stenosis, active upper gastro intestinal haemorrhage.
4. Chronic alcohol or drug abuse.
5. Patients with cirrhosis, renal disorders or any other severe organ disease.
6. Pregnant / lactating women.
7. Patients with hyper sensitivity to study drugs.
8. Poor patient compliance

Study Medication

Group A:

Tab. Omeprazole 20mg twice a day before breakfast and before dinner.
Tab. Tinidazole 500mg twice a day after meals
Cap. Amoxycillin 500mg twice a day after meals

Group B:

Tab. Esomeprazole 40mg twice a day before breakfast and before dinner.
Tab. Tinidazole 500mg twice a day after meals.
Cap. Amoxycillin 500mg twice a day after meals

Group C:

Tab Rabeprazole 20mg twice a day before breakfast and before dinner
Tab. Tinidazole 500mg twice a day after meals.
Cap. Amoxycllin 500mg twice a day after meals

Duration of study: Triple drug treatment was given for 2 weeks followed by the respective proton pump inhibitor, twice daily for 4 weeks.

Study Procedure: The study was started after approval by the local ethics committee. After fulfilling the inclusion and exclusion criteria, the patients were enrolled for the study and the written informed consent was obtained from every patient. A detailed medical history was taken which included diabetes mellitus, renal disease, allergic disorders, hypertension and blood disorders and past history of peptic ulcer. The baseline intensity for heart burn, epigastric pain, vomiting, bloating, haematemesis, malena and frequency of dyspeptic symptoms were noted. Total number of 45 patients was included in the study with 15 patients in each group. It was a double blind, parallel, randomized study. Patients were randomized to 3 study groups, A, B & C. The routine laboratory investigations like complete blood picture which included Red blood cell count, White blood cell count, Hb% and Platelet count. Liver function test like Serum Bilirubin, SGPT. Renal function test like Blood urea and Serum creatinine, Random Blood sugar and occult stools in the blood in the stools were tested. Vital parameters like temperature, blood pressure, heart rate, respiratory rate were recorded. Upper GI endoscopy was done to note the site, number and size of the ulcers and four biopsy samples one each from body and the fundus and two samples from antrum of the stomach were taken. The three samples were checked for evidence of H.pylori, by rapid urease test and one sample from the antrum was collected in 10% neutral formalin, and was sent for histopathological examination.

Group A received:

Tab. Omeprazole 20mg twice a day before breakfast and before dinner.
Tab. Tinidazole 500mg twice a day after meals
Cap. Amoxycillin 500mg twice a day after meals
Group B received
Tab. Esomeprazole 40mg twice a day before breakfast and before dinner.
Tab. Tinidazole 500mg twice a day after meals.
Cap. Amoxycillin 500mg twice a day after meals
Group C received
Tab Rabeprazole 20mg twice a day before breakfast and before dinner
Tab. Tinidazole 500mg twice a day after meals.
Cap. Amoxycllin 500mg twice a day after meals

The eligible patients were randomized to receive either one of the three triple drug regimens for 2 weeks followed by respective proton pump inhibitor twice daily for 4 weeks. Follow up Visits: were done at 2, 4, 6 and 10 weeks of the treatment. Endoscopy, specific dyspeptic symptoms and H/o intake of antacids and side effects if any were recorded at every follow up visit. At every follow up visit specific dyspeptic symptoms were recorded on 3 point scale (epigastric pain, heart burn, anorexia, nausea and vomiting).

Grades:

0 – absent
1 – mild
2 – moderate
3 – severe

At the end of the study all the baseline parameters were repeated. Patient's compliance was considered good if the pill count was > 80%. All the above details were recorded in the case record form.

End points:

1. Absence of peptic ulcers / decrease in the number and size of ulcers with 2 point reduction in ulcer size.
2. Eradication of H.pylori Urease test negativity, Histological clearance of H.pylori
3. Complete absence of symptoms

Statistical Analysis:

1. Mean + SD was calculated
2. ANOVA test was performed
3. Within the group paired T test and Wilcoxan signed rank tests were applied.
4. Level of significance was kept at $P < 0.05$.

RESULTS: A Total of 45 adult subjects of either sex with mean age of 36+12 years were included in the study. The male: female ratio was 7:2 (Table 4).

