Abstract

*Helicobacter pylori* infection is common in paediatric population. The overall prevalence varies from 10% in developed countries to 80% in developing countries at the age of 10. The association of this infection with gastritis, peptic ulcerations and gastric cancer has warranted guidelines on the treatment of this infection in children. **Aim of study:** To determine an effective eradication regimen for *H. pylori* in children with the shortest duration to promote compliance. **Patients and methods:** We conducted a prospective randomised study comparing ranitidine bismuth citrate (RBC) – based triple therapy given for 4 days vs 7 days in 200 children with mean age 12.5 years (92 boys, 108 girls). *H. pylori* infection was diagnosed by $^{13}$C-urea breath test ($^{13}$C-UBT). Children with body weight $>$40 kg received amoxicillin 1 g bid plus clarithromycin 500 mg bid plus RBC 400 mg bid. Dosages of antibiotics were reduced by half in those patients with body weight less than 40 kg while that of RBC remained the same. Outcome measures included success of eradication determined by repeat $^{13}$C-UBT in 6 weeks, drugs adverse effects and patients’ compliance. **Results:** Ninety-three (46.5%) and 107 (53.5%) of children were randomised to receive 7-day and 4-day regimen respectively. All 200 children completed the prescribed treatment according to the protocol. 89.2% of children who had received treatment for 7 days showed successful eradication comparing with 78.5% in those who received treatment only for 4 days (p-value <0.05). There was no statistical difference in terms of side effects between the two regimens. **Conclusions:** RBC-based triple therapy is an effective and well tolerated treatment for eradication of *H. pylori* in children. Seven days of treatment is the shortest duration to ensure effective eradication with the currently available therapeutic agents.

Key words  
Children; Eradication; *Helicobacter pylori*

Introduction

*Helicobacter pylori* infection is a worldwide medical issue in paediatric population. Cross-sectional studies suggest that the infection is usually acquired in early childhood. The major risk factor for acquiring the infection is poor socioeconomic conditions during childhood. In developing countries, up to 70-80% of children are infected by the age of 10 in contrast to the overall prevalence of less than 10% in children living in the developed world. However, the prevalence can significantly increase up to 50% in those socially deprived children in developed countries. As in adults, *H. pylori* infection is associated with chronic gastritis and peptic ulcerations in children. Long term healing of ulcer disease can be achieved following eradication of the infection. The association of *H. pylori* infection with gastric carcinoma and the fact that *H. pylori* has been classified as a group I carcinogen by the World Health Organization has raised serious concerns and questions about the management of this infection in children. It remains a contentious issue whether it is cost-effective to eradicate *H. pylori* in every infected child based on the
potential risk of progression to gastric carcinoma in adult life. 9,12,13 While further research works are pending to clarify the current controversies, guidelines on the treatment of this infection in children are warranted. However, data from the literature remains insufficient as controlled trials with adequate patient numbers are scarce and results from different studies are inconsistent. In children compliance is of particular concern, as paediatric patients will not tolerate a prolonged course of treatment. It is the aim of this study to determine a short but effective therapeutic regimen for eradication of *H. pylori* in children.

**Methodology**

**Patients**

From 1997 to 2000, 232 consecutive children, aged 7 to 15 years, were diagnosed to have *H. pylori* infection using $^{13}$C-urea breath test ($^{13}$C-UBT). These included children presenting to the Paediatric Surgical clinic of the Prince of Wales Hospital with gastrointestinal symptoms warranting investigation for *H. pylori* infection and asymptomatic children found to be *H. pylori*-infected in an epidemiological study conducted by the same unit, whose parents strongly requested for *H. pylori* eradication therapy. Informed consent to enter into the therapeutic trial was obtained from parents of 200 children. There were 92 boys and 108 girls with a mean age of 12.5 years.

$^{13}$C-urea Breath Test

All the children had a 4-hour fast and received test meal with glucose polymer solution. Baseline breath sample was collected. $^{13}$C-urea was then given at the dosage of 50 mg for those with body weight <50 kg or 75 mg for body weight >50 kg. Another breath samples were collected at 30 minutes after. Samples were analyzed by isotope ratio mass spectrometer and positive result was defined by a value of 3.5 delta over baseline.

