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Original Article

Role of Immediate Release and Delayed Release Omeprazole in Patients with Gastro Esophageal Reflux Disease

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Abstract:

Proton pump inhibitors are widely used for Gastro Esophageal Reflux Disease (GERD) treatment. This prospective double blind randomized cross over study was carried out in the Department of Gastroenterology, BSMMU from June 2007 to May 2008 to assess the efficacy of Immediate-release omeprazole (IR-OMEP) & Delayed-release Omeprazole (DR-OMEP) in relieving symptoms & healing of oesophagitis in GERD. All patients who fulfilled the inclusion criteria underwent upper gastrointestinal (UGI) endoscopy to be lebelled as nonerosive and erosive GERD. Among total 69 patients, 43 (62.3 %) had nonerosive and 26 (37.7 %) had erosive GERD. Patients were divided into group A (35) and group B (34) who received group A drugs (20 mg IR-OMEP bd) and group B drugs (20 mg DR-OMEP bd) from day 1-14 respectively. Then drugs were crossed over (group A: 20mg DR-OMEP bd; group B: 20 mg IR-OMEP bd) from day 15-28. Improvement of heartburn, regurgitation in each group were assessed in every week, during drug cross over and at the end and then compared between two groups. There was no significant difference in relieving heartburn and regurgitation between IR-OMEP and DR-OMEP either in erosive or nonerosive GERD ($P>0.50$). Patients with erosive GERD underwent UGI endoscopy at the end of treatment to see healing of esophagitis. Study showed significant healing of oesophagitis in group A after 4 weeks than group B (14%) ($P<0.05$) but there is no superiority of IR-OMEP over DR-OMEP in relieving symptoms of GERD.

Key words: Gastro Esophageal Reflux Disease (GERD), Heartburn, Immediate-release Omeprazole, Delayed-release Omeprazole.

Introduction:

Gastro Esophageal Reflux Disease (GERD) is the failure of normal anti-reflux barrier to protect against frequent, abnormal amounts of gastro esophageal reflux[1]. Heartburn is the classic symptom, but acid regurgitation, dysphagia and epigastric pain are also common[2,3]. In western countries, approximately 40% of adults experience heartburn, 10%-20% at least once per week, 4%-10% have daily heartburn episodes[4-6]. It is uncommon in Asians[7]. In Bangladesh, its prevalence in rural and urban population is 19.4% and 18.1% respectively[8,9].

Transient relaxation of lower esophageal sphincter (LES) is generally associated with reflux. Reduced esophageal clearance, impaired resistance of esophageal mucosa to acid, incompetence of the LES, gastric factor may also contribute to GERD[10-13].

Endoscopically, GERD is divided into nonerosive and erosive reflux disease. GERD is a spectrum of disease, with classic symptoms but without any endoscopic changes on one end, with erosive esophagitis and GERD related complications on the other hand[14]. Heartburn, even in absence of demonstrable oesophagitis, may seriously affect patient's quality of life[10].

There is no single diagnostic test. Symptoms assessment, by structured interview or questionnaire, is central to the diagnosis of GERD. Reliable reflux symptom questionnaires have been developed with content validity[15].

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GERD demands treatment because of considerable morbidity[8], like esophageal stricture, esophageal ulcer, bleeding, Barrett's esophagus[15]. Suppression of gastric acid secretion with histamine-2 receptor antagonists and proton pump inhibitors, is associated with improved symptom relief[16,17]. Efficacy of omeprazole has been studied in Bangladesh[18].

IR-OMEP (20mg or 40mg) capsule, suspension contains 1100mg and 1680mg sodium bicarbonate respectively[19]. Sodium bicarbonate neutralizes gastric acid, protects PPI from acid degradation, allows it to be rapidly absorbed and eliminates the need for an enteric coating[20]. Rapid alkalization of gastric contents by sodium bicarbonate may activate proton pumps which in turn may be inhibited by the peak plasma concentration of omeprozole (within 30 minutes with IR-OMEP)[21]. Gastric pH > 4 is needed for effective mucosal healing. IR-OMEP (40mg, 20mg, once daily) maintain gastric pH > 4 for 24 hours in 77% and 51% of the time respectively which is longer than delayed release compounds[20]. IR-OMEP provides rapid onset of action, fast control of gastric acidity, sustained control of intragastric pH at steady state offers intriguing possibilities for the improved management of night time heartburn[22].