All the patients had single to multiple ulcers. At the baseline, the size of the ulcers in group A, B & C was 8.6+1.7mm, 8.9+1.9 mm, and 7.0+1.4mm respectively (Table 5). The baseline histopathology for H.pylori was positive in 93% in group A and 99% of the patients in group B and C. At the baseline the rapid urease test was positive in all the groups (Table 6). The baseline duodenal ulcer pain frequency in group A, B & C was grade 3 in 73%, 47% and 60% of the patients respectively, and grade 2 in 13%, 47% and 40% of the patients respectively. The baseline duodenal ulcer heart burn frequency was grade 3 in 20% of patients in both group A and B and 60% in group C patients and was grade 2 in 40% of patients in group A and C and 53% of patients in group B (Table 4).

At baseline nausea was grade 3 in 6% of patients in all the groups and grade 2 in 73%, 46% and 66% of patients in group A, B and C respectively. Grade 1 nausea was seen in 20% of group A and Group C patients and 46% of group B patients. Vomiting was present in 20% of patients in group A and 33% of patients in group B and C. Anorexia was present in 80% of patients in group A and 100% of patients in B and C groups (Table 4). There was significant reduction in ulcer size and improvements in signs and symptoms in all the three groups after 2 weeks of treatment.2 weeks after the treatment with triple drug regimen the size of the ulcer was reduced to ($P < 0.001$) 1.4+1.1mm in group A, 0.1+0.1mm in group B and no ulcer in group C which was significant (Table 5).

The percentage of reduction in the size of the ulcer was 83.3%, 98% and 100% of patients in Group A, B & C respectively (P< 0.001). Percentage of healing of ulcer in Group A, B & C was 87%, 93% and 100% respectively (P <0.001) which was significant (Table 7). Histopathology for H.pylori after 2 weeks of treatment was positive only in 33.3% of the patients in Group A, 27% of the patients in Group B and 20% of patients of Group C (P<0.001). Rapid urease test was positive in 47%, 40% and 33.3% in A, B and C groups respectively. (P<0.001) after two weeks of treatment which was significant (Table 6). There was significant relief in duodenal ulcer pain which was 53%, 40% and 73%, (P < 0.001) in group A, B & C respectively. Relief from heart burn was 66%, 73% and 73% respectively in A, B & C group (P <0.001) after 2 weeks of treatment.

66% in group A and 80% in group B & C did not complain of nausea at 2 weeks of treatment (P <0.001). Relief from anorexia was seen in 87%, 80% and 100% in A, B & C groups (P <0.001) respectively. There were no vomitings in all the study groups. (Table 8). At 6 weeks and 10 weeks of follow up there was complete relief of signs and symptoms and there was no ulcer by endoscopic examination. Rapid urease test and histopathology for H.pylori was negative in all the groups. Adverse effects were not reported in any of the three study groups.

Characteristics	Group A (n=15)	Group B (n=15)	Group C (n=15)
Age (yrs) Mean + SE M	42.20 + 3.661	31.26 + 2.385	34 + 2.492
Range	21 – 70	22 – 60	18 – 50
Sex Men % Women %	 60% 40%	 93% 6%	 80% 20%
Baseline ulcer size	8.6 + 1.7mm	8.9 +1.9mm	7.0 + 1.4mm
Epigastric pain	86%	94%	100%
Heart burn	60%	73%	100%
Nausea	73%	46%	66%
Anorexia	80%	80%	100%

Table 3: Patient Demographic and Baseline Characteristic

Group	Drug	Baseline	2 wks	6 wks
A (n=15)	Omeprazole	8.6 + 1.7mm	1.4 + 1.1mm	No ulcer
B (n=15)	Esomeprazole	8.9 + 1.9mm	0.1 + 0.1mm	No ulcer
C (n=15)	Rabeprazole	7.0 + 1.4mm	No ulcer	No ulcer

Table 4: Reduction in Size of the Ulcer (P <0.001)

	Group A	Group B	Group B
Baseline			
Histopathology (+ve)	93%	99%	99%
Rapid urease test (+ve)	100%	100%	100%

2 wks post treatment			
Histopathology (+ve)	33.3%	27%	20%
Rapid urease test (+ve)	47%	40%	33.3%
6 wks post treatment			
Histopathology	Nil	Nil	Nil
Rapid Urease test	Nil	Nil	Nil

Table 5: Histopathology and Rapid Urease Test

Group	Drug	Baseline	% of reduction in size	% of healing
A	Omeprazole	8.6 + 1.7mm	83.3%	87%
B	Esomeprazole	8.9 + 1.9mm	98%	93%
C	Rabeprazole	7.0 + 1.4mm	100%	100%

Table 6: Percentage of Reduction in Size and Healing after 2 weeks (n=15 in each group) P < 0.001

