Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/10435
DOI URL: http://dx.doi.org/10.21474/IJAR01/10435

RESEARCH ARTICLE

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

Shabir Shiekh[1], Zafar Wani[1], Shafat Lone[1] and Feroz Wani[2]

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.

Manuscript Info

Manuscript History
Received: 01 December 2019
Final Accepted: 03 January 2020
Published: February 2020

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 eradicationtherapy were evaluated.

Results: The eradication rates by intention-to-treatanalysis 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). Theeradication rates by per-protocol analysis were 91%(114/124) 95%ci: 89.1%-98.1%) in the LEVO-ST groupand 87% (106/122; 95%ci: 69.4%-81.8%) in the CLA-ST group (p = 0.227). Compliance was 100% in bothgroups. 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 eventswere mild-to-moderate in intensity; there was none serious enough to cause discontinuation of treatmentin 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.[1]H. pylori infection is a known risk factor of upper gastrointestinal diseases, such aschronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer.[2,3] H pylori has been classified by the International Agency for Research on Cancer of the WHO as a class 1 carcinogen.[4]

Eradication of H. pylori reduces the recurrencerate of peptic ulcer disease or recurrent gastric cancerafter endoscopic resection of early gastric cancer, and italso induces the remission of MALT lymphoma.[5,6,7]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, concomitanttherapy, hybrid therapy, and the prescription of novel antibiotics such as quinolones and probiotics.[8]Reasonable treatment regimens need to attain H. pylori eradication rateof higher than 80.0% by intention to treat (ITT) analysis, and higher than 90.0% by per protocol (PP) analysis.[9,10]

In a meta-analysisof 11 randomized, controlled trials, it was shown that the sequential treatment regimen achieved significantlyhigher eradication rates of 90% compared with standard triple therapy.[11]

The threshold of clarithromycin resistance at which this antibiotic should not be used is 15-20%. Clarihtromycin resistance is reported as 17.5% in Southern European countries and 53% in Turkey.[12,13]In addition, the eradication rate of clarithromycincontaining triple therapy is declining globally to anunacceptable eradication rate of less than 80%[14],largely due to the rising clarithromycinresistance.[15]There are wide geographic variations inclarithromycin resistance rates in different countries, rangingfrom 5.2% in Belgium to 55.6% in Japan.[16]

The present study was aimed to compare theH. pylorieradication rates, patient compliance, andadverse 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 hospital of the medical college with 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 $\geq$ 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 rapidurease test by gastric mucosal biopsy from the lesser curvatureof 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 bodyand antrum of the stomach.Video endoscopes used wasGIF 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 withthe provisions of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved bythe 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 toone 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 amoxicillintwice daily for the first week, followed by 40 mg pantoprazole twice daily, 500 mg tinidazoletwice daily, and levofloxacin 500 mg once dailyfor the remaining week. Participants in the 14-dclarithromycin-based sequential therapy group (CLA-STgroup, n=130) received 40 mg pantoprazole and1 g amoxicillin twice daily for the first week, followedby 40 mg pantoprazole, 500 mg tinidazole, andclarithromycin 500 mg twice daily for the remainingone 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 spread sheet 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 (40.7)	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	5 (4)	8 (6.1)	0.393
Non-compliance	4 (3)	6 (4.6)	0.518
Follow-up loss	1(0.76)	2(1.5)	1.000
Discontinued therapy due to adverse events	0 (0.0)	0 (0.0)	1.000

Adverse events and compliance { n (%)}

Adverse events	**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 theupper gastrointestinal disorders including pepticulcer 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, andcolorectal illnesses has been related to H. pylori infection. Furthermore, research suggests that this bacterium may be related to thedevelopment 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 strainand 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 efficacyin 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 therapeuticstrategy for H. pylori infection. Romano et al. [28] found that in an area with greaterthan 15% prevalence of clarithromycin-resistantH. pylori strains, levofloxacin-containing ST is moreeffective than clarithromycin-containing ST, with 96.8versus 80.8% (P<0.0001).

