CONVENTIONAL THERAPY VS NITAZOXANIDE PLUS OMEPRAZOLE FOR THE ERADICATION OF HELICOBACTER PYLORI : A RANDOMIZED CONTROL TRIAL

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Summary

Helicobacter pylori has an important association with Peptic Ulcer Disease (PUD). Numerous trials have proved that eradication of Helicobacter pylori results in healing of PUD and a very low recurrence rate. Attempts at eradication in Bangladesh with different regimens showed poor results. In Bangladesh there is no study with regimen containing Nitazoxanide and Omeprazole that showed to be very effective in several trails in different countries. This study was conducted in the Medicine department, Chittagong Medical College Hospital, from December 2008 to November 2009 to evaluate the efficacy of Nitazoxanide and Omeprazole in the eradication of Helicobacter pylori in PUD patients of Bangladesh. 130 endoscopically proven PUD patients were enrolled in this study when rapid urease test gave positive result & randomized into two halves for comparison of treatment regimens. After six weeks endoscopy was done. Ulcer healing, rapid urease test negativity and absence of Helicobacter pylori in histology was considered as cure. Conventional group treated with Clarithromycin, Amoxicillin, Lansoprazole for 14 days showed cure rate of 80%, whereas nitazoxanide group showed 76% cure, the difference is not statistically significant. This study shows that two regimens are effective and comparable though newer regimen failed to show superiority over conventional treatment.

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Key words
Helicobacter pylori; Eradication; Conventional therapy; Nitazoxanide; Omeprazole; Peptic Ulcer Disease.

Introduction

For more than a century peptic ulcer disease has been a major cause of morbidity and mortality. In a survey conducted in a defined population aged 15 years and above in Bangladesh, the prevalence of duodenal ulcer and gastric ulcer was estimated to be 11.98% and 3.58% respectively [1]. The point prevalence of duodenal ulcer varies from country to country. Approximately 10% of individuals in western countries develop peptic ulcer at some point in their life time [2].

H.pylori is a ubiquitous gram-negative bacterium infecting half of the world's population [3]. More than twenty years have elapsed since Warren and Marshall's discovery of the link between a bacterium called at that time *Campylobacter pylori* and peptic ulcer disease. The infection is mainly acquired in childhood and persists throughout the life, causing chronic gastritis and peptic ulcer disease, particularly duodenal ulcer in children and adults. The prevalence of *H.pylori* infection is very high in Bangladesh. A study conducted on Bangladeshi children by ICDDR.B scientists has shown that 60% are infected by the age of 3 months and 80% are infected by 3 years of age [4]. In adults, about 92% have been found to be seropositive for *H. pylori* antibody [5]. The prevalence among the middle aged adults is over 80% in many developing countries and 20% to 50 % in the developed countries [6].

International consensus conferences have recommended that *H. pylori* eradication should be the treatment of peptic ulcer associated with *H. pylori* [1]. The highest eradication rates are achieved with three regimens and these three regimens have been approved by FDA of USA in 1998: i) A proton pump inhibitor, clarithromycin, and either amoxycillin or metronidazole for 2 weeks,

ii) Ranitidine, bismuth citrate, clarithromycin and either amoxycillin, metronidazole or tetracycline for 2 weeks iii) A proton pump inhibitor, bismuth, metronidazole and tetracycline for 1 to 2 weeks [7]. Some difficulties were identified using several antimicrobials in these trials such as treatment failures were due to high prevalence of metronidazole resistant and some clarithromycin resistant strains of *H. pylori*.

Studies in Bangladesh have largely shown results similar to those of other developing countries with a low eradication rates using different *H. pylori* eradication regimens and a higher rate of re-infection. In most of the studies, the eradication rate was between 30-64% [8,9].

So, an effective eradication regimen which could be recommended for patients with peptic ulcer disease and *H. pylori* infection in Bangladesh has, therefore, not yet been found. In Bangladesh like other developing countries, the prevalence of metronidazole resistant strains of *H. pylori* is found to be very high [10]. This resulted in or may result in treatment failure with standard triple therapy and other therapy which includes metronidazole. Additional factors that may cause high treatment failure rate are poor patient compliance and host factors. On the other hand, clarithromycin based regimens probably will not be suitable for our patients because of the high cost of the drug.

