EFFICACY OF SEQUENTIAL THERAPY (RA-RCT) IN HELICOBACTER PYLORI ERADICATION IN PATIENTS WITH CHRONIC GASTRITIS

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Abstract

Background/Aim: Helicobacter pylori (H.pylori) – associated chronic gastritis is a risk factor of gastric cancer. Recently, standard triple-drug therapy has a low rate of H.pylori eradication due to the resistance of drug, especially Clarithromycin resistance. This study aims to confirm effect of H.pylori eradication of sequential therapy (RA-RCT) and compare with the standard triple-drug therapy (RCT), addition to evaluating the improvement about histology of chronic gastritis after treatment. **Patients/Methods:** 84 chronic gastritis patients with H.pylori infection were included. These patients were divided into two groups: 42 patients were treated with sequential therapy (RA-RCT), 42 patients were treated with standard triple-drug therapy (RCT) during 10 days. After 4 weeks, these patient were indicated endoscopy, check H.pyolori and biopsy to evaluate eradication H.pylori rate and histological improvement. **Results:** The eradication rate of H.pylori in sequential regimen group is 88.6% (per protocol: PP) and 73.8% (intention to treat: ITT). This rate is significant higher than the rates of the standard therapy: 62.5% (PP) and 50% (ITT) ($p<0.05$). There were no significant differences between two groups in side effects of drugs (25.0%: sequential therapy, 27.8% standard therapy). The improvement about inflammation grade at group successful H.pylori eradication is significant, while group with unsuccessful H.pylori eradication is no significant. **Conclusion:** Sequential regimen has good efficacy, safety and good compliance. Further studies will be needed to evaluate the impact of H.pylori eradication by sequential therapy on pathology.

Key words: *Helicobacter pylori (H.p), Sequential regimen, PPI (Proton Pump Inhibitors).*

1. INTRODUCTION

Chronic gastritis is a common disease and a high risk for gastric cancer [4], [23]. Helicobacter pylori is known as a pathogen that plays a role in patients with chronic gastritis [12], [19], [24]. Therefore, management of H. pylori infection is of global interest. For a long time, triple therapy, consisting of a proton pump inhibitor, clarithromycin, and amoxicillin (10-14 days), has been the most recommended and used first-line therapy for the eradication of H. pylori in Asia, Europe as well as American [1], [5], [11], [13]. However, the eradication rates for H. pylori have been declining and have reached an unacceptable levels (<80%) in many countries [2], [11], [16]. *H.pylori* eradication failure has increased to nearly 30% in Vietnam [10], [21]. This finding may be partly from the increasing prevalence of antibiotic resistance, especially clarithromycin resistance. Accordingly, a new strategy that overcomes the falling eradication rates is needed.

A novel, 10-day sequential therapy regimen, consisting of 5 days of simple dual treatment with a proton pump inhibitor plus amoxicillin, followed by 5 days of triple treatment with a proton pump inhibitor, clarithromycin and nitroimidazole, has been the focus of several studies because of the excellent efficacy [22], [23]. Recently, some meta-analysis in Europe, American and Asia was shown that the sequential treatment regimen achieved significantly higher eradication rates compared with standard triple therapy [9], [11], [23]. In Vietnam, study of Bui Huu Hoang (in Southern Vietnam, 2011) shown eradication rates of H.p

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in sequential regimen group were 86.1% (per protocol: PP) and 72.5% (intention to treat: ITT) was significantly higher than triple therapy (62.5% (PP) and 50% (ITT)) [10]. Accordingly, sequential therapy was able to recommend as first-line *H. pylori* treatment in clinical practice. We expected that the sequential regimen would be a good alternative treatment for *H. pylori* eradication in the Vietnam population, considering that the clarithromycin resistance rate was very high.

The present study aimed to aims to evaluate H.pylori eradication rate of sequential therapy (RA-RCT, 10-day) and compare with the standard triple-drug therapy (RCT, 10-day) in patients with chronic gastritis through a randomised. The secondary objective of the study was to evaluate the adherence, adverse events of both regimens and improvement grading chronic gastritis after treatment.

2. METHODS

2.1 Patients

The patients who was >18 years, having consultation at Hue University Hospital from Nov 2012 to Aug 2013 suffered from chronic gastritis associated with *H.pylori* infection and had never received treatment for H.pylori infection.

There were 84 patients divided into 2 groups. **Exclusion criteria were as follows**: (i) Use of proton pump inhibitors, H2-receptor antagonists, a bismuth preparation, and antibiotics in the 4 weeks before enrolment; (ii) Concomitant anticoagulant, nonsteroidal anti-inflammatory drugs, or ketoconazole use; (iii) Severe or unstable cardiovascular, pulmonary, or endocrine disease; (iv) Clinically significant renal or hepatic disease or dysfunction; (v) Pregnancy or lactation, as well as sexually active women of child-bearing years who were not willing to practise reliable contraception for the duration of the study; (vi) Known allergy to the prescribed antibiotics.

