COMPARISON OF TWO COMMONLY USED SEQUENTIAL THERAPY REGIMENS FOR ERADICATION OF HELICOBACTER PYLORI INFECTION

Shabir Shiekh¹, Zafar Wani¹, Shafat Lone¹ and Feroz Wani²
1. Department of Gastroenterology and Hepatology, Government Medical College Srinagar Kashmir India.
2. Department of Bio-Statistics, Preventive and Social Medicine, Government Medical College Srinagar Kashmir India.

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Abstract

Aim: To compare the efficacy of levofloxacin based and clarithromycin based sequential therapies for eradication of Helicobacter pylori infection.

Methods: From January 2017 to December 2018, 260 patients with H. pylori infection randomly received 14 d of levofloxacin-based sequential therapy (LEVO-ST group, n = 130) or clarithromycin-based sequential therapy (CLA-ST group, n = 130). H. pylori infection was defined on the basis of either histologic evidence of H. pylori by modified Giemsa staining; or a positive rapid urease test by gastric mucosal biopsy. Successful eradication therapy for H. pylori infection was defined as a negative 13-Carbon –urea breath test four weeks after the end of eradication treatment. Compliance was defined as good when drug intake was at least 90%. H. Pylori eradication rates, patient compliance with drug treatment, adverse events, and factors influencing the efficacy of eradication therapy were evaluated.

Results: The eradication rates by intention-to-treat analysis were 89% (116/130; 95%CI: 86.2%-95.4%) in the levo-st group and 86% (112/130; 95%CI:65.8%-77.4%) in the cla-st group (p = 0.450). The eradication rates by per-protocol analysis were 91%(114/124) 95%CI: 89.1%-98.1%) in the LEVO-ST group and 87% (106/122; 95%CI: 69.4%-81.8%) in the CLA-ST group (p = 0.227). Compliance was 100% in both groups. The adverse event rates were 17.6 % (22/125) and 28.6% (35/122) in the LEVO-ST and CLA-ST group, respectively (p = 0.038). Most of the adverse events were mild-to-moderate in intensity; there was none serious enough to cause discontinuation of treatment in either group.

Conclusion: The 14-d levofloxacin-based sequential therapy has high efficacy for H. pylori eradication effective. Moreover, it showed excellent patient compliance and safety compared to the 14-d clarithromycin-based sequential therapy.

Corresponding Author:-Shabir Shiekh
Address:- Department of Gastroenterology and Hepatology, Government Medical College Srinagar Kashmir India.
Introduction:-
The identification of Helicobacter pylori (H. pylori) by Warren and Marshall in 1983 has revolutionised our understanding of gastroduodenal diseases. H. pylori infection is a known risk factor of upper gastrointestinal diseases, such as chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer. H. pylori has been classified by the International Agency for Research on Cancer of the WHO as a class 1 carcinogen.

Eradication of H. pylori reduces the recurrence rate of peptic ulcer disease or recurrent gastric cancer after endoscopic resection of early gastric cancer, and it also induces the remission of MALT lymphoma. Several protocols have been suggested in order to overcome treatment failure of TT, including the extending of treatment duration, the use of four-drug regimen, sequential therapy, concomitant therapy, hybrid therapy, and the prescription of novel antibiotics such as quinolones and probiotics. Reasonable treatment regimens need to attain H. pylori eradication rate of higher than 80.0% by intention to treat (ITT) analysis, and higher than 90.0% by per protocol (PP) analysis.

In a meta-analysis of 11 randomized, controlled trials, it was shown that the sequential treatment regimen achieved significantly higher eradication rates of 90% compared with standard triple therapy. The threshold of clarithromycin resistance at which this antibiotic should not be used is 15-20%. Clarithromycin resistance is reported as 17.5% in Southern European countries and 53% in Turkey. In addition, the eradication rate of clarithromycin-containing triple therapy is declining globally to an unacceptable eradication rate of less than 80%, largely due to the rising clarithromycin resistance. There are wide geographic variations in clarithromycin resistance rates in different countries, ranging from 5.2% in Belgium to 55.6% in Japan.

The present study was aimed to compare the H. pylori eradication rates, patient compliance, and adverse events between levofloxacin-based sequential therapy and clarithromycin-based sequential therapy.

Materials And Methods:-
Patient selection:
This was a prospective study carried out between January 2017 and December 2018 in the Department of Gastroenterology at Superspeciality Hospital which is a tertiary care hospital associated with Government Medical College Srinagar, Kashmir India. The endoscopy unit of the hospital receives referrals from the eight associated hospitals of the medical college with a bed strength of approximately 2500. The hospital runs an “open access” endoscopy policy whereby the patients are directly referred to the endoscopy room by their physicians based on their perceived need.

Informed consent for endoscopy was obtained by the endoscopy team before the procedure.

A total of 260 adult patients (age ≥ 18 years) with H. pylori infection of either gender were enrolled in this prospective, open-labeled, randomized study.

