Original Paper

LOW DOSE ASPIRIN AND MUCOPROTECTIVE EFFECTS OF OMEPRAZOLE AND RANITIDINE

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Abstract

Omeprazole and ranitidine are widely used in the treatment of peptic ulcer disease and in association of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) to prevent the mucosal injury of gastrointestinal tract. In the light of above, the study was undertaken to assess the superiority of omeprazole over ranitidine in the protection of mucosal injury caused by low dose aspirin. This is a prospective and comparative study carried out among the people taking low dose aspirin along with either omeprazole or ranitidine at gastroenterology centre of a military hospital over a period of 52 weeks. Respondents were recruited consequently and data were collected on specific data collection sheet with relevant clinical information and endoscopic findings. In ranitidine group 16 patients (40%) were found to have mucosal injury where as 05 patients (12.5%) in the omeprazole group were found to have gastroduodenal mucosal injury. The difference was statistically significant ($p<0.01$). Omeprazole has superior mucoprotective effect over ranitidine in patients taking low dose aspirin.

Key words: **Low dose aspirin, omeprazole, ranitidine, mucoprotection.**

Introduction

Low dose aspirin is used as anti-platelet agent in the ischaemic heart disease, transient ischaemic attack (TIA) and ischaemic stroke widely. It may produce peptic ulcer disease and other gastroduodenal mucosal injury. Patients may be symptomatic or asymptomatic or may present with complications like upper gastrointestinal (UGI) bleeding and perforation[1-6]. Gastrointestinal mucosa, notably the gastric mucosa has many protective mechanisms. Among those, mucus and prostaglandins are the important first line defense. Any factor causes imbalance between acid-pepsin versus mucosal defense mechanisms leads to gastric and mucosal injury[7,8].

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclo-oxygenase enzyme thereby inhibit the prostaglandins which have protective role against the mucosal injury. Aspirin is also a weak acid and migrates across the lipid membrane of epithelial cells leading to mucosal injury. H_2 blockers and proton pump inhibitors protect the gastric and duodenal mucosa by inhibiting the acid secretion. H_2-receptor is one of the pathways of gastric acid secretion activated by histamine and ranitidine blocks that. Other pathways for secretion of acid remain unprotected. On the other hand omeprazole blocks the final pathway of acid secretion common to three pathways namely histamine, acetylcholine and pentagastrin pathways[8-10].

Low dose aspirin carries increased risk of mucosal injury and a small but significant risk of UGI bleeding. Concomitant use of other NSAIDs increases the risk of mucosal injury[6]. The patients with NSAIDs are taking proton pump inhibitors which are more likely to confer protection against UGI bleeding than that of H_2 receptor antagonists[10,11]. H_2 receptor antagonists prevent only duodenal ulcer and therefore cannot be recommended for prophylaxis[5,7,12-14].

The regular use of aspirin is especially associated with ulcers in the prepyloric region of the stomach[8]. Gastrointestinal endoscopy detects the mucosal injury precisely. Histological features do not define NSAID-induced gastritis[14]. It is estimated that during the past two decades 50 million Americans have started taking aspirin for the prevention of heart attack and stroke. However, aspirin doubles the risk of upper gastrointestinal bleeding even at doses as low as 75 mg daily. The efficacy of low-dose aspirin (less than 325 mg daily) in the prevention of cardiovascular and cerebrovascular diseases is well established. Patients who are taking low-dose aspirin, however, have an increased risk of ulcer complications and some of these patients should be given prophylactic treatment. One of the available options for preventing these ulcer complications is the simultaneous use of proton-pump inhibitors, which reduces gastric acidity substantially. In a recent epidemiologic study, the use of a proton-pump inhibitor was found to be associated with a decrease of 80 percent in the risk of gastrointestinal bleeding in subjects taking low-dose aspirin.

In Bangladesh many patients are on aspirin prophylaxis for cardiovascular and cerebrovascular diseases and they are being treated indiscriminately with H_2 receptor antagonists and proton pump inhibitors. Upper gastrointestinal

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endoscopy is one of the best ways to detect mucosal injury. So endoscopic evaluation for mucosal injury of patients with low-dose aspirin prophylaxis will help to judicious use of antisecretory drugs and therefore in prevention of unwanted gastrointestinal complications and reduce the patients sufferings

Materials and Methods

This was a prospective and comparative study carried out at Gastroenterology Centre, Combined Military Hospital (CMH) Dhaka Cantonment starting from November 2006 to October 2007. A total 80 patients were evaluated after determining both inclusion and exclusion criteria. It was a random sampling. The patients were divided into two groups: Group A - patients were getting low dose aspirin (75 mg to 150 mg) plus ranitidine (300 mg in two divided doses) and Group B - patients were taking low dose aspirin (75mg to 150 mg) plus omeprazole (40 mg in two divided doses). They were not agreed to take aspirin without ranitidine or omeprazole. After proper evaluation every patient under went upper gastrointestinal endoscopy by video-endoscope. Endoscopic findings were recorded as gastritis, duodenitis, erosions, ulcers or any other abnormality. Following were selection criteria:

Inclusion criteria

- Age 30 to 70 years
- Patients of any sex
- Patients is getting Aspirin (75mg to 150 mg/day) for 3 or more months of duration
- Non-alcoholics

Exclusion Criteria

- Patients with previous history of peptic ulcer disease
- Patients suffering from chronic liver disease, chronic renal failure, pancreatitis, hypercalcaemia, malignant diseases
- Patients getting NASIDs other than aspirin
- Patients getting prednisolone

The numerical data obtained from this study were analyzed and significance of difference was estimated by using the statistical methods. Comparisons between groups were done by chi square test and by formula of Yate's correction. All data were analyzed by using computer based SPSS programmer. Probability less than 0.05 were considered as significant.

