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Original Article

Standard triple therapy versus sequential therapy for eradication of *Helicobacter pylori* in treatment naïve and retreat patients

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ABSTRACT

Background and study aims: Untreated *Helicobacter pylori* infection causes increased risk of gastric cancer, GI morbidity and mortality. Standard treatment for eradication of *Helicobacter pylori* infection, is the triple therapy which consists of a proton pump inhibitor; together with two antibiotics (amoxicillin 1000 mg with clarithromycin 500 mg or metronidazole 400 mg) given twice daily for 7–14 days. Recent evidence revealed, that cure rates of *Helicobacter pylori* infection with triple therapy had fallen below satisfactory targets. Sequential therapy consisting of a twice daily dose of a PPI for ten days with Amoxicillin given at 1000 mg twice daily in the first 5 days followed by clarithromycin 500 mg and Metronidazole 400 mg given twice daily in the subsequent 5 days, was recommended to improve eradication rates. We performed a randomised open label study to compare the efficacy of sequential against triple therapy in *Helicobacter pylori* naive and retreat patients.

Patients and methods: In a randomised open label observational study 485 patients fulfilling inclusion and exclusion criteria were randomly assigned to be treated with triple therapy ($n = 231$) or sequential therapy ($n = 254$). Eradication of *Helicobacter pylori* was documented with ^{14}C Urea breath test (UBT) performed 6 weeks after the treatment.

Results: The intention-to-treat eradication rate was better in sequential therapy group 84.6% than triple therapy 68% ($p < 0.001$). Eradication rates were significantly higher for treatment naive than retreat patients in triple therapy group (70.5% and 58.3%, respectively, $p < 0.01$). A trend of a better response was observed in eradication rate for treatment naive 88.55% versus retreat 74.6% in sequential therapy group but was not statistically significant ($p = 0.76$). Compliance was similar in the two groups, however side effects were less and the clinical response was better in the sequential therapy group.

Introduction

The standard treatment for eradication of *Helicobacter pylori* (*H. pylori*), is the triple therapy (STT) consisting of a proton pump inhibitor (PPI) at a standard dose; together with two antibiotics (amoxicillin 1000 mg plus either clarithromycin 500 mg or metronidazole 400 mg) all given twice daily for a period of 7–14 days. In the past decade eradication cure rates used to be around 95% worldwide [1]. However, a meta-analysis in 2007 including over 53,000 patients showed that the eradication rate after a standard triple therapy was below 80% [2]. Some European studies have reported even lower rates of eradication, with failure rates of 35–40% [3]. Failure of eradication appears to be related to several factors which include patients' compliance, reinfection and antibiotic resistance. The latter playing the most important role. Recently, we have reported a similar observation with successful eradication cure rates falling from 95% in the year 2000 to 67.8% as concluded from a multicentre retrospective analysis done in the year 2009 [4].

Sequential therapy, a regimen using a proton pump inhibitor (PPI), Amoxicillin, clarithromycin and Metronidazole, drugs with approved well-known indications for *H. pylori* eradication, was introduced by Vaira and co-workers from Italy as an alternative to STT. This regimen is an innovative strategy consisting of a 10-day treatment course given in sequence rather than simultaneously. Early reports showed the sequential therapy had led to 95% eradication rates which are significantly superior to eradication rates achieved with standard triple therapy [5]. Ever since then,

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similar results were reproduced by other researchers in different parts of the world [6]. The sequential regimen appeared to be superior to the standard triple therapy when administered for seven [7,8] or for ten days [5,9]. The sequential therapy yielded almost the same significance when it was used for 10 or for 14 days [10]. It was also noted that sequential treatment has not been affected by the characteristic risk factors for triple therapy failure such as the absence of the gene Cag A or smoking [7]. Cure rates were also similar for non-ulcer dyspepsia and ulcer patients [11]. Although clarithromycin resistance may reduce sequential therapy efficacy, yet the reported reduction in eradication rates due to clarithromycin resistance was far less than that in the reduction in eradication rates for the triple therapy for the clarithromycin resistant patients [12]. Furthermore, reported side effects from sequential therapy were mild and less frequent, however they were not significantly different from those described with triple therapy.

The mechanism underlying sequential therapy's superiority remains unclear. Initial therapy with amoxicillin alone might increase the efficacy of clarithromycin in the second phase of treatment; by virtue of its direct antibacterial effect, reducing and weakening *H. pylori* colonisation and eliminating the clarithromycin resistant strains. The addition of, metronidazole, in the second phase enhances the lethal effect of clarithromycin in this regimen, and this could be another contributing factor as well.