Group (n=15)	Epigastric pain	Heart burn	Nausea	Anorexia
A	53%	66%	66%	87%
B	40%	73%	80%	80%
C	73%	73%	80%	100%

Table 7: Complete relief of Signs and Symptoms at 2 weeks of treatment (n=15 in each group) P < 0.001

DISCUSSION: Pharmacological suppression of gastric acid secretion has traditionally the most rational approach to healing ulcers successfully. Use of only antisecretory drugs initially showed relapse after the withdrawal of treatment. Eradication of H.pylori by antimicrobial therapy in patients with duodenal and gastric ulcer has reduced the relapse rates. The optimal therapeutic regimen to eradicate H.pylori is still not completely clear. The requirement for 90% healing rate makes monotherapy and dual therapy inappropriate.[29]

Proton pump inhibitors represent the most important recent advances in the treatment of acid related gastro intestinal diseases. Compared to H2 antagonists, sucralfate and Bismuth salts, PPIs are considered as the drugs of choice in peptic ulcer disease. Triple drug therapy including two antibiotics and a PPI has become the preferred therapeutic choice for eradication of H.pylori infection in this disease.[2] Among the various treatment regimens used, triple drug therapy was the most successful in eradicating H.pylori.[31]

Triple therapy regimens with a combination of a PPI and two antibiotics have largely replaced the use of bismuth based triple therapy in almost all countries. This is due to better tolerability of the regimen and greater efficacy. PPIs have a synergistic effect with several antibiotics by raising PH, by increasing chemical stability and making it optimal for the activity of other drugs.

PPIS have also shown to exert an antibacterial activity invitro, which is selective to H.pylori.[32] Such antimicrobial power is common to all benzimidazoles and absent in other antisecretory drugs like H2 antagonists. Luigi Gatta et al proved that esomeprazole and omeprazole have a direct antimicrobial activity apart from inhibiting the urease activity of H.pylori.[33] The regimens like PPIs in combination with two antibiotics like clarithromycin, amoxicillin and metroxidazole or tinidazole are advocated as 7-14 day regimen. Combination of PPI with amoxicillin and metronidazole or tinidazole is cheaper compared to clarithromycin based regimen with optimal or moderate efficacy.[12,34]

The primary objective of our present study was to compare the safety and efficacy within and between the treatment groups with three PPIs namely omeprazole, rabeprazole and esomeprazole in triple drug regimen, using amoxicillin and tinidazole along with PPI for 2 weeks, with a continuation of a PPI alone for 4 weeks in eradication of H.pylori infection in patients with peptic ulcer disease. As far as our knowledge goes, there were only few studies, comparing 3 groups of PPIs in a single study. The response rate was assessed by H.pylori eradication rate. Eradication of H.pylori was associated with healing of ulcers, resolution of antral gastritis and a significant fall in the rate of ulcer relapse in > 4 weeks of treatment.

At the end of 2 weeks of treatment in our study H.pylori on histopathology significantly became negative in 66.7% in A group, 73% in B group and 80% in C group. Rapid Urease Test was negative in 53%, 60% and 66.7% of patients in A, B and C groups respectively. Addition of PPI in triple drug regimen leads to eradication rate of 97%.[35] Many studies have used omeprazole as the part of the regimen in eradication of H.pylori. Use of omeprazole 20mg twice daily, metronidazole 400mg twice daily, clarithromycin 250mg twice daily, for 1 week, produced H.pylori eradication rates of 77 to 88%.[36] Bell et al[37] used a 2 week regimen of omeprazole, ampicillin and metronidazole and reported H.pylori eradication rate of 96.4% in metronidazole sensitive cases and of 75% in metronidazole resistance cases. Hence the overall eradication rate of H.pylori with omeprazole varied from 77 – 97% from the previous studies. In our study we got 66% eradication rate with omeprazole after 2 weeks of treatment. It was less compared to the previous data. It may be because of the use of highly effective clarithromycin in the regimen used in previous studies and also due to less sample size (n = 15) used in our study.

In the previous studies with esomeprazole, eradication rates were 77%[38] and 88%.[39,40] In our study the eradication rate with esomeprazole was 73% which was comparable with previous data.

The majority of the recent studies have investigated the efficacy of the rabeprazole as a part of 7 day triple therapy regimens, containing amoxicillin and clarithromycin. The overall eradication rate was between 85 – 97%.[41,42,43] In our study 80% eradication rate was obtained after 2 weeks of treatment with Rabeprazole containing regimen. It was less than that of the data obtained from most of the recent studies. It may be because of use of Amoxycillin in our regimen, where as other studies used clarithromycin in the regimen.

