Effectiveness of sequential v. standard triple therapy for treatment of Helicobacter pylori infection in children in Nairobi, Kenya

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Background. Once the diagnosis of Helicobacter pylori is confirmed, treatment requires at least two antibiotics and an acid inhibitor for a minimum of seven days. Unfortunately, treatment failures are being frequently reported. Treatment regimens that include sequential administration of antibiotics with acid inhibitors have been developed to try and increase the rate of eradication.

Objective. To determine the effectiveness of a novel 10-day sequential therapy compared with the standard 10-day triple therapy for treatment of H. pylori infection in children.

Methods. A double-blinded, randomised, controlled trial was conducted. Children under the age of 16 years with recurrent abdominal pain associated with dyspepsia and diagnosed with H. pylori by histology were randomly allocated either to a 10-day sequential treatment regimen or to a 10-day conventional triple therapy. Analysis of the outcome of this study was based on clinical improvement and confirmed H. pylori eradication based on stool H. pylori antigen detection and/or repeat endoscopy.

Results. Of the 71 patients included in the analysis, 45 (63.4%) were given the 10-day conventional treatment while 26 (36.6%) received the 10-day sequential treatment. There was no difference in clinical improvement after treatment in the two therapies. However, there was a significant difference in the eradication of H. pylori between the conventional v. sequential regimens (48.8% v. 84.6%, respectively; p=0.02, odds ratio 0.19).

Conclusion. The sequential treatment had a significantly higher H. pylori eradication rate than the conventional treatment.


Helicobacter pylori are Gram-negative, spiral, flagellate bacilli that cause acute and chronic gastritis and peptic ulcer disease in both children and adults.1 H. pylori was first isolated in 1983 by Warren and Marshal.2 This discovery was a major breakthrough in the management of dyspepsia.3 The organism has also been recognised as a class 1 gastric carcinogen and infection at a younger age is thought to increase the risk of developing gastric cancer.4 Children are infected with H. pylori at a much younger age in developing countries, some of which report higher rates of gastric cancer.5

The prevalence of H. pylori infection varies from 20% to 50% in industrialised countries,6 while studies have shown that the prevalence is high in regions of Africa and Asia. Therapy can be complicated by various factors including drug costs and availability, treatment side-effects, and the presence of bacterial strains that are antibiotic resistant.7

Antibiotic resistance is an ever-increasing problem in the treatment of most microbial infections including H. pylori. The widespread and sometimes indiscriminate use of antibiotics in developing countries has resulted in a higher prevalence of resistance than in industrialised countries.8 New antimicrobial agents are being developed to overcome the problem of antibiotic resistance in bacterial pathogens, such as a combination of antibiotics with plant extract and other natural products that possess antimicrobial activity.9 The standard and most recommended treatment for the eradication of H. pylori, in all international guidelines, is triple therapy using a combination of two antibiotics (clarithromycin plus amoxicillin or metronidazole) and a proton pump inhibitor (PPI) for at least 7 days.10 However, a recent meta-analysis that included over 53 000 patients showed that the eradication rate after a standard triple treatment is currently below 80%.11 Thus eradication is not achieved in at least 1/5 patients, prompting research on sequential therapy.

A novel 10-day sequential treatment regimen comprising a PPI and amoxicillin double therapy for 5 days followed by a PPI, clarithromycin and tinidazole triple therapy for a further 5 days has been shown to achieve H. pylori eradication rates of 95% and 97% in European adults and children, respectively. This regimen, compared with the conventional triple therapy, improved eradication rates by 18% and 22%, respectively, was well tolerated, safe and had good compliance in both adults and children.12,13

Local data on eradication rates are not available but anecdotal evidence suggests that there are increasing failure rates to the standard triple therapy regimens.

Objective

To establish whether there was any difference in the treatment of H. pylori infection using the 10-day sequential therapy v. the 10-day conventional triple therapy, based on clinical improvement of the patients and H. pylori eradication.
Methods

Study design
A double-blinded, randomised, controlled trial was conducted on children under the age of 16 years.

Study setting and participants
The study was carried out at the Paediatric Gastroenterology Clinic, Aga Khan University Hospital, Kenya between March 2007 and October 2007. Children under the age of 16 years presenting with recurrent abdominal pain (defined as abdominal pain present for at least three months) associated with dyspepsia (pain or discomfort in the upper abdomen) and diagnosed with H. pylori by histology were recruited from the clinic on a consecutive basis. Children previously treated for H. pylori infection, those who had taken any antibiotic, PPI or H2 receptor antagonist 4 weeks prior to the study, and children with known allergies to antibiotics, were excluded.

Permission for this study was granted by the Aga Khan University Hospital Research and Ethics Committee. Informed consent was obtained from the patients or caregivers prior to recruitment. All interviews were carried out in private and all records were accessible only to the investigators.

Data collection
An upper endoscopy was done on all children with recurrent abdominal pain and dyspepsia using the standard paediatric gastroscope under deep sedation with propofol administered by an anaesthetist, and the endoscopy findings were documented. Two biopsy specimens each from gastric antrum and body were obtained and placed in 10% buffered formalin for histopathology. All sections were Giemsa stained to detect H. pylori in 10% buffered formalin for histopathology.

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The sequential therapy group had a mean age of 8.9 ± 3.11 years (SD ±3.096). Final analysis was done on 45 patients (63.4%) in the conventional treatment arm and 26 (36.6%) in the sequential treatment arm (Table 1). There were more males than females (53.5% and 46.5%, respectively) and just more than a third of the patients were >8 years of age. In total, 45/71 (63.4%) patients received conventional therapy while 26 (36.6%) were given sequential treatment.

