

Comparative Efficacy of Quadruple Vs Triple Anti Helicobacter Treatment in The Management of Duodenal Ulcer Disease in Pakistani Population.

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Gastric Helicobacter isolates from the sub continent people have been found to have high prevalence of in vitro resistance for nitroimidazoles and an effective anti helicobacter regimen remains a problem in our set up. Initial ulcer healing has never been a problem rather it is the relapse of the ulcer which is a clinical challenge, and if Hp eradication can be achieved, ulcer relapse should not remain a problem. An ideal Hp eradication regimen should be short, effective, and well tolerated and in order to find one, a randomized study was designed to compare triple Vs quadruple anti Hp regimen. Endoscopically proven uncomplicated rapid urease positive duodenal ulcer patients were divided into two groups of fifty patients each. Group I was given Lanzoprazole 30mg bid along with amoxicillin 1gm bid and clarithromycin 250mg bid for seven days. group II was given all the above medicines plus Tinidazole 500mg bid for seven days. Endoscopy was repeated after three months to evaluate Hp status by doing urease test and histopathology. 46 patients in group I (92%), and 40 patients in group II (80%) completed the seven days course of treatment. Two patients in each group didn't turn up for follow up (4%). At the end of three months, H. pylori was detectable on histopathology in 11(11/46) patients and rapid urease test was positive in 13 (13/46) patients of group I while corresponding figures were of one patient only (1/40) in group II. Interestingly all the patients were reported to have mild chronic active superficial gastritis on histopathology at the end of three months. Thus we conclude that quadruple anti Hp treatment is though less tolerated but is more effective in the eradication of H. pylori as compared to the triple therapy.

Key words: Helicobacter Pylori, Duodenal ulcer disease, eradication treatment.

Helicobacter pylori infection like other infections is endemic in all the under developed countries and so is the case with Pakistan as well^{1,2,4}. Helicobacter pylori is an important link between the acid and ulcer disease and is also a type I carcinogen.^{5,6} Though the incidence of ulcer disease is no different in our country as compared to the western societies^{1,2,3}, (incidence ranging from 12 - 17% in various studies), an easy access to effective anti acid medicines and a poor health delivery and documentation system may give a false sense of assurance about the over all prevalence of the problem.¹ The other pertinent point is a rising incidence of Gastric adenocarcinoma and lymphoma which may be linked to the rising prevalence of Helicobacter pylori infection. Present state of art recommendations in the treatment of duodenal ulcer, gastric ulcer and early MALT lymphoma are eradication of this bacteria as a first line treatment and various combinations have been tried in various studies with variable results^{5,6}. Metronidazole and an effective acid lowering drug have been the essential ingredients of anti helicobacter pylori eradication regimens along with variable number of other antibiotics^{7,8}. Long term efficacy, compliance, and cost effectiveness have been the major drivers in these studies. Societies with a generous over the counter prescribing policies and poor health structure have been identified to give poor overall eradication results as compared to the well structured organized health delivering communities³. Helicobacter pylori isolates from subcontinent have been found to have higher

in vitro nitroimidazole resistance and at times it is suggested that nitroimidazoles may not be used in the communities having a higher in vitro nitroimidazole resistance rates but then there have been studies showing that nitroimidazole containing regimens are more effective.

Materials and Methods

Out of the routine endoscopy list for all indications and reasons, 100 patients suffering from uncomplicated duodenal ulcer having a positive rapid urease test (modified rapid urease test) were selected out and randomized into two groups. They were recruited into the trial with an intention to treat basis and an informed consent was obtained. Patients having past history of intolerance to penicillin, macrolides and nitroimidazoles were excluded from the trial. A coexisting Liver disease, significant cardiopulmonary illness, use of NSAIDS for any reason, rheumatological disorders or a metabolic disorder were exclusion points. The patients coming from far off areas or having a problem in coming back to us later on were also excluded from the trial.

These 100 patients were assigned to two groups with group I getting Lanzoprazole 30mg bid along with amoxicillin 1gm bid and clarithromycin 250mg bid for seven days. group II was given all the above medicines plus Tinidazole 500mg bid for seven days. Patients were not blinded with the treatment regimen used and neither they were told that the results are going to be compared

against some other group. An easy access on telephone or in person was assured and ensured in every case and patients were advised to contact us in case of problem rather than changing medicine at their own. Patients were reevaluated clinically after seven days and endoscopically as well as clinically after three months. In between a regular fortnightly telephonic or a formal clinic contact was maintained to keep them under observation. Rapid urease enzyme test and histopathology of gastric antrum mucosa biopsies carried out at three months of completion of medicines. Results were interpreted as Hp infection present or absent.

Results:

The two groups were comparable in the age and sex distribution (table I).

Table 1.