This study was designed to assess the efficacy of IR-OMEP & DR-OMEP (relieving symptoms, healing oesophagitis) in symptomatic GERD patients in Bangladesh.

Materials and Methods:

This prospective double blind randomized cross over study was carried out in the outpatient department of Gastroenterology of Bangabandhu Sheikh Mujib Medical University (BSMMU) from June 2007 to May 2008. Patients of either sex, age 18 years and above, having heartburn at least 3 days in a week, those with normal physical examination and those willing to take drug for 28 days and came on regular follow up, gave informed written consent were included. Patients with complicated peptic ulcer disease, pregnant and lactating mother, with known heart disease, liver disease, renal disease, debilitating patient, who regularly intake steroids or any ulcerogenic medication (e.g. NSAIDS, antiplatelet and aspirin) were excluded from the study. An approval from the ethical committee was taken to conduct the study. Then the patients were given serial number from 1 to onward. Total 80 patients were enrolled in this study. Following randomization alternate 5 subjects were alternatively submitted into group A and group B respectively. All underwent upper GI endoscopy at the beginning of the study. Patients were educated to maintain a daily diary of symptoms. Two sets of drugs were used; IR OMEP and DR OMEP. All drugs were similar in morphology. Group A and B patients recieved IR OMEP and DR OMEP respectively from day 1-14 twice daily half an hour before meal. After 14 days drugs were crossed over between the groups. Drugs were provided by the department of Gastroenterology, BSMMU and manufactured by a renowned pharmaceuticals company. Drugs were distributed by an assigned medical officer of Gastroenterology department of BSMMU.

Compliance of treatment was monitored by completion of daily diary and pills counting at 14th and 28th day and this was found to be satisfactory.

All data were collected from the daily diary and analysed by SPSS. For statistical analysis chi-square test, Z test were used and P value less than 0.05 was considered as significant.

Assessment of Efficacy of Treatment:

All patients were assessed on 2nd, 3rd, 4th week by analyzing daily diary of symptoms maintained by the patients. Following parameters were analyzed to determine the efficacy i.e.

1. Daily occurrence of heartburn i.e. proportion of patient without heartburn on each day of the study period.

2. Complete resolution of heartburn i.e. no heartburn of any sort in the last 7 days prior to evaluation at week 2nd, 3rd, 4th.

3. Improvement of other symptoms like regurgitation, dysphagia, epigastric pain, nausea at baseline and at the 2nd, 3rd, 4th week of follow-up.

4. First endoscopy categorized erosive & non-erosive GERD. Follow-up upper GI endoscopy was performed after 28 days with erosive GERD patients to see the healing of oesophagitis.

Result:

A total 80 patients were enrolled in this study. Group A-40 (Male 27, Female 13) and group B-40 (Male 19, Female 21). Total 11 (group A-5, group B- 6) patients were dropped out from the study. Remaining 69 patients completed the trial (35 in group A, 34 in group B). Among them, 43 (62.3%) patients had endoscopy negative (non-erosive) and 26 (37.7%) patients had endoscopic positive (erosive) GERD (Table I).

Table I: Erosive and non-erosive GERD in study population

GERD (n=69)	Group A (n=35)	Group B (n= 34)
Non erosive GERD (endoscopic negative) (n=43)(62.3 %)	23 (66 %)	20 (59 %)
Erosive GERD (endoscopic positive) (n=26) (37.7 %)	12 (34 %)	14 (41 %)

Group A:D1 14:IR-OMEP, D15 28 :DR-OMEP, Group B:D1 14:DR-OMEP,D15 28 :IR-OMEP

In group A, at the end of 14 days, with IR-OMEP, in erosive GERD, 9 (75.0%) patients and in nonerosive GERD 12(52.2%) patients had disappearance of heartburn. With DR-OMEP at the end of 28 days 7(58.3%) patients with erosive GERD, 16(69.6%) patients with nonerosive GERD had disappearance of heartburn. In group B, at the end of 28 days, with IR-OMEP, in erosive GERD, 7(50.0%) patients and in nonerosive GERD 11(55.0%) patients had disappearance of heartburn. With DR-OMEP at the end of 14 days 7(50.0%) patients with erosive GERD, 13(65.0%) patients with nonerosive GERD had disappearance of heartburn. There was no significant difference in improvement of heartburn between nonerosive and erosive GERD with either IR-OMEP or DR-OMEP ($p>0.05$) (Table II).

