Review Article on Safety and Efficacy of Sequential Versus Triple Therapies for Treating H. pylori Infection

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Abstract:-
Background : Standard Triple Therapy (STT), Sequential Therapy (SQT) and Bismuth-based Quadruple therapy are among the therapeutic regimen available for the initial management of the H.pylori infection. The goal of therapy is to eradicate H. pylori and is usually initiated with standard triple-drug therapy. During the past few years, with increased in bacterial resistance with time, the efficacy of triple therapy has decreased of less than 80% rate of eradication. Several recent meta-analysis have shown higher eradication rates with sequential therapy regimens than the standard triple therapy.
Objective : The objective of review study was to compare safety and efficacy evaluation of Sequential Versus Triple Therapy in H. pylori Infection.
Method:An electronic search was conducted in PubMed, Google, Google Scholar, ,Medline and Science Direct. Our search strategy was based on key terms; "Helicobacter pylori", "standard triple therapy", "sequential therapy", "PPI". The review was limited to English language and randomized clinical trials (RCTs) and published between 2007 to 2015. Inclusion criteria were a study conducted in adult aged 18 years and above having HP infection and receiving sequential therapy and standard triple therapy. Non-randomized studies, studies done in children and studies covering the retreatment after eradication failure were omitted from the study.
Result:The review comprised 12 RCTs studies, with 10 of them reporting higher eradication rate with sequential therapy. Due to clarithromycin resistance, the review conforms that the STT have poor success rate of infection eradication. According to some studies finding, sequential treatment containing levofloxacin is found to be effective for patients who failed from either sequential therapy containing clarithromycin or triple therapy.
Conclusion : In conclusion, sequential therapy is well tolerated and provides a higher eradication rate than 14-day standard triple therapy in the treatment of H.pylori infection. Assessment of resistance rate is crucial in order to guide treatment and hence it should be performed. In addition, estimating the cost-effectiveness of these treatments is crucial in clinical decision making, especially in the area with high prevalence rate of infection.

Keywords:- *H.Pylori, Sequential Therapy, Standard Triple Therapy.*

I. INTRODUCTION

In 1982, H.pylor become first recognized by Warren and Marshall and is recorded as the most common pathogen thatis related to an extensive range of higher gastrointestinal sicknesses along with gastritis, peptic ulcer disorder (PUD), and gastric cancer(Choi et al., 2012; S. Shrestha, Paudel, Pradhan, Shrestha, & Bhattachan, 2012). Worldwide, the prevalence of infection is more than 90% in developing nations. According to a study conducted by KC Shiva Raj et al, thereported prevalence rate ranges from 30% to 67%. The reported rate of prevalence was higher in developing nations(K.C., Lakhey, Koirala, & Amatya, 2016). Besides this, the reasons for the superiority of contamination are poor sanitation, contaminated water, fundamental hygiene and terrible diets(R. Shrestha et al., 2020).

Various treatment regimens have been recommended for the eradication of H. pylori infection as per Clinical Guideline of the American College of Gastroenterology (ACG) (2007) which are presented in **Table 1**(Chey, Leontiadis, Howden, & Moss, 2017). The first-line therapy to eradicate H. pylori is sometimes initiated with standard triple-drug therapy, which has a proton pump inhibitor (PPI), Clarithromycin 500 mg, and either Amoxicillin 1gm or Metronidazole 500 mg for 7-14 days inU. S and Europe(Lahbabi et al., 2013). However, the efficacy of triple therapy has decreased with eradication rates of less than 80%during the past few years. Eradication rate of infections are decreased primarily due to increased bacterial resistance to STT containing clarithromycin, indicating the need for new first-line treatment(S. Shrestha et al., 2012). Sequential therapy includes PPI, 1gm of amoxicillin, each administered twice daily for 5 days, followed by PPI, 500 mg of clarithromycin, and 500 mg of tinidazole, each administered twice daily for the remaining 5 days(Lahbabi et al., 2013).

