Effectiveness of 14-days course of clarithromycin-based triple therapy as first line therapy for h.pylori infection in egyptian elderly patients

Salamah A.M[1]., Gad M.[1], Deghady A.[2], Elgayar N.H.[1]

Geriatric Unit, Internal Medicine Department, Faculty of Medicine, Alexandria University[1]

Clinical Pathology Department, Faculty of Medicine, Alexandria University[2].

Abstract:The aim of the study is to assess the effectiveness of 14-days course of Clarithromycin-based triple therapy as first line therapy for H. pylori infection in Egyptian elderly patients with normal liver and kidney functions. ***Methods:*** The study was experimental study carried out on 34 elderly patients having H. pylori gastritis with normal liver and kidney functions. We tested for H. pylori stool antigen using a quantitative monoclonal enzyme-linked immunosorbent assay (ELISA) assay before and 4 weeks after the treatment to confirm eradication. Patients received Clarithromycin-based triple therapy (Clarithromycin 500mg twice daily, Amoxicillin 1000mg twice daily, and Omeprazole 40mg twice daily) for H. pylori eradication for 14 days. ***Results:*** The cure rate of Clarithromycin-based triple therapy was 88.2% (30/34) and only 11.8% (4/34) was having persistent infection. None of the patients discontinued the drugs indicating good tolerability .***Conclusion:*** The use of 14-days course of Clarithromycin-based triple therapy as first line therapy for H. pylori infection is highly effective and tolerable in Egyptian elderly patients with normal liver and kidney functions.

Key words: Helicobacter pylori, elderly, Clarithromycin.

Introduction

Helicobacter pylori (H. pylori) are Gram-negative bacteria, belonging to a separate group of Helicobacter species. It contains a hydrogenase, used to obtain energy by oxidizing molecular hydrogen (H2) produced by intestinal bacteria [1]. It produces oxidase, catalase, and urease [2].

The most common routes of H. pylori infection are fecal-to-oral, oral-to-oral, or gastro/oral exposure. Humans appear to be the major reservoir of infection [3].

H. pylori is the most common chronic bacterial infection in humans. At least 50% of all people are infected [4]. The prevalence of Helicobacter pylori infection increases with age and may affect 75% of elderly patients [5].

There are many virulence factors of H. pylori that may be responsible for the pathogenesis of H. pylori related diseases such as ammonia, CAG-A (cytotoxin-associated gene A) and VAC-A (vacuolating cytotoxin A) toxins, lipopolysaccharides, and histidine-rich protein [6-9].

Gastric diseases caused by H. pylori include gastritis (acute, chronic, and atrophic), peptic ulcer disease, non-ulcer dyspepsia, Mucosa associated lymphoid tissue (MALT) lymphoma, hypochlorhydria, and gastric carcinoma [10-12].

Many extra gastrointestinal manifestations of H. pylori include affection of the cardiovascular system, Ear, Nose and Throat and oral cavity, dermatological, hematological, hepato-biliary, endocrinal, ocular, rheumatologic, renal , andrologic, gynecologic, and neuropsychiatric manifestations.

Diagnostic testing of H. pylori is divided into: Invasive tests and non-invasive tests based on the need for endoscopy. Invasive tests are rapid urease test, histological examination, and culture and sensitivity tests. While non-invasive tests include serology, urea breath test, and H. pylori stool antigen [13].

The Faecal Antigen Test (FAT) can be used interchangeably with the urea breath testing (UBT) to identify H. pylori before antibiotic therapy [14]. The FAT has been approved by the U.S. Food and Drug Administration and supported by the European "Maastricht2–2000 Consensus Report" as an alternative to UBT in establishing the cure of H. pylori infection [15]. Recent studies indicate that the FAT may be effective in confirming eradication as early as 14 days after treatment [16,17].