Results

Of 80 patients included in the study 40 were of ranitidine group (group-A) and other 40 were of omeprazole group (group-B). Baseline characteristics are shown in (table-I). In group A 16 patients (40%) were found to have mucosal injuries. Out of 16, thirteen patients had gastric mucosal injury; 1 patient had duodenal mucosal injury, 2 with gastroduodenal mucosal injury.

Table-I: Base line characteristics of the study subjects (n=80).

Characteristics	Group A (n=40)	Group B (n=40)
Age (in years)	30 -70	30 -70
Mean Age (in years)	50.6	49.8
Sex		
Male (n=76)	37	39
Female (n=04)	03	01
Associated Disease		
IHD	40	40
Hypertension	16	13
DM	23	29
Drugs		
Anti hypertensive	40	40
OHA	18	20
Insulin	05	09
Isosorbide mononitrate	12	15
Smoking		
Smoker	05	06
Non /ex- smoker	35	34
Symptomatic	34	22
Asymptomatic	06	18
S. ALT (U/L)	33	29
S. Urea (mg/dl)	32	30
S. Creatinine (mg/dl)	0.8	0.8
S. Calcium (mg/dl)	7.8	8.0

IHD= Ischaemic Heart Disease, **DM**=Diabetes Mellitus, **OHA**=Oral Hypoglycaemic Agent.

Table-II : Symptoms of study subjects (n=80).

Symptoms	Group A (n=40)	Group B (n=40)
Pain abdomen	07	3
Abdominal discomfort	18	6
Bloating	15	5
Heart burn	06	2
Haematemesis	00	0
Melaena	00	0
Chest Pain	20	6

On the other hand group B, 5 patients (12.5%) had mucosal injury. Out of five, 3 had gastric mucosal injury and 2 had duodenal mucosal injury. The difference was statistically significant ($p<0.01$).

Table- III: Outcome of treatment with ranitidine vs omeprazole in patient with low dose aspirin (n=80).

Group	Result		Total	p value
	Mucosal injury	No mucosal injury		
Group A (n=40)	16 (40%)	24 (60%)	40	P<0.01
Group B (n=40)	05 (12.5%)	35 (87.5%)	40	

This superiority was reflected by the protection of gastric mucosal injuries by omeprazole over ranitidine and not by duodenal mucosal injuries where both drugs (ranitidine & omeprazole) were nearly equally protective (Table -IV). It was observed that most of the mucosal injuries were in the forms of gastritis (Table-V).

Table- IV: Outcome according to sites of lesion (n=80).

Group	Duodenal mucosa		Gastric mucosa		P value
	Injury	No Injury	Injury	No Injury	
Group A (n=40)	2 (5%)	38 (95%)	14 (35%)	26 (65%)	p<0.05
Group B (n=40)	2 (5%)	38 (95%)	3 (7.5%)	37 (92.5%)	

Table-V: Types of mucosal injury (n=80).

Group	Type of Injuries		
	Gastritis/Erosion	Ulcer	Duodenitis/Erosion
Group A (n=40)	13 (32.5%)	1 (2.5%)	2 (5%)
Group B (n=40)	03 (07.5%)	0	2 (5%)

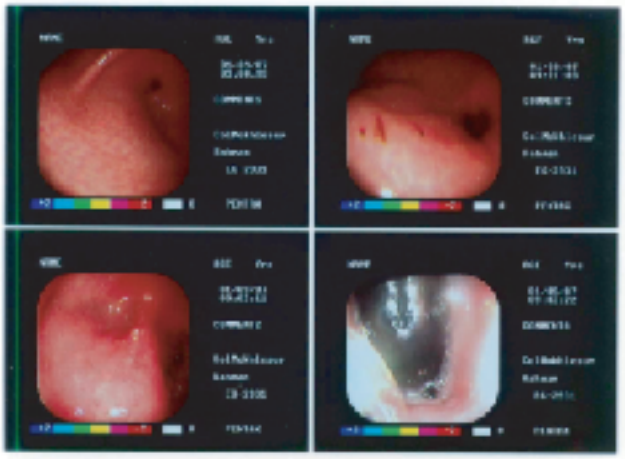

Fig-1 : Aspirin induced antral gastritis in ranitidine group.