	Group I	Group II
Mean age in yr.	42.5 yr.	44
Sex ratio M : F	28: 22	24:26
Absconder at 7 days	02	02
Absconder at 90 days	02	02
Side effects	11	17
nausea	07	09
vomiting	01	03
abdominal cramp	02	05
loose motion	05	03
metallic taste	01	07
insomnia	01	03
restlessness	01	03
No of pt. Completing trial.	46	40
Hp +ve at three months.	13	01
H/P +ve at three months.	11	01
Hp eradication successful	33/46	39/40

Mean age in the two groups was 42.5 and 45 years respectively. In the group I 28 patients were males as compared to 24 in group II and the number of female patients were 22 and 26 respectively. Mean age for male patients was 41.8 and 42 years respectively while it was 45.5 and 46.7 years in case of females in the two groups. Two patients (4%) each in the group I as well II could not be followed after the initial evaluation. 11 patients (22.9 %) in group I and 17 patients (35.41%) in group II complained of side effects but only 2 patients (4.16%) in group I and 8 patients (16.66%) in group II had to discontinue medicine due to intolerable side effects. Thus the side effect profile was much more frequent (35.41% vs. 22.9%) and much worse (16.66% vs. 4.16%) in group II as compared to group I patients which is statistically significant (p value < 0.005). Most common side effect leading to stoppage of the treatment was nausea and restlessness. On the whole 46 patients in group I (92%) and 40 patients in group II (80%) were able to complete the trial. After the completion of treatment period patients were followed at regular interval without any significant thing to mention about. At re- evaluation after three months 13 patients (28.26%) were rapid urease test

positive and 11 patients (23.91%) had histological evidence of Hp infection in group I while only 1 out of the 40 patients (2.5%) completing the trial had a positive urease test and positive histology. Thus helicobacter pylori was found to be eradicated successfully in 39 out of 40 patients (97.5%) in group receiving quadruple therapy i.e. group II as compared to 33 out of 46 patients (71.73%) in group receiving triple therapy i.e. group I at the end of three months thus leading to the conclusion that quadruple combination of the type prescribed to group II is more effective (97.5% vs. 71.73%, p value < 0.005) though less well tolerated.

Discussion:

Helicobacter pylori is the single most important discovery in the recent years which has changed the outlook of ulcer disorders of the upper GI tract^{5,6,16}. The Schwartz's old dictum " once an ulcer and always an ulcer" does not hold true and the successful eradication of helicobacter pylori infection is the single most important predictor of the ultimate outcome of the ulcer related disorders and the previous dictum of " no acid no ulcer" can be modified as "no helicobacter pylori infection then no ulcer". American National Institute of Health consensus meeting on helicobacter pylori in 1994 and then later on consensus meeting of the European Helicobacter study group in 1996 gave the recommendations that active peptic ulcer disease, history of peptic ulcer disease, bleeding ulcer, or low grade MALT lymphoma should be treated by anti helicobacter pylori eradication regimens^{5,6}. Many regimens have been devised for the eradication of H pylori but the most efficacious, patient friendly, and cost effective treatment remains a debatable issue.

Present study addresses to the same issue. The regimens used have been though not the cheapest but nevertheless are effective and patient friendly with a much better side effect profile as compared to the other alternative available cheaper treatment regimens. In two large multicenter trials double therapy comprising of Omeprazole and Amoxicillin gave an eradication rates of 69.8% and 55.6% when the patients were highly motivated and were included with intention to treat basis. In the same studies the comparisons were made to the Bismuth based triple regimen and PPI based quadruple regimen which showed an efficacy of 94.6% (p= 0.001) and 92.5% (p< 0.001) respectively. But one thing is worth remembering that similar results have not been reproduced in the primary care setting because of the poor patient compliance, patient heterogeneity and complex treatment administration rationale^{9,10,11,12,13}. In the populations having high imidazole resistance rates similar triple regimens have given an efficacy rate of 48% only but when imidazoles included with an effective triple PPI based antibiotic combination, the efficacy improves significantly which is confirmed in this study^{13,14,15}. The impact of possible emergence of drug resistance to Clarithromycin and Imidazoles remains to be seen and only time can tell. Cost analysis remains an important

issue^{12,13}. If we try treating the Ulcer patients with H2 antagonists alone, the induction and then yearly maintenance cost with a standard drug is in the range of Rs 4000-4500 but on the other hand when treated with one of the combinations used in this study then per patient initial cost comes out to be Rs 1344, 1400 and projected cost comes out to be Rs 2070 and Rs. 1466/- respectively for the triple and quadruple therapy. So there is a big overall economy by the use of a more potent regimen giving a higher eradication rates and thus ultimately an ulcer cure as compared to using a non eradication treatment or alternatively less effective eradication treatments.

Conclusions

Peptic ulcer disease is a potentially curable disease and all patients suffering from duodenal ulcer should be treated with an anti helicobacter regimen to cure the ulcer disease. A quadruple regimen containing PPI, two antibiotics and an imidazole is a more effective combination as compared to a regimen without imidazoles. Though less well tolerated, initially expensive and slightly more complex in administration but is far more efficacious making it a more recommended regimen.

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