

## Sequential versus Concomitant Therapy for Eradication of *Helicobacter pylori*: A Moroccan Randomized Prospective Study

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### Abstract

**Objective:** The objective of this study is to compare, in a located population in Morocco. the efficacy rates of the concomitant versus the sequential *Helicobacter pylori* (HP) eradication therapy.

**Materials and Methods:** Our prospective randomized study included 108 patients with newly diagnosed *H. pylori* infection, randomized to receive a 10-day concomitant (CC) (IPP 20 mg + Amoxicillin 1 g + metronidazole 500 mg + Clarithromycin 500 mg or 10-day sequential therapy(SQ) (PPI + Amoxicillin 5 days then PPI + Metronidazole + Clarithromycin 5 days). Treatment outcome was assessed by C13-urea breath test at least 4 weeks after therapy. per protocol (PP) analysis of the eradication rates were performed. Secondary end points included patient compliance and safety.

**Results:** 108 patients were included and 97 patients were treated. The mean age of the patients was 33.1±12.9 years with a M / W sex ratio of 1.7. The SQ and CC groups included 49 and 48 patients, respectively. They are comparable in age, gender, clinical presentation and endoscopy. The concomitant therapy group achieved similar eradication rates when compared with the sequential treatment group (86% versus 91.8% respectively). Therapeutic adherence was similar in both groups. The prevalence of sequential side effects was 22.4% (N = 11) versus 27% for the CC group.

**Conclusions:** In our context and in the absence of bismuth quadritherapy, the administration of PPI and 3 antibiotics concomitantly or sequentially showed its efficacy; Although our study did not show any statistical difference between the two approaches, concomitant therapy as recommended by the Maastricht V consensus for 14 days may be more effective as a first-line treatment for HP eradication.

**Keywords:** Sequential; Concomitant Therapy; *Helicobacter pylori*

### Introduction

The prevalence of *Helicobacter pylori* (HP) infection has decreased over the past decade, changed from 66.9 to 54.4% between 1998 and 2011, but its prevalence is still high in Morocco [1]. *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 [2]. 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.

The latest Maastricht V consensus recommendations of 2016 proposes for the eradication of HP in Europe in the first line the abandonment of the Sequential treatment in countries with primary resistance to Clarithromycin higher than 15% due to its demonstrated inferiority compared to concomitant quadritherapy (PPI - amoxicillin - clarithromycin - Metronidazole) for 10 to 14 days [2].

In Morocco, few studies have been done to evaluate Therapeutics protocols against HP. We do not know which one is the best in our context.

This study was undertaken to compare the efficacy, safety profile, compliance between SQ and CC for the eradication of HP.

**Materials and Methods**

This prospective randomized trial was conducted at the Arrazi Hospital, in Marrakech, Morocco, from January 2016 to December 2016. Newly diagnosed *H. pylori*-infected patients were prospectively included in our study. Diagnostic of *Helicobacter pylori* infection was established just by histology. Exclusion criteria included: age under 15 years, previous *H. pylori* eradication therapy, known allergic history to any of the medications used in our study, pregnancy or lactation, ingestion of antibiotics within the prior 4 weeks, patients with previous gastric surgery, and the coexistence of serious concomitant illness which would not allow patients compliance.

**Eligible patients were randomized in two**

Groups, In the concomitant therapy group CC, patients were assigned to a 14-day therapy (20 mg PPI twice daily, 500 mg clarithromycin twice daily, 1g amoxicillin twice daily, and 500 mg metronidazole twice daily). In the sequential therapy group SQ, patients were assigned to a 5-day therapy (20 mg PPI twice daily and 1 g amoxicillin twice daily), followed by another 5-day therapy (20 mg PPI twice daily, 500 mg clarithromycin twice daily, and 500 mg metronidazole twice daily).

To confirm patient compliance, we asked the patients to bring their remaining medication after the end of the treatment.

Patients were also interviewed for reasons responsible for missing any doses of the regimens. Adverse events were classified as minor or major.

Four weeks after the treatment period (with no administration of PPIs or any antibiotics), we confirmed *H. pylori* eradication using C13- Urea Breath Test. In the case of a treatment failure, a second-line eradication therapy was administered.