A systematic review stated that quantitative monoclonal enzyme-linked immunosorbent assay (ELISA) assay for the detection of H. pylori stool antigen has better sensitivity, specificity, Positive predictive value (PPV), and negative predictive (NPV) than the polyclonal test especially in the confirmation of eradication [18,19].

No single drug cures H. pylori infection. Treatment involves taking several medications for 10 to 14 days. Two antibiotics are also generally recommended; this reduces the risk of treatment failure and antibiotic resistance. It is important to confirm eradication of infection. Confirmation should be performed at least 4weeks after eradication therapy has been completed [14].

The resistances of H. pylori to antibiotics may be particularly relevant in elderly patients for two reasons. First, the prevalence of drug consumption including antibiotics is higher in this population. Second, the compliance in elderly population is lower than younger population [20,21].

The aims of the current study were to:

- Assess the use of Clarithromycin-based triple therapy as a first line therapy in Egyptian elderly patients with normal liver and kidney functions.
- Estimate the resistance rate of this therapy.
- Assess the compliance of our elderly patients on this regimen.

Subjects and Methods

This study was carried out on Egyptian non-hepatic non-renal elderly patients (65 years or older) having Helicobacter pylori gastritis attending the geriatric clinic in Faculty of Medicine, Alexandria University at year 2013. There were 34 patients who met the criteria for the study

Inclusion Criteria:

- Elderly patients.
- H.pylori infected.
- The patient did not receive H.pylori eradication therapy before.

Exclusion Criteria:

- Abnormal liver function tests.
- Abnormal renal function tests.
- Patients with history of PPI intake within the past 2 weeks.
- Patients with history of antibiotic intake within the past 4 weeks.

The study was accepted by the local ethical commity and each patient has full explanation about the study and informed consent was signed by each patient.

All patients included in the study were subjected to the following:

I. Thorough history taking.

II. Complete clinical examination.

III. Basic Laboratory investigations:

- Complete blood picture.
- Complete urine analysis.
- Complete stool analysis.
- Serum Glutamic-Oxaloacetic Transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT), serum albumin and prothrombin time (PT) and international normalized ratio (INR) as indicators of liver functions.

- Serum creatinine and Blood Urea Nitrogen (BUN) as indicators of renal function.
- Occult blood in stool.

IV. Abdominal ultrasound

V. ELISA for H. pylori stool antigen [22].

We used the International Immuno-Diagnostic H.pylori stool antigen ELISA Kit – Foster City – Canada – code no. 2038 which is a quantitative monoclonal assay for the detection of H. pylori antigens in stool specimen.

Principle of the test:

Purified H.pylori antibody is coated on the surface of microwells. An aliquot of diluted stool sample is added to wells, and the H. pylori antigens, if present, bind to the antibody. All unbound materials are washed away. After adding enzyme conjugate, it binds to the antibody-antigen complex. Excess enzyme conjugate is washed off and Tetramethylbenzidine (TMB) Chromogenic substrate is added. The enzyme conjugate catalytic reaction is stopped at a specific time. The intensity of the colour generated is proportional to the amount of antigen in the sample. The results are read by a microwell reader compared in a parallel manner with calibrator and controls [18].

ELISA for H.pylori stool antigen is done, and if the test is positive for H.pylori stool antigen the patient is included in the study but if the test is negative the patient is excluded from the study.

VI. Treatment of H. pylori positive patients by 14 days course of:

- Omeprazole 40 mg twice daily.
- Clarithromycin 500 mg twice daily.
- Amoxicillin 1000 mg twice daily.

VII. Repetition of quantitative monoclonal ELISA assay for H. pylori stool antigen 4 weeks after completion of treatment course to detect who became cured and who remained infected.

Results

All patients were elderly patients aged 65 years or more with a range from 65-80 years, a mean of 70.21 years, and a standard deviation of 4.38 years. Patients were distributed as 18 (52.9%) males, and 16 (47.1%) females.

After completion of the treatment course, 88.2% (30/34) were found to be cured from H. pylori infection by repeating the H. pylori stool antigen test and only 11.8% (4/34) was having persistent infection (fig.1).