Improvement of regurgitation in erosive and nonerosive GERD in each group were assessed in every week following initiation of treatment and then compared between two groups. In group A, at the end of 14 days, with IR-OMEP, in erosive GERD, 8(66.7%) patients and in nonerosive GERD 17(73.9%) patients had disappearance of regurgitation. With DR-OMEP at the end of 28 days 6(50.0%) patients with erosive GERD, 17(73.9%) patients with nonerosive GERD had disappearance of regurgitation. In group B, at the end of 28 days, with IR-OMEP, in erosive GERD, 9 (64.3%) patients and in nonerosive GERD 14(70.0%) patients had disappearance of regurgitation. With DR-OMEP at the end of 14 days 7(50.0%) patients with erosive GERD, 15(75.0%) patients with nonerosive GERD had disappearance of regurgitation. There was no significant difference in improvement of regurgitation between nonerosive and erosive GERD ($p>0.05$) (Table III).

Total 26 patients had erosive oesophagitis. At the end of 28th day, in group A (n-12) oesophagitis healed in 6 (50.0%) patients & in group B (n-14) oesophagitis healed in 2(14.3%) patients. There was significant difference in oesophagitis healing between group A & B ($P <0.05$) (Table IV).

Discussion:

The term gastro-esophageal reflux disease (GERD) is the failure of the normal anti-reflux barrier to protect against frequent and abnormal amounts of gastroesophageal reflux. Geneva workshop defined "gastroesophageal reflux disease as being present in all individual who are exposed to risks of physical complications of gastroesophageal reflux or who experience clinically significant impairment of health related well being after adequate reassurance of the benign nature of the symptoms". Heartburn is a classic symptom of GERD, but other symptoms such as acid regurgitation, dysphagia and epigastric pain, are also common. In population based studies in western countries, approximately 20% to 40% have heart burn at least once per week and 4% to 10% have daily heartburn episodes. Now GERD is catagorized into three unique groups of patients : non-erosive reflux disease, erosive oesophagitis and Barrett's oesophagus.

GERD is a well known public health problem affecting the quality of life. It is a chronic medical disorder, although reflux symptoms may appear to wax and wane, they probably do not disappear permanently on the majority of cases who attend for medical care. It is expensive for the individual and the society in terms of drug, surgery and absence from work. It is a potentially serious condition with a risk of complications such as erosions, strictures, Barrett's oesophagus and malignancy which highlights the importance of treatment of GERD.

A strong association between GERD symptoms and oesophageal acid exposures has been demonstrated. The findings of numerous clinical trials have shown that suppression of gastric acid secretion is associated with improvement of symptom relief in GERD. Acid suppression agents, including histamine-2 receptor antagonists and proton pump inhibitors, have become the main stay in the treatment of GERD, whether the patients have erosive oesophagitis or not.

There is paucity of data on GERD in Bangladesh. Although PPI like omeprazole is widely used emperically for GERD. There is no comparative study on efficacy of IR-OMEP & DR-OMEP for treatment of symptomatic GERD in Bangladesh. This was a prospective double blind randomazied cross over study to assess the efficacy of IR-OMEP & DR-OMEP in patient with GERD.