The treatment of the results: was done by the epi-info software and only the P values less than 0.05 were considered significant

**Results**

**Study groups and patients characteristics**

One hundred and eight patients were included originally in our study, randomized in two treatment groups (sequential versus concomitant treatment), each, with 54 patients.

Finally, in the per protocol analysis, 49 patients were included in the sequential treatment group and 48 patients in the concomitant treatment group (Figure 1).

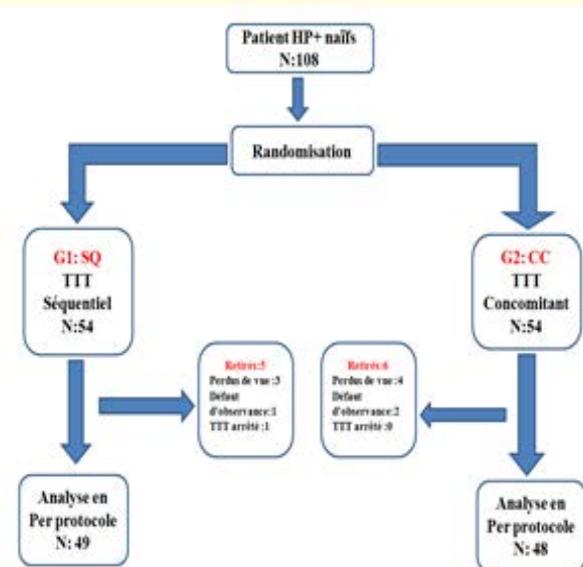


Figure 1: Diagram of patients included in the study.

The study population available for per protocol analysis consisted of 97 patients (SQ group: 49 patients, CC group: 48). The average age of all patients was  $33.1 \pm 12.9$  years. There was no predominance of sex in the two groups (sex ratio M/W was 1.6 in the SQ group, and 1.19 in the CC group,  $P = NS$ ). Tobacco was noted in 34% (33/97) of patients (16.6% in SQ groups and 17.4% in group CC,  $P = 0.8$ ). The baseline clinical and endoscopic characteristics of each group were comparable. The main clinical and endoscopic data of patients are presented in Table 1.

Data of patients	SQ Group (n (%))	CC Group (n (%))	P
<b>Number of patients</b>	49	48	
Age (mean $\pm$ -SD)	34,1 $\pm$ 14,9	35 $\pm$ -10	0,91
Sexe ratio(M/W)	29(59)/20 (41)	26(54)/22(46)	0,92
Tobacco (Y/N)	11(16)/38(78)	9(18)/39(82)	0,77
<b>Endoscopic Findings</b>			
Ulceratice dyspepsia	9(18)	11(23)	0,71
Gastritis	36(73)	32(66)	0,89
Normal endoscopy	4(9)	5(11)	0,78

**Table 1:** Baseline demographic clinical and endoscopic characteristics of the enrolled patients.

### Efficacy

The overall eradication rates of the two treatments was 86% ( $N = 84/97$ ).

The eradication rate achieved with sequential treatment was 91.8% (45/49).

The eradication rate achieved with the concomitant treatment was 89.5% (43/48).

The eradication rate achieved with the sequential treatment was statistically similar to that obtained with concomitant treatment ( $P = 0.3569$ ).

### Compliance and adverse events

Both groups displayed excellent compliance rates (96.7% vs 97.3% in the CC and SQ groups respectively,  $p = 0.067$ ). Major adverse events that led to discontinuation of the treatment were reported in one patient in the sequential treatment group SQ (severe abdominal pain). One or more side effects were observed in 11 patients (22.4%) in the SQ group and 13 patients (27%) in the CC group ( $p = 0.430$ ). Diarrhea and metallic taste were the most common side effects reported by patients in both groups.

All side effects healed spontaneously at the end of treatment. The details of the side effects are summarized in the table 2.

Adverse events	Group SQ n (%)	Group CC n (%)	p
Diarrhea	6(12,2)	5(10)	0,365
Metallic taste	3(6)	4(8)	0,617
Abdominal pain	3(6)	2(4)	0,456
Headache	1(2)	0	-
Constipation	0	1(2)	-
Anorexia	1(0,8)	0	
Nausea	1(2)	1(2)	-
Vomiting	-	1(2)	-
Skin rash	0	1(2)	-
Dizziness	0	0	-
Total	11(25,3)	13 (27%)	0,210

**Table 2:** Minor adverse events in our study population.

### Cost for the protocols used

The estimated costs of therapies administered in this study were 44, 6 Euros for the SQ protocol, and 73.5 Euros for the CC protocol.