After randomisation, the group that received the conventional therapy had a mean age of 9.1 years (SD ±3.12; standard error (SE) ±0.46). The sequential therapy group had a mean age of 8.81 years (SD ±3.12; SE ±0.61). The other

Recruited with upper abdominal pain for >3 months, histology positive for H. pylori (n=104)

Randomly allocated to sequential treatment (n=52)

6 week follow-up (n=41, 76%)

Repeat stool antigen or histology for H. pylori (n=26/41, 63%)

Randomly allocated to conventional treatment (n=52)

6 week follow-up (n=49, 94%)

Repeat stool antigen or histology for H. pylori (n=45/49, 92%)

Fig. 1. Study flow diagram.
demographic factors analysed are shown in Table 2. Although the gender ratio was similar in the two groups, there were more children in the 8 - 11-year and fewer children in the 12 - 16-year age categories in the sequential group v. the conventional group.

Clinical improvement was observed in 88.7% of patients after treatment, while eight (11.3%) did not show improvement. Forty patients (88.9%) in the conventional treatment arm showed clinical improvement v. 23 (88.5%) of those in the sequential treatment arm. There was no significant difference in clinical improvement between the two regimens (p=0.95; odds ratio (OR) 1.04). Neither gender (p=0.19) nor age (p=0.79) of the participants was significantly associated with clinical improvement (Table 3). Clinical improvement (resolution of dyspeptic symptoms) was seen in almost 90% in both treatment groups. Neither age nor sex differences were noted in the two groups.

Of the 71 patients, _H. pylori_ was eradicated in 84.6% of the children who had received the sequential treatment v. 48.8% of those on conventional treatment, the difference being highly significant (p=0.02) (Table 4).

Sequential therapy resulted in significantly higher eradication of _H. pylori_ (84.6%) than conventional therapy (48.8%). Very few patients consented to a repeat endoscopy.

### Discussion

There is a general consensus that more effective first-line treatment regimens for _H. pylori_ are required to bring the eradication rate closer to 100%. Standard triple therapy falls well short of this target, even when it is administered for 14 days.\(^{[14]}\)

This study assessed both clinical improvement of the patient and _H. pylori_ eradication after treatment. There was no difference in clinical improvement for both regimens, suggesting that resolution of symptoms after treatment did not necessarily mean eradication of the organism.

Slightly more than a third of the patients were in the 4 - 7-year age category, suggesting early acquisition of _H. pylori_ and early inflammatory changes. This has been noted in studies from developing countries.\(^{[21]}\)

With reference to _H. pylori_ eradication, patients on the 10-day sequential therapy arm had a much higher _H. pylori_ eradication rate than patients who received conventional treatment (84.6% v. 48.8%, respectively). There was a significant difference in eradication of _H. pylori_ between the two regimens (p=0.02). Previous studies have also shown that sequential therapy achieves better eradication rates than 7-day triple therapy. In a study by Zullo et al.,\(^{[12]}\) eradication rates for the sequential therapy were 92% by intent to treat and 95% per protocol. A recent study from Turkey\(^{[15]}\) found that the eradication rate was higher for sequential therapy (93.7%) than standard therapy (46.4%). These findings are similar to the findings in our study. However, the eradication rates with sequential therapy in our study (84.6%) were still lower. This may be related to the more prevalent misuse of antibiotics in developing countries resulting in more resistant bacterial strains.\(^{[16]}\) The observed low eradication rates on the standard therapy regimen in this study, prompts re-evaluation of the currently used first-line treatment for _H. pylori_ infection in Kenya.
The superiority of sequential therapy over standard therapy may be related to a reduction in bacterial load with the initial phase of treatment with amoxicillin, which reduces the chances of developing mutations causing metronidazole and clarithromycin resistance.\textsuperscript{[17]} A notable finding was resolution of abdominal symptoms in almost 90% of patients in both treatment arms, despite a much lower eradication rate in the conventional treatment group. This may be explained by the antacid effect of the PPI causing symptomatic relief of dyspepsia. Unfortunately, we could not follow the patients for long enough to ascertain if their symptomatic relief was sustained. There were more patients in the 12 - 16-year age category in the sequential than the conventional group in the final analysis. Whether this made a difference in the eradication rates is difficult to predict, but it is expected that teenagers would be more likely to complain if symptoms persisted.

This study is the first in Kenya to assess the effectiveness of the sequential therapy in children in seeking to improve management of \textit{H. pylori} infections.

**Study limitations**

A major setback was that not all patients attended their six-week review. The study protocol also entailed a repeat endoscopy and/or stool \textit{H. pylori} antigen testing at this six-week visit to assess eradication of \textit{H. pylori}. Unfortunately, a substantial number of parents would not agree to repeat testing, especially endoscopy, as the children’s symptoms had improved. After unblinding of the study, it was noted that most of those patients who were lost to follow-up were patients from the sequential treatment arm. Follow-up telephone calls to a few of the parents of these non-attendees confirmed that the patient was symptom free and that the parent did not see the need for a repeat visit and/or endoscopy. It is difficult to predict why more children in the sequential group did not attend the review \textit{v.} the conventional group. It is known that compliance among patients who improve is poor compared with those who are still unwell while cultural practices may also play a role.\textsuperscript{[16,19]} It is tempting to suggest that because the children in the sequential group felt much better than their counterparts in the conventional group, they failed to come for their follow-up visit.

Based on findings from this study, there is a need to conduct a larger randomised, controlled trial in various settings to fully confirm our findings. However, we recommend that a sequential therapy regimen should replace the standard triple therapy treatment for \textit{H. pylori} infection in children in Kenya.

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