Table II: Status of heartburn in each group at weekly follow up in nonerosive & erosive GERD

Group	Day	Heart burn	Non-erosive GERD No.(%) (n=23)	Erosive GERD No.(%) (n=12)	P value*	OR	95 %CI
Group A	Day 1	Present Absent	15(65) 08(35)	09(75) 03(25)	>0.05	1.600	0.335-7.639
	day 7	Present Absent	11(47.8) 12 (52.2)	4(33.0) 8(66.7)	>0.05	0.545	0.128-2.331
	Day 14	Present Absent	11(47.8) 12(52.2)	3(25.0) 9(75.0)	>0.05	0.364	0.078-1.699
	Day 21	Present Absent	9(39.1) 14(60.9)	4(33.3) 8(66.7)	>0.05	0.778	1.413-32.826
	Day 28	Present Absent	7(30.4) 16(69.6)	5(41.7) 7(58.3)	>0.05	1.633	0.383-6.968
Group B			(n=20)	(n=14)	P value	OR	95 %CI
	Day 1	Present Absent	14(70.0) 6(30.0	11(78.6) 3(21.4)	>0.05	1.571	0.319-7.745
	Day7	Present Absent	11(55.0) 9(45.0	11(78.6) 3(21.4)	>0.05	3.000	0.636-14.149
	Day14	Present Absent	7(35.0 13(65.0)	7(50.0) 7(50.0)	>0.05	1.857	0.461-7.482
	Day21	Present Absent	7(35.0 13(65.0	11(78.6) 3(21.4)	<0.05	6.810	1.413-32.826
	Day28	Present Absent	9(45.0) 11(55.0)	7(50.0) 7(50.0)	>0.05	1.222	0.311-4.804

Group A:D1 14 :IR-OMEP,D15 28 :DR-OMEP, Group B:D1 14:DR-OMEP,D15 28 :IR-OMEP, *Chi square test

Table IV: Healing of oesophagitis in erosive GERD patients

Study population (n=69)	Day 1 Erosive GERD No(%) n=26	Non-erosive GERD No(%) n=43	Day 28 Healing No(%) n=12	No Healing No(%) n=14	P value*
Group A (n=35)	12 (34.2)	23 (65.7)	6 (50.0)	6 (50.0)	<0.05
Group B (n=34)	14 (41.2)	20 (58.8)	2 (14.3)	12 (85.7)	

Group A:D1 14:IR-OMEP, D15 28:DR-OMEP, Group B:D1 14:DR-OMEP, D15 28 :IR-OMEP, *Chi square test

Table III: Status of regurgitation in each group at weekly follow up in nonerosive & erosive GERD

Group/day		Non-erosive GERD No. (%) (n=23)		Erosive GERD No. (%) (n=12)		P value*	OR	95 %CI
Group A								
Day 1	Present	12	(52.2)	7 (58.3)	5	>0.05	1.283	0.314-5.253
	Absent	11 (47.8)		(41.7)				
day 7	Present	14	(60.9)	4 (33.3)	8	>0.05	0.321	.074-1.389
	Absent	9 (39.1)		(66.7)				
Day 14	Present	6	(26.1)	4 (33.3)	8	>0.05	1.417	0.310-6.470
	Absent	17 (73.9)		(66.7)				
Day 21	Present	6	(26.1)	3	(25.0)	>0.05	0.944	0.190-4.698
	Absent	17 (73.9)		9 (75)				
Day 28	Present	6	(26.1)	6	(50.0)	>0.05	2.833	0.655-12.263
	Absent	17 (73.9)		6 (50.0)				
Group B		**n= 20**		**n=14**				
Day 1	Present	9(45.0)		9	(64.3)	>0.05	2.200	0.540-8.957
	Absent	11(55.0)		5 (35.7				
Day7	Present	10(50.		6	(42.9)	>0.05	0.75	0.190-2.964
	Absent	10(50.0)		8 (57.1)				
Day14	Present	5(25.0)		7	(50.0)	>0.05	3.000	0.699-12.875
	Absent	15(75.0)		7 (50.0)				
Day21	Present	5(25.0)		8	(57.1)	>0.05	4.000	0.925-17.302
	Absent	15(75.0)		6 (42.9)				
Day28	Present	6(30)		5	(35.7)	>0.05	1.296	0.303-5.540
	Absent	14(70)		9 (64.3)				

Group A: D1 14 :IR-OMEP, D15 28 :DR-OMEP, Group B: D1 14 :DR-OMEP, D15 28 :IR-OMEP, *Chi square test

For this study 80 patients were selected for the trial and divided into group A and B. Total 69 patients completed the trial, 11 patients were dropped out. Among them 35 belong to group A and 34 belong to group B. Total 43 pateint had non erosive disease and 26 patients had erosive oesophagitis. In our study non-erosive GERD is 62.3 % and erosive GERD is 37.7 %. Jones et al, carried out a study in community practice which revealed 70% GERD was non erosive and 30% was erosive GERD[23]. Biswajit D have shown non erosive GERD in 77% and erosive oesophagitis in 23% of patients[18].

