A pilot study of a randomized controlled trial of pragmatic eradication of *Helicobactor pylori* in primary care

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SUMMARY

We report on a pilot study for a randomized control trial of pragmatic eradication of Helicobacter Pylori in primary care. Although the sample size is small, pragmatic eradication is likely to be cost-effective for patients with documented or suspected peptic ulcer disease on maintenance acid suppression therapy in primary care.

Introduction

ERADICATION of *H. Pylori* in patients with peptic ulcer disease dramatically reduces the rate of complications and recurrences.[1] Despite the high prevalence of *H. Pylori* in patients with peptic ulcer disease,[2] and the high associated drug costs for acid suppression treatment, eradication therapy is usually only recommended after a diagnostic test.[3] It is likely that this treatment innovation, like the use of H_2 blockers in dyspepsia, will be used pragmatically with time, particularly in primary care where access to investigations is often limited. However, the costs and benefits of pragmatic eradication are not yet established. We report a pilot study to determine the cost-effectiveness of pragmatic eradication of *H. Pylori* in patients on maintenance acid suppression therapy for documented or suspected peptic ulcer disease in one general practice.

Method

The pilot study, which had ethical approval, was conducted in a four-partner, rural, dispensing, fundholding practice on the border of Nottinghamshire and Lincolnshire. Patients on maintenance acid suppression treatment (defined as three or more months of treatment with either H_2 blockers or proton pump inhibitors during the past year) were identified from the computerized prescribing records. The patients' usual general practitioner (GP) reviewed the medical records to identify patients suitable for pragmatic eradication. Patients were included if they satisfied any of the following criteria in the opinion of the patients' usual GP:

- A definite diagnosis of peptic ulcer disease on barium meal or endoscopy
- A clinical diagnosis of peptic ulcer disease on history or response to treatment
- A definite diagnosis of gastro-duodenitis on endoscopy, or
- A history of chronic dyspepsia that has not been investigated.

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Patients were excluded if they had a definite or clinical diagnosis of reflux oesophagitis, non-ulcer dyspepsia (i.e. normal investigations), or non-steroidal anti-inflammatory drug-related peptic ulcer disease, or had received previous eradication therapy. The number of prescriptions for acid suppression treatment for the six months prior to intervention was collected for all eligible patients.

Patients gave written consent and completed a validated questionnaire[4] to rate their current gastrointestinal symptoms. They were randomized by a blind assessor to one of two eradication regimens: an intervention group consisting of patients who would receive eradication therapy at the start of the study, and a control group consisting of those who would continue their usual treatment from their GP during the study and then be offered eradication at the end of the six-month study period. The eradication regimen used for patients with current gastrointestinal symptoms was 500 mg amoxycillin TDS, 20 mg omeprazole BD for two weeks, and 400 mg metronidazole TDS for one week. Patients who were asymptomatic at the time of eradication had 500 mg amoxycillin TDS, 20 mg omeprazole BD, and 400 mg metronidazole TDS each for a week. For patients with penicillin allergy, clarithromycin was used. There were logistical difficulties in obtaining and using appropriate placebo for this unfunded pilot study.

At the end of six months, patients completed a second questionnaire to rate their gastrointestinal symptoms. Patients who received eradication therapy completed a questionnaire on the effects and duration of eradication treatment taken. The questionnaire data were analysed by a blind assessor. A second set of data for acid suppression prescriptions were collected at the end of the six-month study period for all randomized patients. The records of patients who discontinued acid suppression treatment following eradication were reviewed 12 months after eradication to determine whether acid suppression treatment had been restarted.

The main outcome criteria, in order, were the number of patients who were able to stop maintenance acid suppression treatment for at least six months, a reduction in acid suppression treatment costs, and a reduction in reported gastrointestinal symptoms. Data for investigations, consultations, secondary care referrals, and hospital admissions were collected but were too few to allow any meaningful analysis. The medication was priced according to the January 1995 edition of MIMS (Monthly Index of Medical Specialists).

The data were analysed on an intention-to-treat basis. The Mann-Whitney test was used to test differences between the changes in individual drug costs and symptoms within each group. As this was a pilot study conducted in one practice, all potential patients were invited to participate. The eventual sample size of 15 patients in each group had an 80% power to detect a 50% reduction in the use of acid suppression treatment (from 99% to 49%) at the 0.05 significance level (two-tailed).