None of the patients discontinued the treatment regimen indicating good tolerability (fig.2).

There was no statistical significant difference between the responders and the non-responders as regards the sex and the age (table1).

Discussion

No single drug cures H. pylori infection. There are several regimens for H. pylori eradication [14].

One regimen consists of standard dose PPI (proton pump inhibitor) b.i.d. (twice daily) [Esomeprazole is q.d. (once daily)], Clarithromycin 500 mg b.i.d., and amoxicillin 1,000 mg b.i.d. for 10–14 days. Standard dosages for PPIs are as follows: Lansoprazole 30 mg p.o. (orally), Omeprazole 20 mg p.o., Pantoprazole 40 mg p.o., Rabeprazole 20 mg p.o., or Esomeprazole 40 mg p.o. This regimen achieved 70–85% eradication rate. It should be considered as first line therapy in non-penicillin allergic patients who have not previously received a macrolide [14].

Another regimen consists of standard dose PPI b.i.d., Clarithromycin 500 mg b.i.d., and Metronidazole 500 mg b.i.d. for 10 – 14 days. This regimen achieved 70–85% eradication rate. It should be considered as first line therapy in penicillin allergic patients who have not previously received a macrolide or are unable to tolerate bismuth quadruple therapy [14].

Large randomized trials suggest that the inclusion of amoxicillin or Metronidazole yields similar results when combined with a PPI and Clarithromycin [23].

The bismuth quadruple therapy consists of Bismuth subsalicylate 525 mg p.o. q.i.d. (four times daily), Metronidazole 250 mg p.o. q.i.d., tetracycline 500 mg p.o. q.i.d., and ranitidine 150 mg p.o. b.i.d. or standard dose PPI q.d. to b.i.d. for 10 – 14 days. This regimen achieved 75–90% eradication rate. It should be considered as first line therapy in penicillin allergic patients who have previously received a macrolide. A criticism of this regimen involves its complexity (q.i.d. dosing regimen and high pill count) and perceived frequency of side effects [14].

Another regimen is the sequential therapy regimen which consists of standard dose PPI b.i.d. and amoxicillin 1 g b.i.d. followed for 5 days followed by standard dose PPI b.i.d., Clarithromycin 500 mg, and Tinidazole 500 mg b.i.d. for 5 days. This regimen achieved >90% eradication rate. In the available studies, the reported compliance with therapy has exceeded 90% and side effects have been no greater than those experienced with Clarithromycin triple therapy. But the compliance may be lower in elderly patients. In addition, it is not clear that there is any incremental benefit to providing antibiotic therapy sequentially rather than as a concurrent quadruple regimen. So, further studies are needed to consider this regimen as first line therapy and to compare it with other regimens especially in the elderly patients [14].

So in the current study, Clarithromycin-based triple therapy for 14 days was used as first line therapy for H. pylori infected elderly patients. The regimen has achieved a cure rate of 88% which is slightly better than the recorded cure rate for this regimen. The American College of Gastroenterology Guideline on the Management of H. pylori Infection 2007 stated that this regimen can achieve a cure rate up to 85% [14].

In elderly patients, either 14-days course or 7-days course can be used. A recent meta-analysis of seven studies including more than 900 patients found that a 14-day course of Clarithromycin triple therapy provided better eradication rates than a 7-day course of therapy [24].

In the current study, a twice daily dosing of PPI was used instead of once daily dosing because data from a recent meta-analysis of 13 studies suggested that twice daily dosing of a PPI in Clarithromycin-based triple regimens is more effective than once daily dosing [25].

Helicobacter pylori resistance is an important factor involved in the failure of treatment. The prevalence of primary resistance of H. pylori to clarithromycin has been reported to range from 2.2 to 24% in different countries [26-29]. The prevalence of H. pylori resistance to metronidazole has been reported to range from 8 to 80% in different countries. The prevalence is much higher in developing countries (>60%) than in developed countries [30-32]. The prevalence of primary resistance of H. pylori to quinolones has been reported to range from 2 to 22% in different countries [27,33].