### Discussion

In Morocco, the prevalence of *H. pylori* infection exceeds 75% in adults, which is higher than in Western countries [3]. Therefore, it is necessary to find new therapeutic approaches to cure this infection. Due to the increased overall prevalence of resistance to clarithromycin and metronidazole [6], standard triple therapy for HP has lost efficacy [7] and should be discontinued as primary therapies in several parts of the world, including Morocco [8,9]. Therefore, European recommendations (Maastricht V) do not recommend the use of standard triple therapies in areas with a high prevalence of clarithromycin resistance (higher than 15%) and recommends first-line quadritherapy based on bismuth or, alternatively, non-bismuth and mainly concomitant treatment of 14 days. Since bismuth are currently unavailable in several countries, including Morocco, the use of a bismuth-free quadritherapy becomes inevitable. Studies comparing the results of the eradication regimens based on a non-bismuth quadritherapy, in particular a sequential treatment or a concomitant treatment of 14 days, are few in particular in countries where self-medication and the irrational use of antibiotics is important. Our study aimed to comparing the efficacy of two quadratherapies (sequential and concomitant) showed 90.3% of the eradication rate after concomitant treatment CC and 85.5% after sequential treatment SQ in per protocol in first-line treatment for eradication of *H. pylori*.

The administration of PPI and 3 antibiotics, concomitantly or sequentially, showed a better eradication rate than standard triple therapy in all most meta-analysis [10-12]. However, the eradication rate of concomitant and sequential therapy showed no statistical difference ( $P = 0.3433$ ) in our study. The results of previous studies comparing the efficacy of concomitant therapy with sequential therapy for *H. pylori* eradication were controversial. In a randomized controlled trial, concomitant therapy showed a better eradication rate than sequential therapy (intention to treat (ITT), 79.4% versus 70.7%, per-protocol (PP) for SQ, 94, 90% in ITT and 84.4% in PP for the CC) [4]. Another randomized controlled trial also showed a better eradication rate after concomitant treatment compared to sequential therapy (ITT, 87.0% vs. 81.0%, and PP, 91.0% vs 86.0 %) [5].

However, many other studies have shown no difference in eradication rates between concomitant and sequential therapy. In a randomized study, the rates of eradication by ITT analysis were 80.8% in concomitant group and 75.6% in sequential group, and PP analyzes were 81.3% and 76, 8%. The eradication rate between the two groups showed no significant differences [6]. A randomized trial of 232 patients infected with *H. pylori* from Taiwan also showed similar eradication rates in both therapies [6].

According to these studies, the rate of eradication of *H. pylori* with CC or ST is variable throughout the world. This variability may be due to the difference of resistance to antibiotics against *H. pylori*.

Therapeutic adherence in the SQ and CC group was similar in our study. In a study by Wu., *et al.* adherence in the SQ and CC group was 95.7% and 98.2%, respectively [6] whereas Lim., *et al.* In their study, therapeutic adherence was better in the CC than in the SQ group (95.3% versus 96.2%,  $P = 0.80$ ) [7]. Although the sequential treatment has fewer tablets, its complex dosing schedule makes its use difficult for the patient especially the illiterate. The most common side effects in the SQ and CC group were diarrhea (12.2%), (10%) and metallic taste (6%) and (8%), respectively. There was no statistically significant difference in the profile of side effects between the two groups. Wu., *et al.* In their study found a bad taste (15.7%) as a major side effect in the concomitant group and fatigue in the sequential group (11%) [6]. Diarrhea was the major side effect in the SQ and CC groups in a study by De Francesco., *et al* [9].

### Conclusion

The management of patients infected with *H. pylori* remains complex and still imperfect. The gastroenterologist having an essential role. To improve it in our context and in the absence of bismuth quadritherapy, administration of PPI and 3 antibiotics concomitantly or Sequential has shown its effectiveness; Although our study did not show any Statistical difference between the two approaches, concomitant therapy recommended in The Maastricht V consensus for 14 days may be more Effective as a first-line treatment for HP eradication.

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