At the end of 6 weeks of treatment period, the eradication rate was 100% in A, B and C groups respectively. Eradication rates in various studies from West ranged from 80-90%.[31,44] In the present study we observed that triple drug therapy was highly effective in eradicating H.pylori infection in all the three groups. It was higher than results obtained from west. The percentage of

eradication rate in our study was comparable with previous studies conducted using PPIs with clarithromycin and amoxicillin[2,41,45] which was about 94%.

There was significant relief in duodenal ulcer pain which was 53%, 40% and 73% in group A, B and C groups respectively. Relief from heart burn was 66%, 73% and 73% respectively in A, B & C group after 2 weeks of treatment. Previous studies reported improvement in frequency and severity of epigastric pain in 80 – 82% of patients and heart burn in 63% of patients.[39] In our study the complete relief of epigastric pain varied from 53 – 73% which was less than the data obtained elsewhere. It may be because of small sample size. Heart burn was 66% in our study which was comparable to the previous data (63%). 66% in group A and 80% in group B and C did not complain of nausea at 2 weeks of treatment. Relief from anorexia was seen in 87%, 80% and 100% in A, B and C groups respectively after 2 weeks. Prior to treatment most common symptom was epigastric pain (86%) followed by dyspepsis (80%) and then nausea (73%). Meta-analysis of published clinical studies showed that 71% of patients treated with omeprazole 20mg daily had complete relief of symptoms within 2 weeks.[46]

All three treatment regimens OAT, EAT and RAT were safe and effective in eradicating H.pylori in the patient population studied, after 2 and 6 weeks of treatment. Rabeprazole and esomeprazole are new proton pump inhibitors which appear to have comparable therapeutic profiles with omeprazole and lansoprazole.[12,47] In our study we have observed that all the three PPIs namely Omeprazole, Esomeprazole and Rabeprazole were equally effective in H.pylori eradication. Same results were also reported in other studies[48,49,50] where different PPIs showed equal efficacy in eradication of H.pylori infection.

It has been demonstrated in one study that Rabeprazole had higher eradication rate than omeprazole[51] as well as with potent and rapid acid suppression.[52,53] In our study, we have noted that Rabeprazole, amoxicillin and tinidazole was the most effective regimen which showed faster eradication rate and rapid acid suppression. There was also complete healing of ulcer in Rabeprazole group after 2 weeks of therapy when compared to other two groups, therefore showing faster healing rate. Though the percentage of eradication was higher in Rabeprazole amoxicillin and tinidazole group, we could not find statistically significant difference compared to other two groups. Hence the three groups were equieffective at 2 and 6 weeks of treatment.

The gastric ulcer study (GU study) by Dekkers et al[54,55] also supports our study where they produced inconsistent results, since rabeprazole was superior to omeprazole in gastric ulcer patients only with regards to symptom relief but as potent as omeprazole with respect to healing rates.

Rabeparzole was more effective than esomeprazole in increasing intragastric PH and maintaining PH >3 and >4. It had faster onset of action than omeprazole in patients with severe heart burn.[56]

In healthy volunteers rabeprazole had similar or faster onset of action than omeprazole and Rabeprazole. In addition rabeprazole had a greater antisecretory effect over a 24 hr period than esomperazole, omeprazole, lansoprazole and pantoprazole. Rabeprazole had a duration of action of > 24 hrs.[27]

Invitro Esomeprazole 'S' isomer of Omeprazole showed increased antimicrobial activity against H.pylori which could contribute to improving the outcome of eradication of the infection.[57] Most of patients receiving esomeprazole, reported either improvement or resolution from the

baseline symptoms of epigastric pain, heart burn, dyspepsia and nausea.[24] Esomperazole has been shown to be as effective as omeprazole in PPI based triple therapy for eradication of H.pylori infection. The safety profile of esomeprazole seems to be similar to that reported for omeprazole.[28] In our comparative study there was no statistically significant difference in safety and efficacy between omeprazole, esomeprazole and rabeprazole groups. The other study showed that esomeprazole based triple therapy effectively eradicated H.pylori infection and promoted peptic ulcer healing with good tolerance, capable of achieving more speedy pain relief than omeprazole based therapy.[58] Among the three study groups we found that esomeprazole was next to rabeprazole in eradication rate and quick relief of signs and symptoms.

Based on pharmacokinetic and pharmacodynamic properties all the PPIs share the same mode of action by inhibiting gastric proton pump.