Randomisation and Treatment Protocol

The 200 children were prospectively randomised by computer to receive either a one-week or 4-day *H. pylori* eradication regimen. The treatment consisted of three therapeutic agents. Children with body weight >40 kg received ranitidine-bismuth-citrate (RBC) 400 mg bid, amoxicillin 1 g bid and clarithromycin 500 mg bid. For children with body weight less than 40 kg the dosages of amoxicillin and clarithromycin were reduced by half while that of RBC remained the same.

**Parental Counselling and Phone Interview**

A senior paediatric surgeon prior to the commencement of treatment interviewed the parents of all the 200 children. The importance of drug compliance, all possible drug adverse effects, as well as the unproven benefits of eradication of *H. pylori* in asymptomatic children were very carefully explained. Informed consent for recruitment into the study and randomisation was obtained. A dedicated research nurse was present during the parental counselling and informed consent, and would be responsible to phone all the parents during and at the end of the treatment so as to ensure good drug compliance and that every single side effect be well documented.

Evaluation of Treatment Success

All 200 children had a repeat $^{13}$C-UBT six weeks after the completion of treatment to evaluate the eradication rates in both treatment groups.

**Results**

Ninety-three out of 200 children (46.5%) were randomised to receive one-week regimen while 107 (53.5%) received 4-day regimen. All 200 children completed the prescribed treatment according to the protocol. Of the 107 children randomised to receive 4-day regimen, 84 (78.5%) were found to have successful eradication of *H. pylori* as demonstrated by the negative results of $^{13}$C-UBT. Eighty-three out of 93 (89.2%) who had received one-week regimen showed successful eradication. The difference of the two treatment groups were statistically significant (p-value=0.041). There was no difference between males and females in the eradication rates in both treatment groups (Table 1).

On direct questioning during phone interview, 49 of the 200 children (24.5%) described to suffer from one or more side effects which included loose bowel motions (18%), dyspepsia (19.5%), headache (9%), mild skin rash (1%). All the side effects were mild and self-resolving and all children completed the treatment. It was also noted that 66.5% of the patients noticed blackening of stool as a result of the intake of bismuth compound. The one-week and 4-day regimen accounted for 44.7% and 55.3% of the overall side effects respectively. There was no statistical difference in terms of side effects between the two groups (p-value=0.48) (Table 2).
Discussion

Epidemiological studies have shown clear evidence that *H. pylori* infection is primarily acquired in childhood.\(^1\)\(^3\) The fact has shifted the focus of investigation from adults to children. However, to date the knowledge about this infection in children remains limited. The mode of acquisition, the natural history of the infection, the relationship between infection and symptoms, are still poorly understood. In adults, the combination of a proton-pump inhibitor (PPI) plus two of the following antibiotics: clarithromycin, amoxicillin and metronidazole, has been advocated as the first-line eradication therapy in several consensus conferences and meta-analysis has shown an eradication rate of 80% on intention-to-treat analyses.\(^14\)\(^-\)\(^17\) However, data in the literature is insufficient to determine the ideal treatment for children because randomised controlled trials are scarce and most of the reports consist of open case series. Oderda et al has recently published a systematic review of *H. pylori* eradication regimens in children.\(^18\) From 1987 to 2000 only 30 full articles and 16 abstracts were found involving 870 and 1552 children respectively, compared with over 1000 treatment arms that have been studied in adult population in last decade.