In this situation, finding of an alternate regimen which will be effective and cheaper has become important.

Nitazoxanide (NTZ) a nitrothiazolyl-salicylamide compound first described by Rossignol and Cavier, has a broad spectrum of activity against microaerobic and anaerobic bacteria, anaerobic protozoa, and helminthes [11]. Side effects included loose stools, diarrhoea, abdominal pain, flatulence, nausea, vomiting, dyspepsia, xerostomia, discolored urine (Yellow-green), and headache [12].

In a clinical study, NTZ was found to be well tolerated by humans, with a high rate of eradication of *H. pylori* when it was administered with omeprazole. An eradication rate of 83% was reported among 91 patients using NTZ in combination with omeprazole (1 gm of NTZ twice daily with 20 mg of Omeprazole once daily) for seven consecutive days [13].

In Bangladesh different modalities of treatment for peptic ulcer are available e.g proton pump inhibitor, H_2 receptor antagonist and anti helicobacter pylori regimen. But in our country anti *helicobacter pylori* regimen is very costly. Previously used regimen contains more number of drugs. There is also some report of resistance and patients compliance remains poor.

So using nitazoxanide and omeprazole for the eradication of *H.pylori* could be a milestone in Bangladesh by reducing the cost of the anti helicobacter regimen.

Material and methods

The study was a double blind randomized control trial, was carried out in the in-patient and out-patient Department of Medicine, Chittagong Medical College Hospital (CMCH) Chittagong, Bangladesh, during the period of December 2008 to November 2009.

Patients admitted and attending in in-patient and out-patient department of Medicine with abdominal pain and/or heart burn were selected for endoscopy of upper gastrointestinal tract after explaining objectives, nature, purpose and potential risk of all procedures and obtaining informed written consent. Inclusion criteria of this study was endocopically proven PUD, presence of *H. pylori* proven by rapid urease test in biopsy materials and patients aged above 13 years (According to the admission criteria in Medicine unit of CMCH). Exclusion criteria was history of being treated with *H. pylori* eradication regimen in the past, complicated duodenal ulcer patients (Narrowing of duodenal bulb, active bleeding and perforation) female patients who were pregnant, breast fed or intended to become pregnant within the duration of study and patients not willing to give informed written consent.

Sample size of the study was total 130, divided in two equal groups of 65 patients.

After taking history and physical examination, endoscopy of upper gastrointestinal tract was performed. During endoscopy when ulcer became visible biopsy was taken for rapid urease test for *H.pylori.* If test became positive then randomization was done by lottery method to determine which study subject will get conventional therapy and who will get nitazoxnide plus omeprazole. 65 cards were marked by C (Conventional group) and another 65 cards were marked by NO (Nitazoxanide plus Omeprazole,

i.e. treatment group). Cards were kept in a box. Each study subject has drawn a card from the box without prior knowledge about the marking on the card. If the drawn card was C he/she got conventional therapy and if the drawn card was NO then he/she got Nitazoxanide plus Omeprazole. Conventional group was treated by Clarithromycin, Amoxycline and Lansoprazole for 14 days. Nitazoxanide plus Omeprazole group was treated by Nitazoxanide 1 gm twice daily and Omeprazole 20 mg twice daily for 14 days (Treatment group). During the therapy the study subjects were blinded as to which group he/she belonged to. Both the therapy was continued for 14 days. After 6 weeks endoscopy of upper gastrointestinal tract was repeated. Biopsy was taken from previous ulcer sites for rapid urease test & histology. During endoscopy and histology the individuals (Person doing endoscopy and histology) were blinded as to the study group. Healing was confirmed by absence of ulcer on endoscopy. Eradication was confirmed by negative urease test from biopsy material and absence of *H. pylori* in modified Giemsa stained histological section. Healing and *H. pylori* eradication rate was compared between two groups.

Data Collection: The history and findings of physical examination including investigational findings were recorded after taking informed consent from the patients. All data were collected in individual case record form. In the case record form data were collected first and each form contained different ID numbers. The necessary investigation results were collected and recorded in an attached sheet.