This study showed that IR-OMEP is not a more effective drug to relieve heartburn compare to DR-OMEP. In this study in erosive GERD (endoscopy positive) patients resolution of heart burn occured more in patient taking IR-OMEP (75%) than in patient taking DR-OMEP. A clinical trial conducted by Ricter et al, showed that at the end of 4 weeks 76% of patients had complete resolution of heartburn with DR-OMEP[24]. Biswjit D has also shown resolution of heartburn by DR-OMEP is 76% patients[18].

In this study, at the 14th day of treatment, in group A (taking IR- OMEP), 9 (75.0%) patients with erosive GERD, 12 (52.2%) patients with nonerosive GERD had disappearence of heartburn, in Group B (taking DR-OMEP), 7 (50.0%) patients with erosive GERD, 13 (65.0%) patients with nonerosive GERD had disappearence of heartburn. In this study, at the 28th day of treatment, in group A (taking DR-OMEP), 7 (58.3%) patients with erosive GERD, 16 (69.6%) patients with nonerosive GERD had disappearence of heartburn, in Group B (taking IR-OMEP), 7 (50.0%) patients with erosive GERD, 11 (55.0%) patients with nonerosive GERD had disappearence of heartburn. Difference of resolution of heratburn was not statistically significant between erosive and nonerosive GERD ie, heartburn is not related to the presence or absence of erosive or non erosive GERD. This finding is consistent with other studies. David and Pierre, in randomized control comparison study showed that PPI (Pantoprazole) resulted in higher complete resolution of heartburn compared to placebo therapy in GERD patients but heartburn relief was not significantly different between the erosive and endoscopic negative GERD[25].

Carlsson et al used 10mg and 20 mg of omeprazole to treat both endoscopic negative and endoscopic positive patients with GERD symptoms. After 4 weeks of treatment resolution of heartburn was approximately same in both groups[26].

Symptoms of regurgitation were improved with both IM-OMEP and DR-OMEP and there was no statistically significant difference in improvement of regurgitation with IR-OMEP. Carlsson et al showed that after 4 weeks of treatment with omeprazole, symptoms of acid regurgitation, epigastric pain, nausea and dysphagia were resolved more often in endoscopy positive (erosive GERD) patients than in those without endoscopic finding (nonerosive GERD)[26]. Bishwajit D showed that acid regurgitation improved in 90% of patients in both endoscopy positive and negative groups[18].

In this study, total 26 patients had erosive oesophagitis. At the end of 28th day, in group A (n-12), oesophagitis healed in 6 (50.0%) patients. In group B (n-14) oesophagitis healed in 2 (14.3%) patients and did not heal in 12 (85.7%) patients. There was significant difference in oesophagitis healing between group A & B. Katz P et al showed bed time IR-OMEP provided more rapid control of night time gastric pH and decrease in nocturnal acid break through compared to lansoprazole & esomeprazole. Nocturnal acid control with IR-OMEP was superior to lansoprazole & esomeprazole[27].

In this study, omeprazole showed a good response in GERD patients but there was no significant difference in relieving heartburn and regurgitation between IR-OMEP and DR-OMEP. No significant difference was observed between endoscopy positive (erosive) & negative (nonerosive) patients to relieve the GERD symptoms.

Conclusion:

GERD is a common & difficult to treat problem in medical practice. This study showed no significant difference in relieving symptoms (heartburn and regurgitation) between IR-OMEP and DR-OMEP groups. It is difficult to say healing of oesophagitis is due to IR-OMEP or DR-OMEP. However, as the sample size of this study was small further studies with large sample size can be conducted in future to achieve more accurate data.

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