2.2. Study design randomized, controlled

2.3. Methods

84 patients underwent upper gastrointestinal endoscopy and biopsy.

- *H.pylori* infection was defined when the results of rapid urease test is positive.

- Chronic gastritis is a histopathologic characterized by chronic inflammation of the stomach mucosa [12]. Grade of chronic gastritis represent the semiquantitative assessment of the combined severity of mononuclear and granulocytic inflammation scored in both antral and corpus biopsy samples. Grades range from 0 (absence of inflammatory cells in any of the specimens) to 4 (a very dense infiltrate in all the biopsy samples) (Fig. 1) [18], [19], [20].

		CORPUS			
		No Inflammation (G0)	Mild Inflammation (G1)	Moderate Inflammation (G2)	Severe Inflammation (G3)
ANTRUM	No Inflammation (G0)	GRADE 0	GRADE I	GRADE II	GRADE II
	Mild Inflammation (G1)	GRADE I	GRADE II	GRADE II	GRADE III
	Moderate Inflammation (G2)	GRADE II	GRADE II	GRADE III	GRADE IV
	Severe Inflammation (G3)	GRADE II	GRADE III	GRADE IV	GRADE IV

Figure. 1 Grading: intensity of the inflammatory cells (lymphocytes, plasma cells, and granulocytes) within the lamina propria is graded as absent (0), mild (1), moderate (2) and severe (3) according to the visual analogue scales of the Updated Sydney System. The final grade of inflammation results from the combination of the grades of the inflammatory lesions in antral and corpus mucosa.

These patients were divided randomly into 2 groups: 42 patients were treated with sequential therapy (RA-RCT), 42 patients were treated with standard triple-drug therapy (RCT) during 10 days. Dosage and used as after:

- Sequential regimen: 20 mg of Pariet, and 1 g of Amoxicillin, twice daily for the first 5 days, followed by 20 mg of Pariet, 500 mg of clarithromycin and 500 mg of Tinidazole twice daily for the remaining 5 days.

- The standard triple regimen: 20 mg of Pariet, 1 g of amoxicillin and 500 mg of clarithromycin twice daily for 10 days.

Patients were asked to return 4 weeks after the end of antibiotic treatment to undergo endoscopy and biopsy to determine the outcome of eradication therapy, assess treatment adherence, adverse events and improvement about grading of chronic gastritis.

- The infection was considered to have been successfully eradicated when the rapid test urease was negative. Both intention-to-treat (ITT) and per-protocol (PP) analyses were used for the assessment of the eradication rates of H. pylori infections in the two groups. The ITT analysis included all randomly assigned patients who had taken at least one dose of the study medications. The PP analysis was limited to patients who were medications adherence and completed follow-up.

- Adverse events were evaluated using a structured questionnaire and open-ended questions.

- Improvement about grading of chronic gastritis: comparing average grade score before and after treatment

The analysis was performed using SPSS for Windows.

3. RESULT

3.1. Patients characteristics

Table 1. Characteristics of patients treated with sequential regimen

Characteristic		Sequential therapy (n = 42)	
		n	%
Gender	Male	20	47.6
	Female	22	52.3
Age (mean _ s.d.), years		45.98 ± 10.86	
Grading of chronic gastritis	Grade 0	15	35.7
	Grade 1	18	42.9
	Grade 2	8	19
	Grade 3	1	2.4
	Grade 4	0	0

A total of 84 patients with H. pylori infection were enrolled and randomly assigned to sequential (n = 42) or standard (n = 42) therapies. As shown in Table 1 showed demographic and histological characteristics of sequential therapy groups.

Overall, 11 patients (6 patients randomised to the sequential treatment and 5 allocated to the standard treatment) lost follow-up because they did not undergo endoscopy after treatment. Three patients were not medications adherence. Therefore, the final PP population consisted of 70 patients (Fig 2).