We excluded patients who were pregnant or breastfeeding, patients previously treated with H. pylori eradication therapy, history of allergy to any of these drugs, patients who previously underwent gastric surgery, presence of severe concomitant diseases like liver dysfunction, renal failure and patients with malignant neoplasm.

H. pylori infection was defined on the basis of either a positive rapid urease test by gastric mucosal biopsy from the lesser curvature of the body and antrum of the stomach or histologic evidence of H. pylori by modified Giemsa staining in the lesser and greater curvature of the body and antrum of the stomach. Video endoscopes used were GIF Q 150 Olympus Optical Co., Ltd., Tokyo, Japan.

Esophagitis was defined as mucosal breaks extending proximally from the squamocolumnar junction. Peptic ulcer was defined as a mucosal break in the stomach, duodenum, or both, greater than 5 mm in diameter.
This study protocol was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Institutional Review Board of each participating facility. Informed consent was obtained from all patients.

**Study Design:**
We compared 14-d levofloxacin based sequential therapy with 14-d clarithromycin based sequential therapy for eradication of *H. pylori* infection.

The 260 participants were randomly assigned to one of the two treatment groups using a computer generated numeric sequence. The 14-d levofloxacin based sequential therapy group (LEVO-ST group, n=130) received 40 mg pantoprazole and 1 g amoxicillin twice daily for the first week, followed by 40 mg pantoprazole twice daily, 500 mg tinidazole twice daily, and levofloxacin 500 mg once daily for the remaining week. Participants in the 14-d clarithromycin-based sequential therapy group (CLA-ST group, n=130) received 40 mg pantoprazole and 1 g amoxicillin twice daily for the first week, followed by 40 mg pantoprazole, 500 mg tinidazole, and clarithromycin 500 mg twice daily for the remaining one week.

All of the patients were asked about adverse events. Successful eradication therapy for *H. pylori* infection was defined as a negative 13C-UBT (urea breath test) four weeks after the cessation of eradication treatment. The primary outcome was to study *H. pylori* eradication rates and secondary outcome was treatment related adverse events.

**Statistical Analysis:**
Collected data was compiled and entered in a spreadsheet Microsoft excel and exported to Data editor of SPSS computer software, version 20 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were summarized as frequency and percentage.

| Demographic and clinical data at baseline (intention to treat population) n (%) | LEVO-ST | CLA-ST | P value |
|---|---|---|---|
| Included in ITT analysis | 130 | 130 | NS |
| Age (yr), mean ± SD | 42.3 ± 14.1 | 41.4 ± 13.1 | 0.594 |
| Gender (male) | 55 (42.5) | 43 (30.7) | 0.124 |
| BMI (kg/m2), mean ± SD | 22.9 ± 2.2 | 22.7 ± 2.9 | 0.532 |
| Current smoker | 18 (13.7) | 15 (12.3) | 0.576 |
| Diabetes | 4 (3) | 5 (4) | 1.000 |
| Hypertension | 10 (7.69) | 23 (17.7) | 0.015 |
| Previous history of peptic ulcer | 12 (15.0) | 11 (8.46) | 0.827 |
| Endoscopic diagnosis | | | |
| Gastritis | 110 (84) | 112 (86) | 0.725 |
| Gastric ulcer | 4 (3.0) | 5 (4) | 1.000 |
| Duodenal ulcer | 10 (7.69) | 8 (6.1) | 0.625 |
| Gastric and duodenal ulcer | 1 (0.76) | 0 (0.0) | 1.000 |
| *H. pylori* testing | | | |
| Positive RUT | 121 (93) | 118 (91) | 0.494 |
| Histology | 125 (96) | 122 (94) | 0.393 |
| Drop out | | | |
| Non-compliance | 5 (4) | 8 (6.1) | 0.393 |
| Follow-up loss | 1 (0.76) | 2 (1.5) | 0.518 |
| Discontinued therapy due to adverse events | 0 (0.0) | 0 (0.0) | 1.000 |

| Adverse events and compliance  { n (%)} | LEVO-ST (n=125) | CLA-ST (n=122) | P-value |
|---|---|---|---|
| Bloating/dyspepsia | 6 (4.8) | 8 (6.5) | 0.550 |
| Taste distortion | 5 (4) | 7 (5.7) | 0.525 |
| Epigastric discomfort | 4(3.2) | 4(3.3) | 1.000 |
Nausea                                      5 (4)  8 (6.55)  0.368
Abdominal pain                              0 (0.0)  2 (1.66)  0.242
Diarrhea                                    2 (1.6)  6 (4.9)  0.168
Total events                                22 (17.6 %)  35 (28.7 %)  0.038
Compliance, n (%)                           125 (100.0)  122 (100.0)