Since the success rate of standard triple therapy has been declining over time, different alternative treatment regimens have been proposed for Helicobacter pylori eradication and one of them aresequential therapy. Mostly used treatment guidelines in Asia and Europeare summarized in the table below:

Table 1: Different Recommended treatment guidelines for eradication of H.Pylori infection in Asia, Europe and U.S with dosage regimen.

Guideline
American College of Gastroenterology (Chey et al., 2017) • **Proton pump inhibitor–based triple therapy:** PPI once or twice daily, Clarithromycin 500 mg twice daily, Amoxicillin 1 g twice daily or metronidazole 500 mg twice daily • **Bismuth-based quadruple therapy:** PPI or H2 RA once or twice daily, Bismuth subsalicylated 525 mg 4 times daily, Metronidazole 250–500 mg 4 times daily, Tetracycline 500 mg 4 times daily • **Sequential therapy:** PPI once or twice daily on days 1–10, Amoxicillin 1 g twice daily on days 1–5, Metronidazole 250–500 mg twice daily on days 6–10, Clarithromycin 250–500 mg twice daily on days 6–10.
Asia- Pacific guidelines (Fock et al., 2009) • **Proton pump inhibitor–based triple therapy:**PPI once or twice daily Clarithromycin 500 mg twice daily Amoxicillin 1 g twice daily • **Bismuth-based quadruple therapy:** PPI or H2 RA once or twice daily, Bismuth subsalicylated 525 mg 4 times daily, Metronidazole 250–500 mg 4 times daily, Tetracycline 500 mg 4 times daily • **Levofloxacin-based triple therapy:**PPI once or twice daily, Amoxicillin 1 g twice daily Levofloxacin 250 mg twice daily • **Rifabutin-based triple therapy**
Maastricht(Malfertheiner et al., 2012) • **Clarithromycin containing triple-drug therapy:** PPI once or twice daily Clarithromycin 500 mg twice daily Amoxicillin 1 g twice daily or metronidazole 500 mg twice daily • **Bismuth-containing quadruple therapy:** PPI or H2 RA once or twice daily, Bismuth subsalicylated 525 mg 4 times daily Metronidazole 250–500 mg 4 times daily Tetracycline 500 mg 4 times daily (for high clarithromycin resistance)

This review aimed was to evaluate and compare the evidence of the efficacy, adverse effects, and cost of sequential therapy with standard triple therapy in patients with documented H. pylori infection.

II. LITERATURE SEARCH METHODOLOGY

A review was conducted using PRISMA guidelines. An electronic search was conducted in Google Scholar, PubMed, Hinari, Medline, and Science Direct to identify the relevant articleon this topic using the keywords of Helicobacter pylori, standard triple therapy, sequential therapy, PPI, and collected the relevant articles published between 2007 to 2015. The search was limited to English language and randomized clinical trials (RCTs),

Study Population:

Inclusion and exclusion criteria:

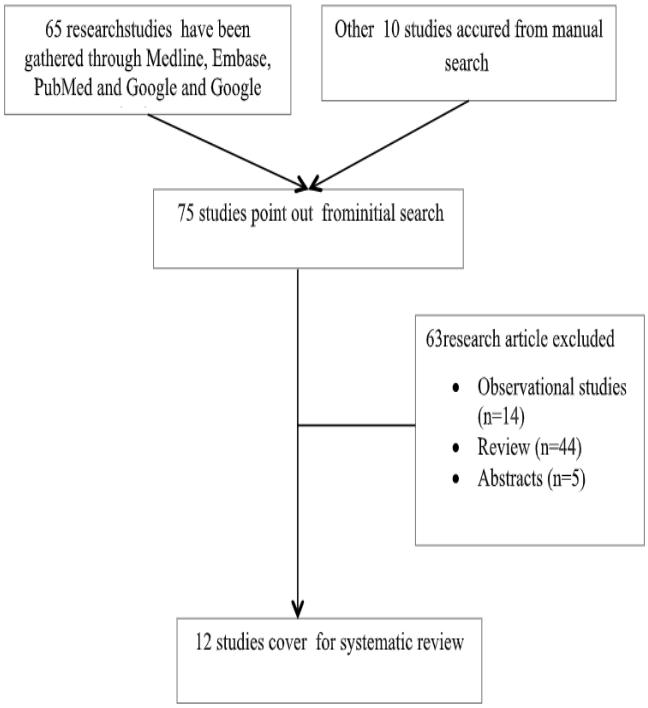
(1) Included criteria:

- Patientsaged 18years and above with HP infection receive sequential therapy anda standard triple therapy eradication regimen,
- Articles that were presented in the English language were included in this review
- Persistence of H.pyloriassessed by UBT, histology, or H. pylori stool antigen test

(2) Excluded criteria:

- Non-randomized studies,
- Treatment failure after eradication treatment, and
- Studies were conducted on children.

Data screening and Extraction



III. RESULTS

These review studies were concerned the safety and efficacy of the STT and SQT treatment regimen are summarised in **Table 2** and these studies were performed in different countries in Europe, Asia, and Latin America and mostly were randomised controlled trials.

Table 2: Studies conserning STT and SQT to eradicate H.pyori Infection.

Author	Research area, Duration, and Population	Standard triple therapy	Sequential therapy	Diagnostic test	Eradiation rate (%)	Interpretation
Greenberg Robert E et al.,(Greenberg et al., 2011)	Studied in seven Latin American. Between September 2009, and June 2010, Men and women aged 21–65 years	Lansoprazolefor 5 days +amoxicillin +clarithromy BD for 14 days **Concomitant therapy** Lansoprazole + Amoxicillin + Clarithromycin + Metronidazole for 5 days	Lansoprazole5 days +amoxicillin followed by Lansoprazole +Clarithromycin + Metronidazole BD for 5 days	UBT(^{13}C-labelled urea)	Standard therapy was 82·2%. with Sequential therapy was 76·5%	Standard triple-drug therapy is effective to concomitant or sequential therapy as empiric therapy.
Kim Y.S et al.,(Kim et al., 2011)	Study was conducted at Chuncheon Sacred Heart Hospital in northeastern South Korea. Between October 2008 and February 2009 with the patient of 18 years of age	**For 14 days regimen:** Pantoprazole + Amoxicillin + clarithromycin BD	**For 5 days regimen:** Pantoprazole + Amoxicillin BD Pantoprazole + Clarithromycin + Metronidazole BD	Rapid urease test Urea breath test Upper endoscopy	PPI-based triple therapy and sequential therapies were 75% and 85.9% respectively (ITT)	Sequential therapy achieved significantly higher eradication rates than the standard PPI-based triple therapy in Korea.
Lahbabi M et.al.,(Lahbabi et al., 2013)	The study was conducted at Hassan II University in June 2009 population aged of 45yrs and above.	PPI + amoxicillin + metronidazole for 7 days (AM group)/clarithromycin (AC group)	**For 5 days:** PPI + amoxicillin **Remaining 5 days:** PPI + Clarithromycin + Metronidazole	13C-urea breath test	Sequential therapy was found to be 94.2% in ITT and 96% in PP.	Sequential treatment was better tolerated than standard triple therapies
Liou Ming-J et al.,(Liou et al., 2013)	The study was conducted in 6 centers of in Korea from Dec 28, 2009, and Sept 24, 2011, with patients aged ≥ 20 years	**For 14 days:** Lansoprazole + Amoxicillin + Clarithromycin	**First 7 days:**Lansoprazole + Amoxicillin **Another 7 days:** Lansoprazole + Clarithromycin + Metronidazole	Endoscopic examination	The eradication rate was 90·7% in the S-14 group, 87·0% in the S-10 group, and 82·3% in the T-14 group.	Sequential treatment is superior to the standard first-line treatment for H pylori infection.
Nasa M et al.(Nasa, Choksey, Phadke, & Sawant, 2013)	The study was conducted in Mumbai between July 2011 and June 2012 with patients aged over 20 yrs of age	**For 14 days:** Pantoprazole, + Clarithromycin + Amoxicillin, BD	**First 5 days:** Pantoprazole + Amoxicillin, each administered BD **Remaining 5 days:** Pantoprazole + Clarithromycin +	Gastroscopy RUT or Biopsy	The per-protocol eradication rate of sequential therapy was 92.4% vs. 81.8 % for standard	Sequential therapy was significantly better than standard therapy for eradicating H. pylori infection.