PPIs are exclusively metabolized by hepatic route, and show rapid hepatic elimination. Their potency depend on the serum AUC of the free pro-drug and its chemical activation and half- life at PH-1 relative to its serum elimination half-life. The characteristics are similar for all PPIs. Therefore the available PPIs display the same potency and efficacy.[54] On the basis of their identical pharmacodynamic and similar pharmacokinetic properties (minor differences in bioavailability and non-linearity in the disposition of omeprazole), all presently marketed PPIs can be used interchangeably. In regard to the interaction potential of various PPIs, omeprazole might be regarded as slightly less favourable than the other PPIs.[13] Whereas other studies showed that there was significant difference in the pharmacokinetic characteristics among different PPIs[27,59,60,61,62] shown in table 2.Three large studies have investigated the comparative efficacy of rabeprazole with other antiulcer agents. Rabeprazole is a well-tolerated PPI with a quick onset of action, and increases intragastric pH more then other PPIs. It has proven efficacy in healing, symptom relief, and prevention of relapse of gastric ulcer, duodenal ulcer and GORD and can form part of effective H.pylori eradication triple therapy regimens. Rabeprazole may have less potential for drug interaction than omeprazole which may make useful in the elderly and others in multiple drug therapy.[27] However there are no cases withdrawn during the course of treatment as no adverse events were reported.

In conclusion all the triple drug regimens were safe and equally effective in eradicating H.pylori after 2 and 6 weeks of treatment in A, B & C groups. All the groups showed urease test negative with 100% eradication rates after 6 and 10 weeks of follow up indicating no recurrence. Rabeprazole group patients however became asymptomatic faster than others with rapid H.pylori eradication rate.

SUMMARY AND CONCLUSION: Proton pump inhibitors suppress gastric acid secretion by inhibition of enzyme H^+ K^+ ATPase present on the secretory surface of the parietal cell. This blocks the final step in gastric acid secretion. Both basal and stimulated acid secretions are inhibited and peptic activity is reduced. They suppress H.pylori organisms in the stomach.

H.pylori infection is responsible for the majority of duodenal and gastric ulcers. Helicobacter pylori eradication has become the mainstay of therapy for most patients with peptic ulcer disease to prevent recurrences and development of gastric cancer. The life time risk of peptic ulcer in a person infected with H.pylori ranges from 3% in US to 25% in Japan and around 60% in India.

Omeprazole is the standard commonly used in the triple drug regimen. The other PPIs are Rabeprazole, Esomeprazole, Pantoprazole and Lansoprazole. They mainly differ from Omeprazole in their individual pharmacokinetic properties. Omeprazole is an acid labile drug. The absorption of omeprazole is dose dependent. Its oral bioavailability is 25 – 40%. The elimination half-life of omeprazole is 0.5 – 3 hrs.

Rabeprazole has oral bioavailability of 52%. Peak plasma concentration occur at 3.5 hrs after an oral dose. The plasma half-life is about one hour. It is chemically more stable and also has greater inhibitory effect on H.pylori than Omeprazole.

Esomeprazole is the S-isomer of Omeprazole. It is rapidly absorbed and produces higher plasma concentration for longer periods and as a result produces more effective and complete gastric acid suppression than omeprazole. Peak plasma levels occur at 0.5 – 2hrs after an oral dose. The plasma half-life is about 1.3hrs and has less first pass metabolism than omeprazole and low plasma clearance. The oral bioavailability of esomperazole increases with the dose, it is 68% for 20mg dose and 89% for 40mg dose. It has been reported that Rabeprazole is more effective than esomeprazole in raising the intragastric pH.

This study was conducted to see whether the difference in pharmacokinetic properties show any differences in the safety and efficacy parameters between treatment with Omeprazole, Rabeprazole and Esomeprazole in the triple drug regimen for eradication of H.pylori infection in peptic ulcer patients in Gastroenterology / clinical pharmacology department of Osmania General Hospital, Hyderabad, A.P

It was randomized double blind parallel and comparative study. A total of 45 adult subjects were divided into three groups (n =15) with 15 in each group. Patients with normal baseline biochemical parameters and with endoscopically proven peptic ulcer with evidence of H.pylori infection determined by, rapid urease test and histopathology were enrolled in the study. The eligible patients were randomized to receive either one of the three triple drug regimens for 2 weeks followed by respective proton pump inhibitor twice daily for 4 weeks. Group A received Tab. Omeprazole 20mg twice a day before breakfast and before dinner, Tab. Tinidazole 500mg twice a day after meals and Cap. Amoxicillin 500mg twice a day after meals. Group B received, Tab. Esomeprazole 40mg twice a day before breakfast and before dinner, Tab. Tinidazole 500mg twice a day after meals and Cap. Amoxicillin 500mg twice a day after meals. Group C received, Tab. Rabeprazole 20mg twice a day before breakfast and before dinner, Tab. Tinidazole 500mg twice a day after meals and Cap. Amoxycillin 500mg twice a day after meals.