Accordingly, 14-days course of Clarithromycin-based triple therapy (Omeprazole 40 mg twice daily, Clarithromycin 500 mg twice daily, and Amoxicillin 1000 mg twice daily) is highly effective as first line therapy for treating H. pylori infected elderly patients in Egypt with a cure rate of about 88% and very high tolerability rate.

So, the use of 14-days course of Clarithromycin-based triple therapy is recommended as first line therapy for elderly patients infected with H. pylori.

Further studies should be done to assess the use of this regimen as a second line therapy if other regimen has failed as first line therapy.

Comparative studies should be done between this regimen and other regimens as first line therapy for elderly patients infected with H. pylori.

Acknowledgments

Conflict of Interest: None

Guarantor of the article: Salamah A.M.

Specific author contributions:

Salamah A.M., manuscript preparation.

Gad M., manuscript review.

Deghady A., laboratory investigations and manuscript review.

Elgayar N.H., manuscript review.

Financial support: None.

References

Thanks for our 34 patients for their compliance with the treatment and with the study because without them this work would not have been completed.

1. Olson, J.W. and Maier, R.J. (2002) Molecular hydrogen as an energy source for Helicobacter pylori. Science, 298(5599), 1788-1790.
2. Stark, R.M., Gerwig, G.J., Pitman, R.S. et al. (1999) Biofilm formation by Helicobacter pylori. Letters in applied microbiology, 28(2), 121-126.
3. Kusters, J.G., van Vliet, A.H. and Kuipers, E.J. (2006) Pathogenesis of Helicobacter pylori Infection. Clin Microbiol Rev, 19(3), 449-490.
4. Zaterka, S., Eisig, J.N., Chinzon, D., et al. (2007) Factors related to Helicobacter pylori prevalence in an adult population in Brazil. Helicobacter,12,82-88.
5. Suzuki, H., Iwasaki, E. and Hibi, T.(2009) Helicobacter pylori and gastric cancer. Gastric Cancer, 12(2),79-87.
6. Tsujii, M., Kawano, S., Tsuji, S., et al. (1992) Mechanism of gastric mucosal damage induced by ammonia. Gastroenterology, 102(6), 1881-1888.
7. Atherton, J.C., Cao, P., Peek, R.M., et al.(1995) Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori. Association of specific vacA types with cytotoxin production and peptic ulceration. J Biol Chem, 270(30),17771-17777.
8. Appelmelk, B.J., Simoons-Smit I., Nergrini, R. et al. (1996) Potential role of molecular mimicry between Helicobacter pylori lipopolysaccharide and host Lewis blood group antigens in autoimmunity. Infect Immun, 64, 2031-2040.
9. Ge, R. and Sun, X. (2011) The in vivo functions of a histidine-rich protein Hpn in Helicobacter pylori: linking gastric and Alzheimer's diseases together? Med Hypotheses,77(5),788-790.
10. Dixon, M.F., Genta, R.M., Yardley, J.H. et al.(1996) Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston, 1994. Am J Surg Pathol, 20(10),1161-1181.
11. Liou, J.M., Lin, J.T., Lee, Y.C. et al.(2008) Helicobacter Pylori Infection In The Elderly. Inter J Gerontol, 2(4),145-153.
12. Fiocca, R.1., Villani L, Luinetti, O. et al.(1992) Helicobacter colonization and histopathological profile of chronic gastritis in patients with or without dyspepsia, mucosal erosion and peptic ulcer: a morphological approach to the study of ulcerogenesis in man. Virchows Arch A Pathol Anat Histopathol, 420(6),489-498.
13. Peura, D.A and Crowe, S.E. (2010) Helicobacter pylori. In: Feldman M, Friedman LS, Brandt LJ, (eds). Sleisenger & Fordtran's gastrointestinal and liver disease. 9thed. Philadelphia: WB Saunders Company; 833-843.
14. Chey, W.D. and Wong, B.C. (2007) American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol, 102(8),1808-1825.