In early reports on treatment of *H. pylori* infection in children, dual therapy with or without bismuth salts was shown to have an eradication rates varying from 43% to 80%.\(^19\)\(^-\)\(^23\) However such regimens were usually given for 4 to 8 weeks. The long duration of treatment and the strong taste of ammonia associated with liquid bismuth invariably resulted in poor compliance in children. The experience of bismuth-based triple therapy was reported by Cucchiara et al\(^24\) and Walsh et al\(^25\) in 30 and 22 patients with an eradication rate of 75% and 95% respectively. Suboptimal drug compliance accounts for the discrepancy of the two reports. In the late nineties, antisecretory agent-based triple therapy including a proton-pump inhibitor and two antibiotics was reported in several open trials in children. Eradication rates varied from 63% to 92%.\(^26\)\(^-\)\(^29\) Besides the inconsistency of the results, the drug durations were different and the patient numbers were small in most of the series. Recently, Gottrand et al\(^30\) has published their results of a prospective randomised study on the efficacy of omeprazole plus amoxicillin and clarithromycin given for one week in children. Eradication rate for such regimen was 74.6% in intention-to-treat analysis in 63 children. All these results suggest that antisecretory agent-based triple therapy given in one week in children probably has similar efficacy as in adults. However, there are still uncertainties in interpreting the data in the literature. Firstly, the series of studied children are usually small because most of the trials were conducted in developed countries where the prevalence of infection is low and only very few are randomised studies. Secondly, unreliable drug compliance which happens commonly in children adds extra difficulties in analyzing the efficacy of different treatment protocols. In our study design, we increased the sample size by recruiting both symptomatic and asymptomatic children who had been shown to be *H. pylori*-infected in previous epidemiological study. Parents had been counseled about the unproven benefits of *H. pylori* eradication in asymptomatic children and informed consent was obtained. \(^13\)C-UBT test has been proven to be accurate

<table>
<thead>
<tr>
<th>Table 1 Results of eradication</th>
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<tbody>
<tr>
<td><strong>No. of children receiving the regimen</strong></td>
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<td>No. of children with successful eradication</td>
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<tr>
<td>No. of children with failed eradication</td>
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<td>p-value=0.041</td>
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<th>Table 2 Drugs adverse effects</th>
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<td><strong>7-day regimen</strong></td>
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<tr>
<td>Loose bowel motions</td>
</tr>
<tr>
<td>Dyspepsia</td>
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<tr>
<td>Headache</td>
</tr>
<tr>
<td>Skin rash</td>
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<tr>
<td>Blackening of stool</td>
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<td>NS=no statistically significant difference</td>
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Based on the results, we can conclude that the 7-day regimen has a higher eradication rate compared to the 4-day regimen. However, further studies with larger sample sizes are needed to confirm these findings.
in diagnosing *H. pylori* infection in children and evaluating the success of eradication after treatment.\(^3\) Its use promoted the acceptance of this study by the patients and their parents. In this study drug compliance was ensured by two measures: 1) Before treatment the parents were interviewed by a senior paediatric surgeon about the importance of completion of treatment and the potential drug adverse effects. 2) The parents were interviewed on phone by our research nurse during the treatment period and at the completion for further counselling and monitoring of compliance. With such measures, all children completed the treatment according to our protocol.

Meta-analyses suggest that ranitidine bismuth citrate (RBC) when used in conjunction with two antibiotics works equally well as proton pump inhibitor-based triple therapy.\(^\text{17,32}\) Some studies have shown that RBC-based triple therapy may be less influenced by the antibiotic resistance than their PPI-based counterparts.\(^\text{33,34}\) Although data of RBC-based therapy in children is scarce, its components of ranitidine and bismuth have been widely used in paediatric population before. In our study, an eradication rate of 89.2% was achieved when RBC plus amoxicillin and clarithromycin were given to children for 7 days. The result corresponds very well to adult series. More side effects were documented in this study than the data in the literature and were most probably a result of direct questioning on the phone interview. Although they were usually mild and well tolerated in children, this signifies that no treatment protocols are without risk and further studies are required to better define indications for eradication treatment for *H. pylori*-infected children. The common finding of blackening of stool as a result of bismuth compound emphasises the importance that both the parents and patients should be warned about this prior to commencement of treatment.

This prospective randomised study in 200 children with optimal compliance allows us to conclude that ranitidine bismuth citrate plus amoxicillin plus clarithromycin given for one week is an effective and safe regimen to eradicate *H. pylori* infection in children. Efficacy drops significantly when the therapeutic agents are given for less than a week. The simple way of administration and short treatment duration promotes compliance in paediatric population. It should never be overemphasised that good compliance is the key for successful treatment and this depends on both an appropriate therapeutic regimen and adequate parental counselling by enthusiastic clinicians.

References

17. Laheij RJ, Rossum LG, Jansen JB, Straatman H, Verbeek AL. Evaluation of treatment regimens to cure *Helicobacter pylori*