Followup was done at 2, 6 and 10 weeks. Endoscopy, rapid urease test, histopathology, signs and symptoms and ADRS were recorded.

Two weeks after triple drug treatment, H.pylori was negative in 66.7%, 73% and 80% and Rapid urease test was negative in 53%, 60% and 66% in group A, B and C respectively. Endoscopy findings showed significant reduction in size and healing of ulcers in group A, B and C. There was improvement in signs and symptoms by 53 to 80%, after 2 weeks. Hence after therapy with triple drug regimen H.pylori eradication was 66-80% and healing of ulcers was 83 – 100% which was higher in Rabeprazole group. At 6 weeks, there was complete relief of signs and symptoms. At the followup of 10 weeks there was no ulcer recurrence. No adverse effects were noted in all the groups.

In conclusion, Triple drug regimen had shown to eradicate H.pylori infection in the treatment of Peptic ulcer. There was healing of ulcers in all the groups which was highly significant. There was no recurrence of peptic ulcer with these regimens in all the groups. However Rabeprazole group patients became asymptomatic rapidly than other groups with better H.pylori eradication.

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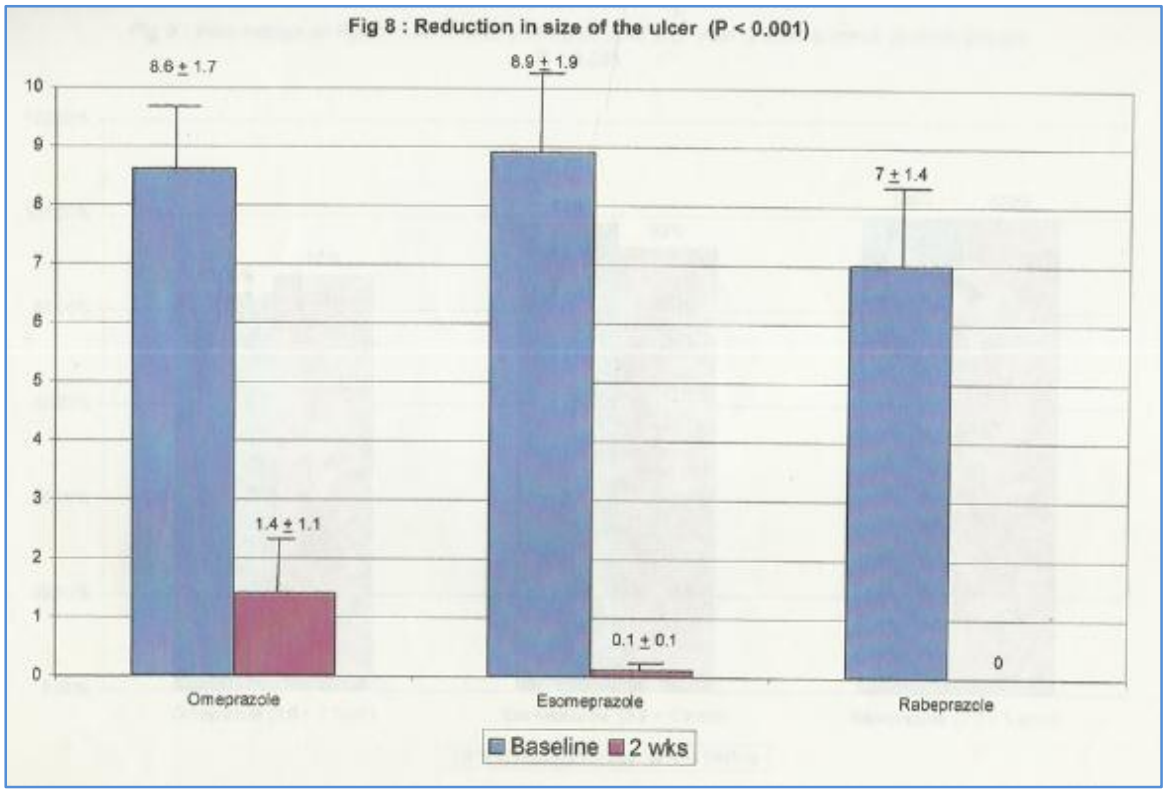