15. Malfertheiner, P., Megraud, F., O'Morain, C. et al.(2002) Current concepts in the management of Helicobacter pylori infection--the Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther, 16(2),167-180.

16. Cutler, A.F., Elnaggar, M., Brooks, E. et al.(1998) Effect of standard and high dose ranitidine on 13 C-urea breath test results. Am J Gastroenterol , 93,1297-1299.

17. Savarino, V., Tracci, D., Dulbecco. P, et al.(2001) Negative effect of ranitidine on the results of urea breath test for the diagnosis of Helicobacter pylori. Am J Gastroenterol , 96,348-352.

18. Ahmed, F., Chey, W.D. and Murthy, U. (2005) Evaluation of the Ez- HBT Helicobacter blood test to establish Helicobacter pylori eradication. Aliment Pharmacol Ther , 22,875- 880.

19. Gisbert, J.P. and Pajares, J.M. (2004) Stool antigen test for the diagnosis of Helicobacter pylori infection: A systematic review. Helicobacter, 9,347-368.

20. Pilotto, A. and Salles, N.(2002) Helicobacter pylori infection in geriatrics. Helicobacter ; 7 (Suppl 1):56-62.

21. Megraud, F.(1997) Resistance of Helicobacter pylori to antibiotics. Aliment Pharmacol Ther , 11,43-53.

22. Cutler, A.F. (1996) Testing for Helicobacter pylori in clinical practice. Am J Med, 100,35S-41S.

23. Bochenek, W.L., Peters, S., Fraga, P.D. et al. (2003) Eradication of *Helicobacter pylori* by 7-day triple-therapy regimens combining pantoprazole with clarithromycin, metronidazole, or amoxicillin in patients with peptic ulcer disease: Results of two double-blind, randomized studies. Helicobacter,8,626–642.

24. Calvet, X.,Garcia, N., Lopez, T. et al. (2000) A meta-analysis of short versus long therapy with a proton pump inhibitor, clarithromycin and either metronidazole or amoxycillin for treating Helicobacter pylori infection. Aliment Pharmacol Ther, 14(5),603-609.

25. Vallve, M., Vergara, M., Gisbert, J.P. et al. (2002) Single vs. double dose of a proton pump inhibitor in triple therapy for Helicobacter pylori eradication: a meta-analysis. Aliment Pharmacol Ther, 16(6),1149-1156.

26. Torres, J., Camorlinga-Ponce M., Perez-Perez G. et al. (2001): Increasing multidrug resistance in Helicobacter pylori strains isolated from children and adults in Mexico. J. Clin. Microbiol.39, 2677–2680.

27. Kim JM, Kim JS, Kim N et al.(2006) Comparison of primary and secondary antimicrobial minimum inhibitory concentrations for Helicobacter pylori isolated from Korean patients. Int. J. Antimicrob. Agents,28,6–13.

28. Duck, W.M., Sobel. J., Pruckler, J.M. et al. (2004) Antimicrobial resistance incidence and risk factors among Helicobacter pylori-infected persons, United States. Emerg. Infect. Dis.10, 1088–1094 .

29. Mollison, L.C., Stingemore, N., Wake, R.A. et al. (2000) Antibiotic resistance in Helicobacter pylori. Med. J. Aust, 173,521–523.

30. Di Mario F., Cavallaro, L.G., Scarpignato, C. (2006) 'Rescue' therapies for the management of Helicobacter pylori infection. Dig. Dis.24, 113–130.

31. Wong, W.M, Gu Q., Wang W.H. et al.(2003) Effects of primary metronidazole and clarithromycin resistance to Helicobacter pylori on omeprazole, metronidazole, and clarithromycin triple-therapy regimen in a region with high rates of metronidazole resistance. Clin. Infect Dis, 37,882–889.