Data Analysis: All collected data were compiled and analyzed using Statistical Package for Social Science (SPSS, version 18.0) for Windows. Data analyses were done by using appropriate descriptive and inferential statistical methods: frequency, percentage, means, standard deviation etc. Comparison of qualitative and quantitative variables between two groups were analyzed by Pearson's chi-square test and Student's 't' test respectively. Presentation of the results were done by univariate and multivariate tables as applicable. A two tailed p value <0.05 was considered to be statistically significant.

Results

The study was conducted among 130 endoscopy proven PUD patients, in the Medicine departments of CMCH, Chittagong, from December 2008 to November 2009, with positive urease test, proved by biopsy, and randomly assigned into one of the two study groups. Among the respondents 65 (Sixty five) received Tab. Nitazoxanide & Cap. Omeprazole, and on other hand, 65 (Sixty five) received conventional treatment (Cap. Amoxycillin, Tab. Clarithromycin & Cap. Lansoprazole), for same duration.

The baseline socio-demographic data (Table I) revealed the mean age of the study subjects being 38.7 years and 41.7 years in the treatment and conventional groups respectively. Males were predominant in both groups (71% Vs 69%). Most of the patients were Muslims (88% Vs 91%), married (87% Vs 87%), and within middle class socio-economic status (72% Vs 69%). The risk factors of PUD (Table II) showed no significant predominance among the study groups.

The baseline socio-demographic factors and risk factors of PUD demonstrated no significant difference between the treatment and conventional groups ($p > 0.05$).

The clinical and investigative findings among the study subjects showed, most of the patients complained abdominal pain and heart burn in both treatment and conventional groups (96% Vs 100% and 94% Vs 95% respectively). 94% of treatment group and 81% of conventional group had past history of taking anti-ulcerant drugs. Only 6% patients had previous history of hypertension in both groups. Only 27% in treatment group and 26% in conventional group showed signs of anaemia. All patients (100%) felt abdominal tenderness in both groups. Both the groups revealed almost normal blood pressure (140/85 Vs 135/85 mmHg) (Table III).

Endoscopy of upper GIT and rapid urease test from biopsy materials were done in both groups before and after intervention. Repeat endoscopy was done after the completion of therapy and biopsy materials were also taken from antral region for rapid urease test and histopathology. Initial endoscopy revealed various types of ulcers in both the groups, while in repeat endoscopy all patients showed ulcer healing in both groups (88% Vs 82%).

Pre treatment rapid urease tests were found positive in all patients (100%) in both groups, while in repeat rapid urease tests only 24% and 13% were positive in the study groups respectively. During repeat endoscopy and rapid urease test, 8 patients from treatment group and 12 patients from conventional group were dropped out. So, the end result might be concluded like that, almost 100% patients were declared cured endoscopically, after intervention, in both groups (Table IV).

Histopathology revealed positive results for H. Pylori in 24% and 20% in treatment and conventional groups respectively.

Association between endoscopy & urease tests with histopathology findings were seen. Among different types of PUD patients detected by endoscopy, only 16 and 13 patients were found positive in histology in treatment and conventional groups respectively. In the treatment group, out of 16 positive urease test patients, 14 were found positive in histology, while within 41 negative test cases, 2 were found positive in histology. In the conventional group, out of 9 positive urease test patients, 5 were found positive in histology, and within 44 negative test cases, 8 were found positive in histology. However, the associations were not found to be significant statistically ($p > 0.05$) (Table IV).

Table 1 : Baseline socio-demographic factors among the study groups (n = 130)

Base line demography	Treatment group (n = 65)	Conventional group (n = 65)	P value
Age (Years)	38.69 ± 11.41	41.69 ± 13.07	0.351
Mean ± SD (Range)	(15 - 60)	(13 - 60)	
Sex : Male/Female	46/19	44/21	0.425
M : F Ratio	2.4 : 1	2.1 : 1	
Religion : Islam/Hindu/Buddhist	57/6/2	59/5/1	0.795
Marital Status : Married/Unmarried	57/8	57/8	0.605
Socio-economic Status : Middle/Low/High	47/17/1	45/18/2	0.814

Table II : Risk factors of PUD among the study groups (n = 130)

Risk Factors of PUD	Treatment group (n = 65)	Conventional group (n = 65)	χ^2 test value
Smoking : Yes/No	33/32	36/29	0.363
Alcohol : Yes/No	3/62	3/62	0.660
Stress : Yes/No	1/64	0/65	0.500
Family History : Yes/No	6/59	3/62	0.246