Fig 8 : Reduction in size of the ulcer (P < 0.001)
8.6 ± 1.7
8.9 ± 1.9
7 ± 1.4
1.4 ± 1.1
0.1 ± 0.1
0
10
9
8
7
6
5
4
3
2
1
0
Omeprazole
Esomeprazole
Rabeprazole
Baseline
2 wks

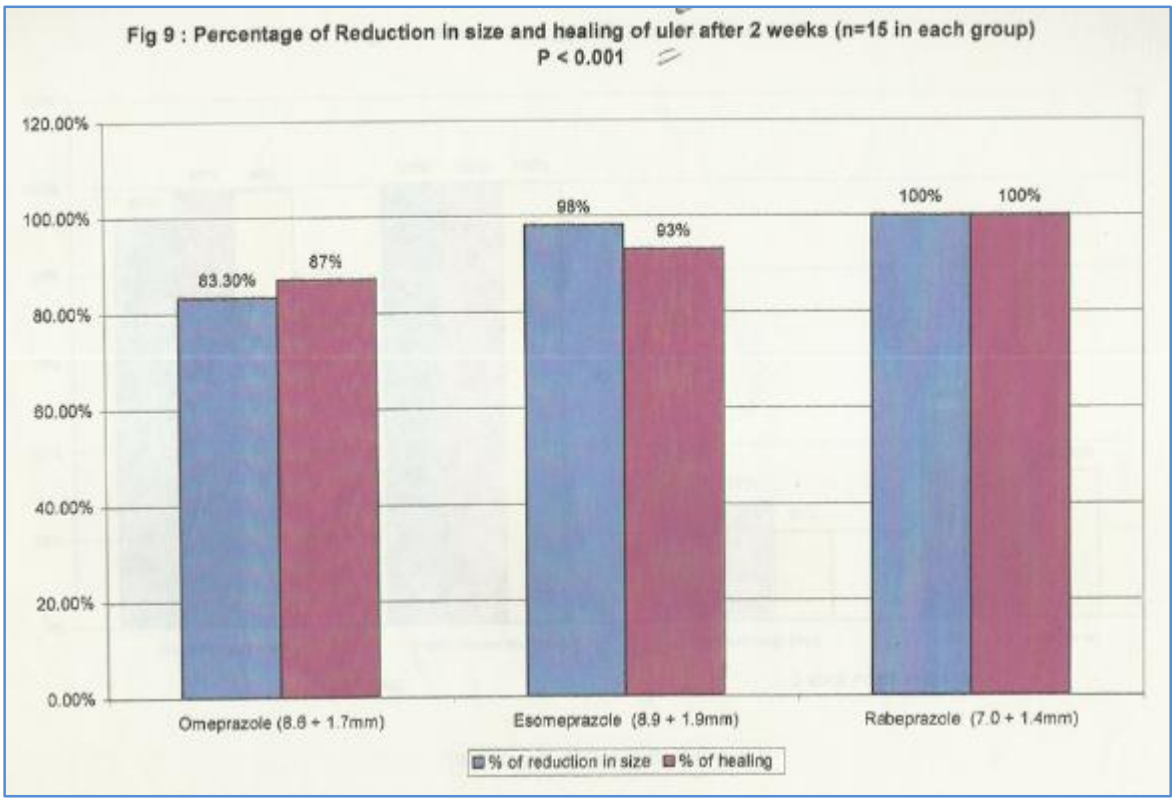


Fig 9 : Percentage of Reduction in size and healing of ulcer after 2 weeks (n=15 in each group)
P < 0.001
120.00%
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
83.30%
87%
98%
93%
100%
100%
Omeprazole (8.6 + 1.7mm)
Esomeprazole (8.9 + 1.9mm)
Rabeprazole (7.0 + 1.4mm)
% of reduction in size
% of healing