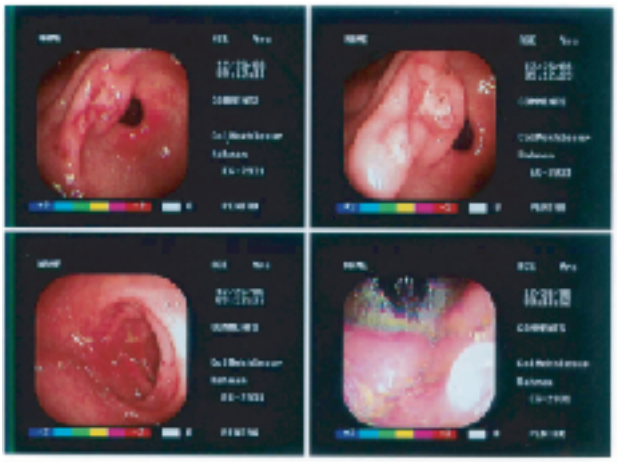

Fig-2: Aspirin induced antral ulcer in ranitidine group.

Discussion

Aspirin mediated gastroduodenal mucosal injury is well documented. As such the effective treatment as well as prophylactic treatment can be delivered to the patient to prevent or reduce the mucosal injury and its complications. Few studies were done to compare omeprazole with ranitidine and to observe the superiority or inferiority of one medicine over other, in groups of people with or without risk factors. Nearly all the studies reflected the superiority of omeprazole over ranitidine in terms of protection as well as treatment of gastro duodenal mucosal injury[15-18].

The striking finding in this study is that the efficacy of omeprazole (87.5%) was superior to that of ranitidine (60%) in the protection of gastroduodenal mucosal injury caused by low dose aspirin on long term basis and it is statistically significant ($p<0.01$). The superiority of omeprazole over ranitidine appeared in the protection of gastric mucosal injury ($p<0.05$), but not in the duodenal mucosal injury in which both omeprazole and ranitidine were equally effective. The explanation is that, the ranitidine not like omeprazole with regular dose is not enough to raise the intragastric pH to prevent the diffusion of aspirin into the cell to such extent to block both local topic effect and cyclo-oxygenase inhibition evoked by aspirin completely. Therefore partial protective effect of ranitidine with 150 mg twice daily dose was observed. On the other hand by inhibition of acid secretion ranitidine raised the pH at duodenum enough to block both the above actions of aspirin like omeprazole. The current findings regarding superiority of efficacy of omeprazole over ranitidine are consistent with those reported in most previous studies carried out for short-term users of aspirin and non aspirin NSAIDs[1,2,4-6,15-18]. But few studies differ partially[3,19]. They noted that nocturnal (8 pm) co-administration of ranitidine 300 mg reduces almost completely gastro duodenal lesions evoked by 300 mg aspirin. Probably single 300mg ranitidine at night raises the intragastric pH to such extent to block the adverse effects of aspirin. Simon et al, Muller et al and Lanas et al showed the superiority of omeprazole/lansoprazole (79% to 80% protection) over the ranitidine (63% protection) in the protection of gastric mucosal injury evoked by low dose aspirin[15-17]. In another study, ranitidine was found almost ineffective in preventing gastric ulcers[18]. NSAID users usually develop acute gastritis or ulcer at body and antrum. Long term users differ. One of the important finding of this study was that long-term low dose aspirin users developed antral or pre-pyloric gastritis. This finding regarding types of lesions and site of lesion are consistent with the earlier study[8,14].

Kurata et al study revealed that old age was independent risk factor in NSAID associated ulcers[19]. The incidence of mucosal injury increases with the age may lead to

fatal outcome and the incidence of mucosal injury is increased over the age of 70 years. As all the subjects are between 30 years and 70 years age group in the study, there was no significance difference in this age group. A very recent study showed that damage to the stomach appeared weakly dose-related and older age did not increase the risk of erosions[20].

In the study of Chiverton et al observed that smoking was important risk factor for peptic ulcer disease and that habit delayed the ulcer healing[21]. Correlation between mucosal injury and smoking could not be made possible in this study as most of the study subjects were ex-smoker or non-smoker. There was an important observation in presenting symptoms. Most of the patients in both in ranitidine group and omeprazole group presented with mild gastrointestinal symptoms like abdominal discomfort, gas, fullness of stomach, etc. Low risk group of patients with low dose of aspirin usually have mild gastrointestinal symptoms but do not present with fatal gastrointestinal out-come[18,22].

Now-a-day, low dose aspirin is widely used by the patients as anti-platelet agent to reduce the incidence of disease. But such low dose is not free from gastrointestinal side effects. Even as low as 30 mg aspirin per day causes gastroduodenal mucosal injury and at the same time it is effective as anti-platelet agent. So Omeprazole as prophylaxis may be used in the protection of gastric and duodenal mucosal damage in patients particularly with risk factors taking low dose aspirin.

Conclusion

From this study, it can be concluded that omeprazole is very much superior to ranitidine in the protection of gastric mucosal injury as prophylaxis associated with low dose aspirin getting more than 03 months of duration. Side effects are unremarkable in the both groups. It is also cost effective (20 mg Omeprazole vs 300 mg Ranitidine). It is important to note to conduct a large scale study for further evaluation.

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