Table III : Clinical findings of patients among the study groups (n=130)

Clinical Findings	Treatment group (n = 65)	Conventional group (n = 65)	p value
Chief Complaints :			
Abdominal Pain : Yes/No	63/2	65/0	0.248
Heart Burn : Yes/No	61/4	62/3	0.500
Past History :			
H/O Hypertension : Yes/No	4/61	4/61	0.641
H/O Anti-ulcerant Drug : Yes/No	61/4	53/12	0.030
Clinical Signs :			
Anaemia : Yes/No	18/47	17/48	0.479
Abdominal Tenderness : Yes/No	65/0	65/0	-
Blood Pressure (mmHg) : Mean Systolic/Diastolic	140/85	135/85	0.064

Table IV : Investigation findings, association between endoscopy and rapid urease test with histopathology among the study groups (n=130)

Study Groups	Endoscopy of Upper GIT	Positive	Histopathology Negative	Not Done	Total
Treatment group (n = 65)	Duodenal Ulcer	3	13	2	18
	Gastric Ulcer	11	18	5	34
	Gastro-duodenal Ulcer	2	10	1	13
	Total	16	41	8	65
Conventional group (n = 65)	Duodenal Ulcer	5	6	4	15
	Gastric Ulcer	4	22	7	33
	Gastro-duodenal Ulcer	4	12	1	17
	Total	13	40	12	65
Study Groups	Rapid Urease Test	Positive	Histopathology Negative	Not Done	Total
Treatment group (n = 65)	Positive	14	2	0	16
	Negative	2	39	0	41
	Not Done	0	0	8	8
	Total	16	41	8	65
Conventional group (n = 65)	Positive	5	4	0	9
	Negative	8	36	0	44
	Not Done	0	0	12	12
	Total	13	40	12	65

Discussion

H. pylori eradication should be the treatment of choice in PUD associated with *H. pylori*. Numerous trials using a variety of treatment regimens have provided convincing evidences that successful eradication of *H. pylori* results in the healing of duodenal ulcer disease and a very low recurrence-rate [9,10,11,14].

Several international consensus conferences recommended that all patients with duodenal or gastric ulcer who have *H. pylori* infection should receive anti *H. pylori* therapy to cure the infection. The highest eradication rates are achieved with the three regimens and these three regimens have been approved by FDA Of USA in 1998: i) A proton pump inhibitor, Clarimromycin, and either Amoxicillin or Metronidazole for 2 weeks ii) Ranitidine, Bismuth citrate, Clarithromycin and either Amoxicillm, Metronidazole, or Tetracyclinc for 2 weeks iii) A proton pump inhibitor, Bismuth, Metronidazole and Tetracycline for 1 to 2 weeks [7,13].

Prevalence of *H. pylori* infection is high in Bangladesh [5]. Several trials for *H. pylori* eradication were undertaken in Bangladesh which have largely shown a low eradication rate with different *H. pylori* eradication regimens and a higher rate of re-infection [4,6]. In most of the studies, the eradication rate was between 30-64%. Re-infection rate was found to be 13% after one year and recrudescence rate was found to be 14% within first three months [15]. Most studies in other *developing* countries indicate that eradication rate is much lower than those obtained in western countries and the recurrence rate is also higher [12,13,16,17].

In this study, conventional group was treated by Clarithromycin, Amoxycline and Lansoprazole for 14 days and treatment group was treated by Nitazoxanide 1 gm twice daily and Omeprazole 20 mg twice daily for 14 days; showed cure rate of 76% (40) in treatment group and 80% (41) in conventional group. In a pilot study of Nitazoxanide 1 gm twice daily for treatment of H. pylori in association with 20 mg Omeprazole twice daily showed an eradication rate of 83% [18]. In a study conducted by Rahman & co-worker showed *H. pylori* eradication rate of 55.38%. They used Omeprazole 20 mg twice daily plus Amoxicillin 1 gm twice daily plus Furazolidone l00 mg four times daily for two weeks. Rahman et al studied three regimens: Regimen-A: Omeprazole 20 mg bid, Metronidazole 400 mg bid and Amoxicillin 1 gm bid for 7 days (OMA) Regimen-B: colloidal Bismuth subcitrate 120 mg qid, Metronidazole 400 mg tid and Amoxicillin 500 mg tid for 14 days (BMA) and Regimen-C: Omeprazole 20 mg bid, Clanthiomycin 500 mg bid and Amoxiciliin 1 gm bid for 7 days (OCA). *H. pylori* eradication rates were 53.33% in OMA group, 52% in BMA group, and 63.66% in OCA group [19,20,21,22].