			Tinidazole		drug therapy. Intention-to-treat eradication rates were 88.2 % vs. 79.1 % respectively	
Vaira D et al., (Dino Vaira et al., 2007)	This study was conducted in 3-centers between September 2003 and April 2006, consecutive patients aged 18 years.	**10 days:** Pantoprazole, + Clarithromycin, + Amoxicillin, each BD	**First 5 days:** Pantoprazole 40 mg + Amoxicillin + Placebo each administered BD **Remaining 5 days:** Pantoprazole + Clarithromycin+ Tinidazole, each administered BD	13C-urea breath test Upper endoscopy Histologic evaluation Rapid urease test	In standard therapy, the eradiation rate for standard intention-to-treat was 77% ITT, 78 modified intention-to-treat analyses, and 79% per protocol. In sequential Therapy, the eradication rate was 89%, 91%, and 93% respectively.	Sequential therapy is statistically significant compared with standard therapy for eradicating H. pylori infection
HaiderRana B et al.,(Haider et al., 2015)	study was carried out in a tertiary referral teaching hospital (Adelaide and Meath Hospital, Dublin, Ireland) from July 2013 until December 2014, consecutive patients aged over 18 yrs	Omeprazole + Amoxicillin + Clarithromycin (all taken twice daily).	**5-day treatment:** Omeprazole + Amoxicillin followed by Omeprazole + Clarithromycin + Metronidazole all taken twice a day	13C-urea breath test	-	Sequential therapy is not statistically significant over standard triple therapy in this study.
Uygun A et al.,(Uygun et al., 2008)	This study was conducted in Turkey from January 2003 and December 2005, with a patients aged ≥18 years.	**For 14 days**: Pantoprazole + Amoxicillin + Clarithromycin	**For 7 days**: Pantoprazole + Amoxicillin **Next 7 days:** Pantoprazole + Tetracycline + Metronidazole	Upper endoscopy with biopsy and 14C-urea breath test	-	In this study a 14-day sequentialregimen achieved a significantly higher eradication comparedwith the standard