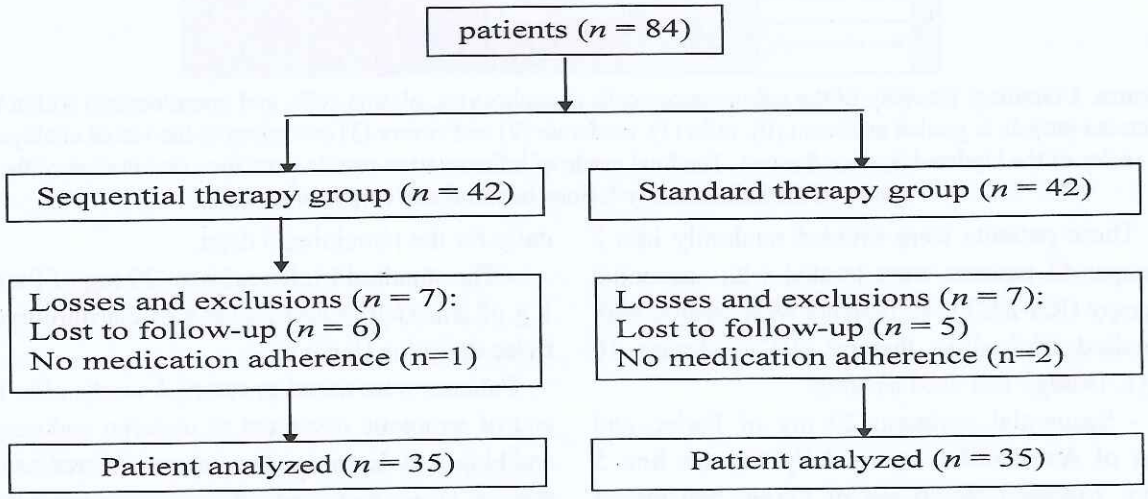

Figure 2. Flowchart of participants through study

3.2. Eradication rates

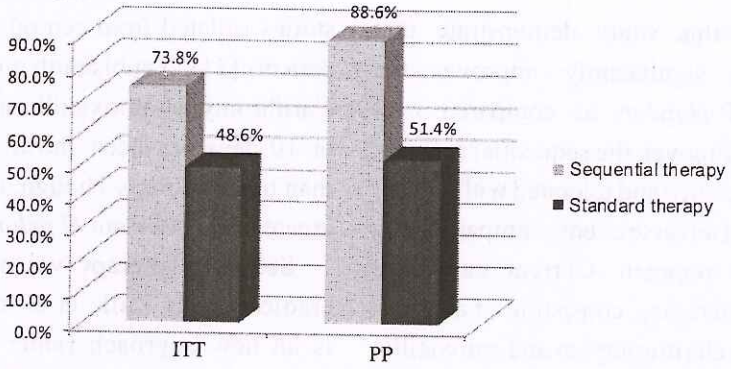

Figure. 3. *H.pylori* eradication rates of the treatment groups according to ITT and PP

As illustrated in figure 2, the eradication rates achieved by sequential therapy were significantly higher than standard therapy based on ITT (73.8% vs. 42.9%, $p < 0.05$) and PP analyses (88.6% vs. 51.4%, $p < 0.05$).

3.3. Adherence and adverse events

Table 2. Adverse events (AE) in the sequential therapy and triple therapy2

Adverse events	Sequential therapy (n=36)		Standard therapy (n=37)		p value
	n	*%*	*n*	*%*	
Loss of appetite	0	0	3	8.3	
Fatigue	3	8.3	5	13.9	> 0.05
Nausea	0	0	4	11.1	
Constipation	1	2.8	0	0	> 0.05
Diarrhoea	0	0	2	5.6	
Dry mouth	4	11.1	5	13.9	> 0.05
Bitter taste	4	11.1	9	25	< 0.05
Metallic taste	3	8.3	0	0	
Total	9	25	10	27.8	> 0.05
Withdrawal due to AE	0	0	1	2.7	
No adherence	1	2.8	1	2.7	> 0.05

Nine patients (25%) treated with the sequential regimen and 10 patients (27.8%) who receive the standard therapy reported at least one adverse event. The incidence of adverse events was similar between the two groups ($p > 0.05$). In the sequential group, the most frequently reported adverse events were dry mouth, bitter taste and fatigue. In the standard group, bitter taste, dry mouth and nausea were also most common. One patient in the standard group discontinued treatment because of bitter taste.

3.4. Improvement about grading of chronic gastritis

Table 3. Assessing the improvement of inflammation grade before and after treatment with sequential therapy

Grading of chronic gastritis	*Successful in H.pylori eradication*		*Unsuccessful in H.pylori eradication*	
	Before treatment	after treatment	Before treatment	after treatment
Grade 0	0	13	0	0
Grade 1	14	14	2	2
Grade 2	16	4	2	2
Grade 3	1	0	0	0
Average grading score	2.58±0.564	1.71±0.693	2.50±0.58	2.50±0.58
	p<0.05			

In successful eradication group, the average grading score before treatment was 2.58±0.564, after treating this reduced 1.71±0.693. The reduction is statistical significance ($p<0.05$).