A multicentric study fromTaiwan (29) suggestedthatmodified sequential treatment containing levofloxacin is effective for patients who failed from either sequentialor triple therapy and supported the use of sequential treatment as analternative to triple therapy for fi rst-line treatment ofpatients 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 inWestern 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 shouldbe continually adjusted according to local bacterialresistance patterns.

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

Limitations the results of this single centre hospital badsed 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 dug regimens and we found superiority of levofloxacin based regimenin 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 .

Bibliography:-

1. Warren JR. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;1:1273
2. Moss SF, Malfertheiner P. Helicobacter and gastric malignancies. Helicobacter. 2007;12Suppl 1:23–30.
3. Yamada T, Searle JG, Ahnen D, Aipers DH, Greenberg HB, Gray M, et al. Helicobacter pylori in Peptic Ulcer Disease. JAMA. 1994;272:65–69.
4. International Agency for Research on Cancer. Infection with Helicobacter pylori. IARC MonogrEvalCarcinog Risks Hum 1994;61:177–240.
5. Leodolter A, Kulig M, Brasch H, Meyer-Sabellek W, Willich SN, Malfertheiner P. A meta-analysis comparing eradication, healing and relapse rates in patients with helicobacter pylori-associated gastric or duodenal ulcer. Aliment PharmacolTher. 2001;15:1949–58.
6. Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, Isaacson PG. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet. 1993;342:575–7.
7. Bae SE, Jung HY, Kang J, Park YS, Baek S, Jung JH, Choi JY, Kim MY, Ahn JY, Choi KS, et al. Effect of Helicobacter pylori eradication on metachronous recurrence after endoscopic resection of gastric neoplasm. Am J Gastroenterol. 2014;109:60–7
8. Lee SW, Kim HJ, Kim JG. Treatment of helicobacter pylori infection in Korea: a systematic review and meta-analysis. J Korean Med Sci. 2015;30:1001–9.
9. Lam SK, Talley NJ. Report of the 1997 Asia pacific consensus conference on the management of helicobacter pylori infection. J Gastroenterol Hepatol.1998;13:1–12.
10. Kim N, Kim JJ, Choe YH, Kim HS, Kim JI, Chung IS. Korean college of helicobacter and upper gastrointestinal research; korean association of gastroenterology. Diagnosis and treatment guidelines for helicobacter pylori infection in Korea.Korean J Gastroenterol.2009 ; 54:269–78.
11. Tong JL, Ran ZH, Shen J, Xiao SD. Sequantial therapy vs. standardtriple therapies for Helicobacter pylori infection: meta-analysis. JClin Pharm Ther 2009;34:41-53.

12. Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, et al. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013;62(1):34—42.
13. Onder G, Aydin A, Akarca U, Tekin F, Ozutemiz O, Ilter T. High Helicobacter pylori resistance rate to clarithromycin in Turkey. J ClinGastroenterol 2007;41(8):747—50.
14. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut 2010;59:1143–53.
15. Megraud F, Lamouliatte H. Review article: the treatment of refractory Helicobacter pylori infection. Aliment PharmacolTher 2003;17:1333–43.
16. 16 Tepes B, O'Connor A, Gisbert JP, et al. Treatment of Helicobacter pylori infection 2012. Helicobacter 2012;17(Suppl 1):36–42.
17. Hajimahmoodi M, Shams-Ardakani M, Saniee P, Siavoshi F, MehrabaniM,Hosseinzadeh H, et al. In vitro antibacterial activity of some Iranianmedicinal plant extracts against Helicobacter pylori. Nat Prod Res 2011;25:1059–1066.
18. Franceschi F, Gasbarrini A. Helicobacter pylori and extragastricdiseases.BestPract Res ClinGastroenterol 2007; 21:325–334.
19. Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, et al.Review article: the global emergence of Helicobacter pylori antibioticresistance. Aliment PharmacolTher 2016; 43:514–533.
20. Diab M, El-Dine S, Aboul-Fadl L, Shemis M, Omran Z. Helicobacter pyloricag pathogenicity Island genes among dyspeptic patients with chronic gastritis. Egypt J Med Microbial 2009; 18:43–53.
21. Waleed A. Ismail, Ehab F. Mostafa .A comparison between conventional triple therapy andsequential therapy on tolerance of treatment and eradication of Helicobacter pylori infection in Egyptian patients. The Egyptian Journal of Internal Medicine 2018, 30:90–95
22. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al.Kyoto global consensus report on Helicobacter pylori gastritis. Gut 2015; 64:1353–1367.
23. De Francesco V, Zullo A, Margiotta M, Marangi S, Burattini O, Berloco P, et al. Sequential treatment for Helicobacter pylori does not share the risk factors of triple therapy failure. Aliment PharmacolTher 2004;19:407-14.
24. Oh HS, Lee DH, Seo JY, Cho YR, Kim N, Jeoung SH, Kim JW, Hwang JH, Park YS, Lee SH, Shin CM, Cho HJ, Jung HC, Song IS. Ten-day sequential therapy is more effective than proton pump inhibitor-based therapy in Korea: a prospective, randomized study. J GastroenterolHepatol2012; 27: 504-509
25. Lim JH, Lee DH, Choi C, Lee ST, Kim N, Jeong SH, Kim JW,Hwang JH, Park YS, Lee SH, Shin CM, Jo HJ, Jang ES, Song Is,Jung HC. Clinical outcomes of two-week sequential and concomitanttherapies for Helicobacter pylori eradication: a randomized pilotstudy. Helicobacter 2013; 18: 180-186
26. Polat Z, Kadayifci A, Kantarcioglu M, Ozcan A, Emer O, UygunA.Comparison of levofloxacin-containing sequential and standard tripletherapies for the eradication of Helicobacter pylori.Eur J Intern Med2012; 23:165–168.
27. Qian J, Ye F, Zhang J, Yang YM, Tu HM, Jiang Q, et al. Levofloxacin containing triple and sequential therapy or standard sequential therapy as the first line treatment for Helicobacter pylori eradication in China. Helicobacter 2012; 17:478–485.
28. Zullo A, de Francesco V, Hassan C, Ridola L, Repici A, Bruzzese V, etal.Modified sequential therapy regimens for Helicobacter pylori eradication: asystematic review. Dig Liver Dis 2013; 45:18–22
29. Romano M, Cuomo A, Gravina AG, Miranda A, Iovene MR, Tiso A, et al.Empirical levofloxacin-containing versus clarithromycin-containing sequentialtherapy for Helicobacter pylori eradication: a randomised trial. Gut 2010;59:1465–1470.
30. 29 Jyh-Ming Liou, Chieh-Chang Chen et al , Sequential versus triple therapy for the fi rst-line treatment of Helicobacter pylori: a multicentre, open-label, randomised trial. Lancet 2013; 381: 205–13.
31. 30. Kim SE, Park MI, Park SJ, Moon W, Choi YJ, Cheon JH, Kwon HJ, Ku KH,Yoo CH, Kim JH, et al. Trends in Helicobacter pylori eradication rates by first-line triple therapy and related factors in eradication therapy. KoreanJ Intern Med. 2015;30:801–7.
32. Moayyedi P, Chalmers DM, Axon AT. Patient factors that predict failure ofomeprazole, clarithromycin, and tinidazole to eradicate Helicobacter pylori.JGastroenterol. 1997;32:24–7.
33. Suzuki T, Matsuo K, Ito H, Sawaki A, Hirose K, Wakai K, Sato S, Nakamura T, Yamao K, Ueda R, et al. Smoking increases the treatment failure forHelicobacter pylori eradication. Am J Med. 2006;119:217–24.
34. Mégraud F. H pylori antibiotic resistance: prevalence, importance, and advances in testing. Gut 2004; 53: 1374-1384
35. Kim N, Kim JM, Kim CH, Park YS, Lee DH, Kim JS, Jung HC, Song IS. Institutional difference of antibiotic resistance of Helicobacter pylori strains in Korea. J ClinGastroenterol2006; 40: 683-687.