						PPI-based triple regimen.
Polat Z etal.,(Polat et al., 2012)	This study was conducted in Gastroenterology, Gulhane Military Medical Academy, Ankara, Turkey from January 2009 to March 2010	Esomeprazole+ Amoxicillin + Clarithromycin all for BID for 2 weeks	**First week:** Esomeprazole+ Amoxicillin followed by **Second week:** Esomeprazole + levofloxacin + Metronidazole	14C Urea Breath Test (UBT), upper endoscopy and biopsy	The eradication rate per per-protocol was 90% in sequential versus 57% in standard treatment groups	Levofloxacin-containing sequential therapy is significantly better than the standard triple therapy.
Choi HSet al.,(Choi et al., 2012)	The study was conducted at Korea University Anam Hospital from March 2008 to August 2011.	**7, 10, 14 days:** Rabeprazole + Amoxicillin + Clarithromycin twice daily	**First 5 days:** Amoxicillin + Rabeprazole twice daily followed by **Remaining 5 days:** Rabeprazole + Clarithromycin + Tinidazole twice daily	Urea breath test and histopathological diagnosis	The overall eradication rate was 81.0%. for standard triple therapy and sequential therapy	There are no significant differences between the 10-d sequential therapy and standard triple therapy tested (7-, 10- and 14-d regimens)
A. Zulloet al(Zullo et al., 2005)	Prospective, open-label, three-center, randomized Trial with dyspeptic patients aged >65 years.	**7-day regimen BD:** Rabeprazole 20 mg + Clarithromycin 500 mg + Amoxicillin 1 g	**First 5-day BD:** Rabeprazole 20 mg + Amoxicillin 1 g **Remaining 5-days:** Rabeprazole 20 mg + clarithromycin 500 mg + tinidazole 500 mg (all BD)	Rapid urease test and the histological examination (Giemsastaining)	Sequential regimens were significantly higher than those of triple therapy, at both ITT (94.4% vs. 80% and PP (96.6% vs. 82.8%.	The eradication rate of the 10-day sequential Regimen was significantly higher than standard triple therapy.
Omero Alessandro Paoluzi(Paoluzi et al., 2010)	The prospective, open-label, randomized single-center study	**For 7 days BD regimen:** Esomeprazole 20mg + Amoxicillin 1000 mg + Clarithromycin 500 mg	Esomeprazole 20 mg bid, for 8 days and for 10 days, associated with amoxicillin 1000 mg bid for early 4 days, followed by clarithromycin 500 mg bid plus tinidazole 500mg bid, both in the last 4 days	Urea breath test	Eradication rates after SQT-8 and SQT-10 for both ITT were 83% and 86% vs. 66% and for PP were 90% and 88% vs. 75%	SQT, for 8 or 10 days, is well tolerated and highly effective in H. pylori eradication and could represent a valid alternative to STT.

IV. DISCUSSION

Out of 14 RCTs studies, 10 studies in this review reported a better eradication rate with sequential therapy. The results of the present review comply with the previous meta-analyses which comparedwith STT and SQT treatment regimens.In the study conducted by Greenberg et al the probabilities reported for the H. pylori regimen of less than 80% with 5-day concomitant and 10-day sequential regimens(Greenberg et al., 2011), whereas meta-analyses had reported probabilities greater than 90% for both. Geographical variations of H. pylori resistance to antibiotics might be the reason for inconsistencies with the results. In clinical study from several countries included in our review, clarithromycin resistance in H. pylori has been reported to be less prevalent than in Europe, and metronidazole resistance substantially more prevalent (as high as 80%)(S. Shrestha et al., 2012). In a recent study conducted in Korea,H.pylori resistant to clarithromycinincreased from 16.7% to 38.5% from 2007 to 2009. Thus, the study design cannot show an improved effect with sequential therapy due to the sequential administration or the additional antibiotic used (i.e. metronidazole). Though metronidazole resistance decreased from 34.8% to 27.6% and the eradication rate (85.9%) of less than 90% in the intention-to-treat analysis (Kim et al., 2011). Among these RCTs studies, some study findings suggest that SQT with levofloxacin is effective for patients who failedH.pylori treatment of either sequential therapy with clarithromycin or triple therapy(Liou et al., 2013). Low eradication rateshave also been reported with standard therapy in Europe, Australia, and Asia in the treatment of H.pylori infection.(Haider et al., 2015; Lee et al., 2014).

This review confirms poor success rates of infection eradication with standard therapy and suggests that this may be due to clarithromycin resistance. Bacterial resistance to antibiotics, adherence to therapy(Fischbach, Van Zanten, & Dickason, 2004), bacterial load in the stomach, CagA status, smoking habit, and gastroduodenal pathology are associated factores that affect the efficacy of STT.

V. LIMITATIONS

Antimicrobial minimal inhibitory concentrations and the sensitivity to the antibiotic were not determined. Most of the published articles included in the study don't have antibiotic resistance data, which would substantially have an effect on treatment outcomes.

VI. CONCLUSIONS

Based n the results of these RCTs, We have concluded that preferred triple therapy is not as effective as sequential therapy for H. pylori eradication.Resistance rates should be investigated in order to enhancedtreatmentguidelines.Further more determining the cost effectiveness of these treatments is critical in clinical decision making, particularly in areas where H.pylori prevalence is high.

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