This paper presents a work done in the UAE, to compare the standard triple therapy vs the sequential therapy with a view to restore the previously achieved eradication rates, and its impact on clinical response, compliance and possible adverse reactions that may emerge with antibiotic use.

The overall eradication rates and their 95% confidence intervals were obtained by intention-to-treat. Quantitative variables were given as mean ± SD. A univariate analysis including age, sex, body mass index, ethnicity, smoking habit (active smoker *vs* non-smoker), baseline disease (organic *vs* functional), was performed. Variables achieving a *p*-value lower than 0.3 were included in a multivariate analysis performed by logistic regression. *p*-values lower than 0.05 were considered significant. Calculations were performed using the IBM SPSS 20.0 software.

Patients and methods

We conducted a prospective randomised open label observational study to compare the efficacy of standard triple therapy (STT) versus sequential therapy (ST). The study extended over a year period from September 2011 to 2012.

The primary end point was to compare the successful cure rates for both groups of patients which were determined between 6 and 8 weeks after completing the treatment. Eradication rates were analysed in two subsets of patients: patients who were naïve to treatment and those who were retreated. Secondary end points in this study were evaluation of the clinical response to successful eradication of *H. Pylori* infection and the frequency of side effects when they occur in both groups.

Inclusion criteria

All consenting patients, 12–80 years of age who presented with upper gastrointestinal symptoms, and were diagnosed to have dyspepsia (functional or organic) attributed to *H. pylori* infection with a solid evidence were included. *H. pylori* infection was confirmed either upon upper GI endoscopy or by the ^{14}C Urea breath test (UBT). For those who did upper GI endoscopy the diagnosis was established by CLO urease, histology or both. For those who did not have an upper GI endoscopy done for them, the diagnosis was established by UBT.

Exclusion criteria

Standard exclusion criteria were applied to assure that safety of treatment was considered when patients were given the treatment for *H. pylori* infection and to exclude any comorbid illness that might affect the response to medications. Exclusion criteria included pregnancy and lactation, history of allergic reactions to any of the used medications, chronic renal or hepatic insufficiency, neoplastic disease, patients with severe immune deficiencies and patients who were on chemotherapy. Patients who had received clarithromycin for any reason within the preceding six months prior to enrolment and patients diagnosed by the office serology test only, were also excluded from the analysis.

Proof of eradication was documented by a negative UBT performed 6 weeks or later from the completion of treatment. Values obtained as determined by Heliprobe II, and defined as counts per million were taken as a reflection of the intensity of colonisation. The drop in values post treatment was used to assess response to treatment.

Results

Group A

A cohort of 231 subjects who satisfied the inclusion and exclusion criteria was recruited in this group. Females prevailed slightly (1.2:1), the mean age was 37.3 with a range of 12–66 years. The mean body mass index was 27.4 Kg/m [2] (range 18–42) with (31.6%) having a normal BMI (35.1%) overweight and (33.3%) being frankly obese (Table 1a). Clinical findings are summarised in Table 1b.

Each patient was given a standard clarithromycin based triple therapy for 10 days. Patients were seen for follow up 6–8 weeks after completing the eradication treatment for clinical assessment and to do the UBT.

Group B

A cohort of 254 subjects who satisfied the inclusion and exclusion criteria was randomly assigned to this arm. Male to female ratio was (1.1:1) the mean age was 38.8 with a range of 12–74 years. The mean body mass index was 26.9 Kg/m [2] being normal in (36.2%), overweight in (33.9%) and frankly obese in (29.9%) (Table 1a). Clinical findings are summarised in Table 1b.

Each patient was given a twice daily standard dose of a proton pump inhibitor, for ten days. Amoxicillin 1000 mg twice daily was added to the proton pump inhibitor in the first five days of treatment only. Clarithromycin 500 mg and metronidazole 400 mg twice daily were given in the subsequent five days to replace amoxicillin. Patients were seen again after 6–8 weeks from completing the treatment for clinical assessment and to do the UBT.

The eradication rate achieved for patients in group A (STT) was 68%. The eradication rate for patients of group B (ST) was 84.6% which was significantly higher than the eradication rate for the standard triple therapy group ($p < 0.001$) (Fig. 1).

Table 1a
Demographic details of the two treatment groups.

	Standard triple therapy	Sequential therapy
Female:Male	1.2:1	1:1.1
Mean age	37.3 (12–66) years.	38.8 (12–74) years.
BMI (mean)	27.4 Kg/m^2 (18–42)	26.9 Kg/m^2 (19.4–38)
Normal BMI	31.6%	36.2%
Overweight	35.1%	33.9%
Obese	33.3%	29.9%

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