This study shows overall preponderance of male over female (2.4 : 1). The higher number of cases among male is probably due to the fact that females are brought less frequently to hospitals because of various social, financial and religious bars in our male dominated society and also due to male goes outside more, takes outside food more frequently than female. Studies done in other countries show that economic status has little influence over the incidence of PUD [1,2,4].

Clinical examination revealed that 27% in treatment group and 26% in conventional group had anaemia. All patients in both groups had abdominal tenderness, 6% had history of high blood pressure in both groups. Almost all patients had history of taking different types of anti-ulcerent drugs in different duration; 94% in treatment group and 81% inconventional group. In Bangladesh anti-ulcerent drugs are found as an OTC drugs in every pharmacy. People easily buy these drugs without any prescription for temporary relief of pain.

Twelve patients in conventional and five patients in treatment group were droped out. One patient in treatment group developed yellow green colouration of skin and treatment was discontinued. This is a rare but known adverse effect of nitazoxanide [23]. Six patients had positive urease test that was negative in histology and 10 negative rapid urease tests had positive histology. Urease producing anaerobic organism may present in throat as a commensal so urease test may have some false positive result, conversely very small amount of *H. pylori* present in the gut may give false negative result. Urease test is less sensitive and specific than histology, which is considered as a gold standard.

There are a few published studies with Nitazoxanide based regimens [24,25]. In a study from India, Norfloxadin 400 mg b.d. has been preliminarily assessed in a 2-week dual therapy regimen with proton pump inhibitors, achieving eradication rates up to 76.9% [26]. Another study from India has evaluated a 2-week eradication treatment including Pefloxacin 400 mg b.d. given with Lansoprazole and Secnidazole (a Nitroimidazole claimed to be better tolerated than Metronidazole), obtaining eradication in only 71% of cases [27].

From this study, it appears that adequate eradication rate is not achieved by this *H. pylori* eradication therapy in PUD patients with drug regimen shown to result in high eradication rates in developed countries. In this study comparative randomized trial of Nitazoxanide and conventional treatment for eradication of *H. pylori* indicates that the two treatments are effective and comparable. Here newer regimen failed to show superiority over conventional treatment. Conventional regimen (80% eradication) is superior than newer regimen though it is not statistically significant. This study have shown conventional treatment is more effective in gastric ulcer (22/26) 84% and gastroduodenal ulcer (12/16) 75% rather than duodenal ulcer (6/11) 54%, on the other hand newer treatment is more effective in duodenal ulcer (13/16) 81% and gastroduodenal ulcer (10/12) 83% rather than in gastric ulcer (18/29) 62%. 24% and 20% failure of eradication rates in this study may be due to factors which were beyond the scope of this study.

Although a previous study showed a promising high *H. pylori* eradication rate of 83%, when 1 gm of NTZ was given for 7 days in combination with Omeprazole [17]. In our study, NTZ had no such high eradication rate when it was given as a single agent. Despite our negative outcome, there may still be a role of NTZ in the treatment of *H. pylori* infection in combination therapies.

Limitations of this study were that, firstly, sample size was small, and long term follow up could not be done due to time constrain. Secondly, initial histology was not done due to financial constrain. Thirdly, pre-treatment assessment of microbial sensitivity to drug was not assessed as culture and sensitivity test in my study. Another factor for low eradication rate may be due to bacterial virulence factor. The virulence factors and their relation to *H. pylori* eradication needs further study.

Conclusion

In this study, Nitazoxanide appears to be as effective as conventional therapy in the eradication of *H.pylori* though superiority of Nitazoxanide has not been proved by this study. A firm conclusion is not possible to draw from this study with this small sample size and so many limitation of this study. We cannot claim this study as a real reflection of the situation prevailing among the whole population. Large scale clinical trial and in vitro drug sensitivity of different strains of *H.pylori* is needed for definite inference.

Disclosure

All the authors declared no competing interest.

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