H. pylori eradication rate

|                      | LEVO-ST          | CLARI-ST         | P-value |
|----------------------|------------------|------------------|---------|
| ITT Analysis eradication rate | 89 % (116/130) | 86 % (112/130) | 0.450   |
| PP Analysis eradication rate      | 91 % (114/125) | 87 % (106/122) | 0.277   |

Discussion:-
Helicobacter pylori is the main cause of the upper gastrointestinal disorders including peptic ulcer disease (gastric and duodenal), chronic gastritis, gastric mucosal-associated lymphoid tissue lymphoma, and gastric cancers.17 Besides numerous extragastric disorders like neurodegenerative, cardiovascular problems and metabolic, as well as hepatobiliary, pancreatic, and colorectal illnesses has been related to H. pylori infection. Furthermore, research suggests that this bacterium may be related to the development of skin disorders, which includes urticaria in addition to rheumatic diseases.18

Our study showed that gastritis is the most common endoscopic feature. This agrees with Diab et al.19,20 who found a strong association between H. pylori infection and patients with gastritis. Kyoto global consensus 2015 also agrees that the most common cause of chronic gastritis worldwide is infection with H. pylori.21

Various explanations are postulated for higher efficacy of sequential regimen. Amoxicillin administered in the first half of the regimen damages cell wall of H. pylori; this is thought to overcome antibiotic resistance and increase eradication rate by two mechanisms. First, damage to the cell wall damage may ease the penetration of subsequent antibiotics into the H. pylori strain and damaged cell wall may have less number of efflux channels for antibiotics.

Data from Italy corroborated the hypothesis that the CagA gene is a real predictor of H. pylori eradication. If the infection is made by Cag A (+) H. pylori bacteria, that shows that it is cytotoxic, it can be eradicated more easily. It was also suggested that sequential therapy was equally effective in CagA (+) and CagA (−) bacteria.22

Various studies showed that resistance to antibiotics in H. pylori treatment is increasing, and that clarithromycin-based sequential therapy might already be suboptimal in areas with high prevalence of clarithromycin resistance.23, 24, Polat et al.25 in their study concluded that clarithromycin resistance is the main cause of H. pylori eradication failure.

Qian et al.26 discovered that standard-ST produced unacceptably therapeutic efficacy in China. Simplest levofloxacin-containing ST produced a suitable end result. Zullo et al.27 found that levofloxacin-based sequential treatment is better than standard triple therapy, confirming that the ‘sequential’ of drugs is a successful therapeutic strategy for H. pylori infection. Romano et al.28 found that in an area with greater than 15% prevalence of clarithromycin-resistant H. pylori strains, levofloxacin-containing ST is more effective than clarithromycin-containing ST, with 96.8% versus 80.8% (P<0.0001).

A multicentric study from Taiwan (29) suggested that modified sequential treatment containing levofloxacin is effective for patients who failed from either sequential or triple therapy and supported the use of sequential treatment as an alternative to triple therapy for first-line treatment of patients with H. pylori infection.

A study from Korea reported that female gender could be associated with treatment failure, based on the fact that H. pylori strain with point mutation in the 23S rRNA were preferentially infected in women which could result in treatment failure with clarithromycin [30]. Also, smoking may increase treatment failure by reducing antibiotics delivery to gastric mucosa, because smoking decreases gastric blood flow and mucus secretion and smoking itself is an indicator for poor compliance [30–32]. However, we could not find any statistically significant clinical factor to predict successful eradication of H. pylori.
Mégraud F. et al in their meta-analysis evaluating H. pylori strains in Western populations found fluoroquinolone-resistance prevalence in less than 5.0%[33]. In Gyeonggi Province, Korea, the rates of resistance were 5.0% for levofloxacin and moxifloxacin, 5.0% for amoxicillin, 16.7% for clarithromycin, 34.3% for metronidazole, and 8.0% for tetracycline[34]. Therefore, we could explain that the reason levofloxacin-based sequential therapy is more effective than clarithromycin-based sequential therapy. We suggest that appropriate H. pylori-eradication therapies should be continually adjusted according to local bacterial resistance patterns.

We found that the adverse effects including nausea, vomiting, abdominal pain, bloating, and diarrhea were less in levost than clar-st group, but difference was of no statistically significant (all P>0.05). This is similar observation were reported by Waleed et al. (20) Polat et al. [25] and Qian et al. [26] who showed that levofloxacin-based ST is better tolerated than clarithromycin based-TT. In both groups, the adverse events were mild to moderate; none was serious enough to require discontinuation of treatment or impaired quality of life.

Limitations the results of this single centre hospital based study may not be applicable to other geographical regions. No information about the drug sensitivity and resistance patterns.

In conclusion, our large, prospective, hospital based study compared the two commonly used sequential three drug regimens and we found superiority of levofloxacin based regimen in terms of eradication of H. pylori and adverse events as well.

Disclosures:
Author contributions:
All authors wrote and edited the manuscript.

ShiekhShabir is the article guarantor.

Financial disclosure:
None to report.
Informed consent was obtained from the patients /guardian.

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