Fig 10 : Histopathology and Rapid Urease Test

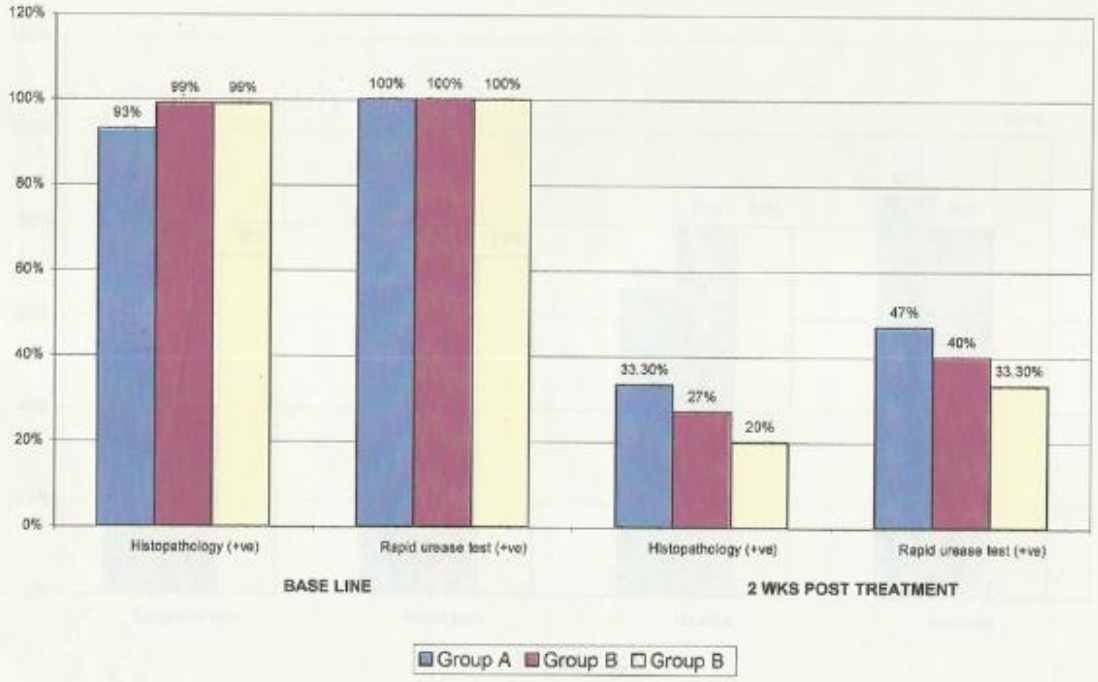
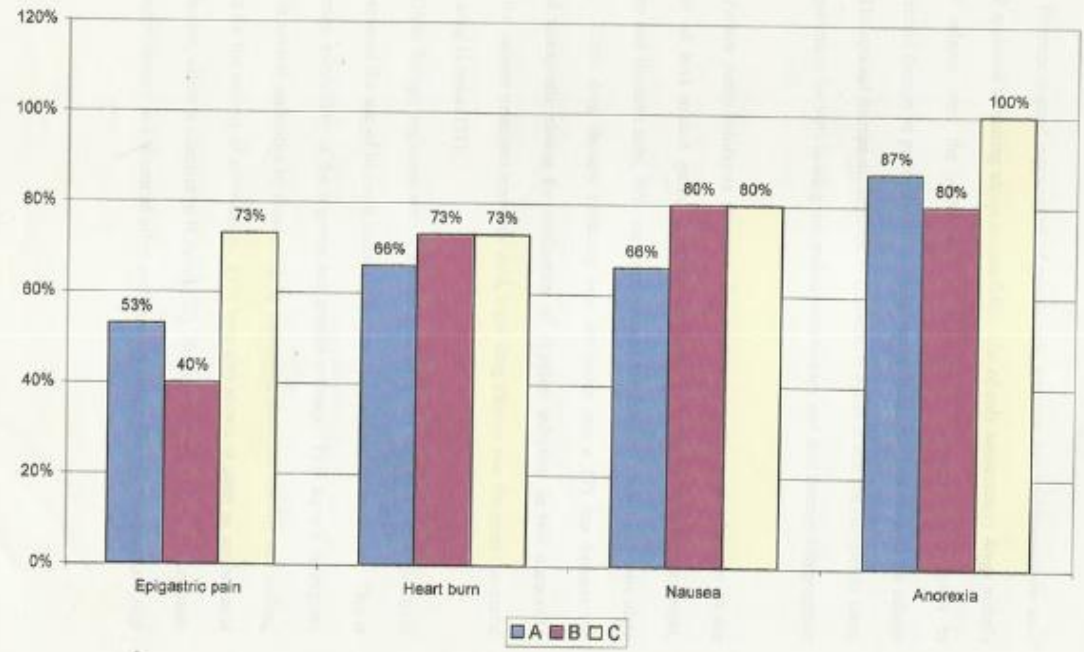


Fig 11 : Complete relief of Signs and Symptoms at 2 weeks of treatment (n=15 in each group)
P < 0.001



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