32. Tsugawa, H., Suzuki, H., Nakagawa., I. et al.(2008) α-ketoglutarate oxidoreductase, an essential salvage enzyme of energy metabolism, in coccoid form of Helicobacter pylori. Biochem. Biophys. Res. Commun,376,46–51.

33. Zullo, A., Perna, F., Hassan, C. et al. (2007) Primary antibiotic resistance in Helicobacter pylori strains isolated in northern and central Italy. Aliment. Pharmacol. Ther.25, 1429–1434.

34.

Tables and Graphs

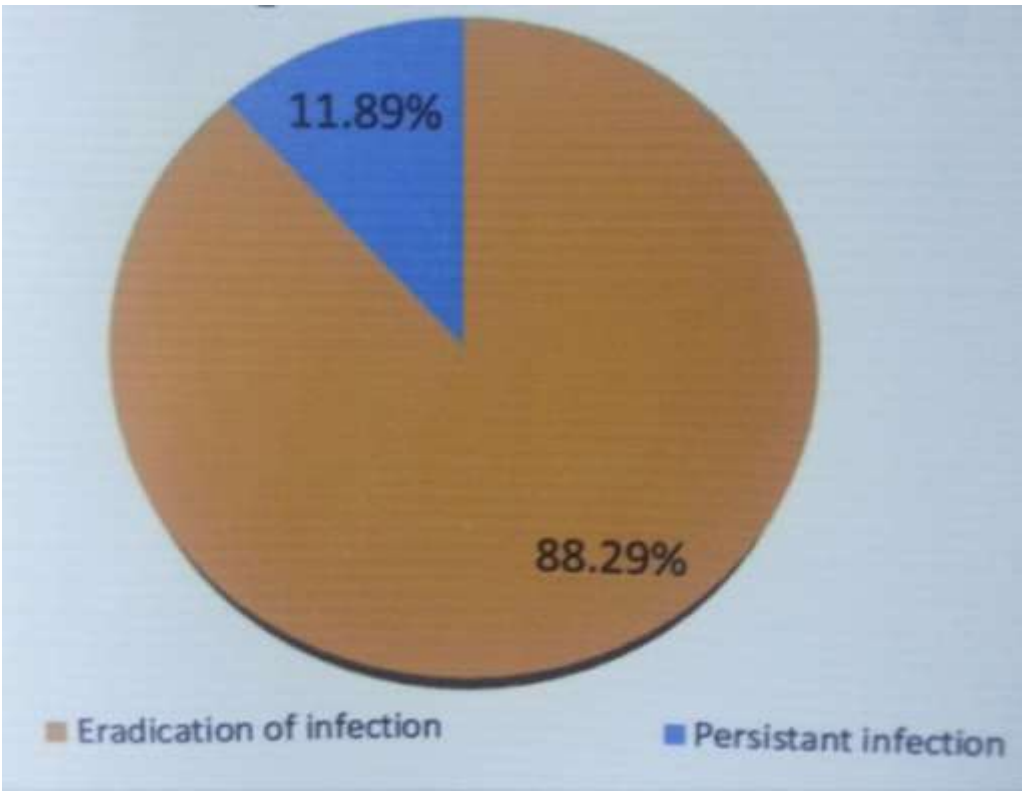

Fig.1: Response to Treatment

Fig.2: Treatment Tolerability

Table (1): Comparison between the two groups according to demographic data

	Responders (n=30)		Non Responders (n=4)		Test of sig.	P
	No.	%	No.	%		
Sex Male Female	 16 14	 53.3 46.7	 2 2	 50.0 50.0	□□□□□□□	p=1.000
Age (years) Min. – Max. Mean ± SD Median	 65.0 – 80.0 70.60 ± 4.47 69.50		 65.0 – 70.0 67.25 ± 2.22 67.0		t=1.461	0.154

χ^2: Chi square test

t: Student t-test