4. DISCUSSION

The results of this study demonstrate that sequential therapy significantly improves the eradication rate of *H.pylori* as compared with standard therapy. Moreover, the sequential regimen was equally well accepted and tolerated with similar rates of self-limiting adverse events compared with the standard triple regimen. Current guidelines recommend triple therapies, consisting of a proton pump inhibitor plus clarithromycin and amoxicillin or metronidazole, as the first-line treatment for eradication of *H.pylori* infections worldwide [1], [5], [13]. Early studies of first-line standard triple therapies demonstrated eradication rates of >85%. However, over the past 10 years, a critical fall in the efficacy of these therapies has been observed in the United States, Europe and Asia [2], [3], [6], [7], [16]. Our study confirms these reports on the disappointingly low cure rates with standard triple treatment (48.6% in the ITT population and 51.4% in the PP population). This finding is most likely a result of increased bacterial resistance to antibiotics, particularly clarithromycin. Indeed, a systematic review of *H.pylori* eradication therapy by Jafri et al reported that with respect to clarithromycin resistance, a mean drop in efficacy of 18% was found for clarithromycin-containing regimens [8]. Several studies in Vietnam have reported that clarithromycin-resistant *H. pylori* strains had continuously increased 38,5% (Dinh Minh Nhan Le et al, 2006), 42.9% (Trung Nam Phan et al, 2013) [21]. Therefore, to improve the efficacy of first-line therapy in a setting with a high prevalence of clarithromycin-resistant *H.pylori* strains, several therapeutic strategies have been proposed. Attempts to extend the duration of triple therapy from 7 days to 10 or 14 days have achieved controversial results. It has been proposed that quadruple therapy (protonpump inhibitor, bismuth salt, tetracycline, and metronidazole) may increase the success rate of eradicating *H.pylori* infections. However, medication adherence rate is very low because of adverse events. Levofloxacinbased triple therapy instead of clarithromycin may be another alternative. The problem primary levofloxacin-resistant strains are rapidly increasing. In fact, a recent study showed a high prevalence of levofloxacin resistance (44.6%) in *H.pylori* strains isolated from central region of Vietnamese patients [21]. Nonbismuth quadruple therapy (PPI-clarithromycin-amoxicillin-nitroimidazole) for 7 or 10 days has been shown to be more effective than triple therapy. Though, this regimen is easy to create multi-resistant *H.pylori* strains.

Sequential therapy was introduced for *H. pylori* eradication by Zullo et al in 2000. This regimen is an new approach rather than a new strategy because it is based on a different combination of well-known for H. pylori eradication [22], [23]. The use of amoxicillin to which resistance is rare in the initial therapeutic phase offers further advantages. It is known that bacteria can develop efflux channels for clarithromycin, which rapidly transfer the drug out of the bacterial cell, preventing binding of the antibiotic to the ribosome. Because amoxicillin acts on the bacterial cell wall and damages it, the initial phase of treatment may prevent the development of efflux channels by weakening the cell wall of the bacterium [23]. Randomised controlled trial, Zullo et al reported eradication rates for sequential therapy of 92% by ITT and 95% by PP analyses [22]. Since then, many trials have reported superiority of sequential therapy over standard triple therapy. Several meta-analyses and pooled analyses have demonstrated that eradication rates with sequential therapy were >90% compared with <80% for standard triple therapy based on ITT analysis [3], [8], [9], [17]. Nevertheless, in the present study, eradication rates of sequential therapy were somewhat lower than >90% reported in original studies and subsequent meta-analyses a trial conducted. In Turkey, where clarithromycin resistance is highly prevalent, demonstrated that sequential therapy eradicated H. pylori in 77.6% of patients according to PP analysis. In Vietnam, *H.pylori* eradication rate is 72.5% ITT and 86.1% PP. However, sequential therapy has been shown to achieve better eradication rates than triple therapy [10]. Therefore, we believe that triple therapy should no longer be used as a first-line anti-H. pylori regimen and sequential treatment may be a promising therapeutic approach, at least for now.

About effect after *H.pylori* eradication, according to Wantanabe et al, Helicobacter pylori infection alone is not directly associated with gastric carcinogenesis but has an indirect relation to gastric cancer through the development of atrophic gastritis. Successful eradication, we can stop the inflammation of gastric mucosa, stop the development of atrophic gastritis, thus reducing gastric cancer rate [24]. Although this study had limitation: a sample size for assessing improvement about grading of chronic gastritis is small, the result of this study contributed to confirm hypothesis.

5. CONCLUSION

10-day sequential therapy for the eradication of *H. pylori* infection is significantly superior to standard triple therapy and well-tolerated. Low successful rate after standard triple therapy in this study suggested that sequential treatment may be a first-line treatment for *H. pylori* eradication, even though our study did not achieve excellent eradication rates (>90%) with sequential therapy. The improve in histology suggested the efficacy of eradication therapy in reducing the development of gastric cancer.

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