Results

Of the 5634 patients registered with the practice, 213 (4%, all

adults), received a prescription for acid suppression treatment during the previous year. One hundred and seventeen patients (2%) had received three or more prescriptions, meeting our definition for maintenance therapy. On doctors' review, 49 patients (42%) met the inclusion criteria and were considered suitable for pragmatic eradication. Of these, 31 patients (63%) agreed to take part and were randomized. Table 1 shows the baseline characteristics of the 16 patients randomized to the intervention group and the 15 patients randomized to the control group. Twelve patients in the intervention group took the eradication therapy and four did not. Of the 15 patients randomized to the control group, three insisted on receiving eradication therapy at the start of the study (i.e. at the same time as the intervention group), which resulted in imperfect randomization. Five patients in the intervention group and one from the control group were able to discontinue acid suppression treatment. This difference was not statistically significant (χ^2 (with Yates correction) = 1.63; $P = 0.17$). None of these patients needed to restart treatment over the next 12 months. There was a significant reduction in the costs of acid suppression treatment for the intervention group for the six months before and after the intervention, compared with any change found in the control group (Mann–Whitney U = 70.5; $P = 0.05$, Table 1). All 31 randomized patients completed the first questionnaire for gastrointestinal symptoms and 25 patients (81%) returned the second questionnaire. Apart from patients in the intervention group reporting a significant improvement in reflux symptoms (Mann–Whitney U = 27.0; $P = 0.02$), there were no other significant changes in gastrointestinal symptoms (Table 2). Of the 12 patients in the intervention group who received eradication therapy, nine completed the course but only three patients did so without any side effects. In total, eight patients reported side effects; three reported diarrhoea, two reported sore mouth, two reported stomach pains, and one reported nausea and headache.

Discussion

To our knowledge, this is the first study of pragmatic eradication of *H. Pylori*. We have shown that pragmatic eradication is likely to be cost-effective for patients with documented or suspected peptic ulcer disease on maintenance acid suppression therapy in primary care. If our results from a community sample are representative, there will only be a few patients in each practice likely to need pragmatic eradication, which makes such an initiative

Table 2. Gastrointestinal symptoms at randomization and six months after intervention for cases and controls.

	Mean symptom score[a]		
Gastrointestinal symptoms	Cases (n = 16)	Controls (n = 15)	P-value[b]
Reflux			
At randomization	1.8	1.7	0.02
After six months	1.5	1.8	
Belching			
At randomization	1.5	2.2	0.18
After six months	1.4	1.7	
Bloating			
At randomization	1.7	1.8	0.51
After six months	1.4	1.5	
Hunger pains			
At randomization	1.4	1.6	0.10
After six months	1.2	1.9	
Nausea			
At randomization	1.4	1.7	0.69
After six months	1.3	1.5	
Rumbling			
At randomization	1.6	1.9	0.18
After six months	1.3	1.7	
Stoamch pains			
At randomization	1.5	1.9	0.37
After six months	1.4	1.8	
Heartburn			
At randomization	1.4	1.8	0.12
After six months	1.5	1.5	

[a]Mean score for gastrointestinal symptoms where 0 = no discomfort; 1 = mild–moderate discomfort; 2 = severe discomfort.
[b]Two-tailed P-value of difference between symptoms at baseline and six months for cases compared with controls using Mann-Whitney test corrected for ties.

Table 1. Characteristics and acid suppression treatment costs for cases and controls.

	Cases	Controls	P-value
Total number of patients randomized	16	15	–
Mean age	64.9	57.4	0.14[a]
Sex			
Female	8	11	
Male	8	4	0.34[b]
Number of patients who received eradication	12	3	–
Number of patients who stopped acid suppression treatment	5	1	0.17[b]
Median acid suppression treatment costs (£)			
For six months prior to intervention (IQR)	96 (82)	91 (39)	0.80[c]
For the six months after intervention (IQR)	83 (130)	109 (67)	0.16[c]
Median change before and after intervention (IQR)	-14 (55)	18 (37)	0.05[d]
Cost of eradication therapy (£)			
Total cost	497	118	–
Cost per person undergoing eradication	41	39	–

[a]t-test; [b]Fisher's exact test; [c]Mann-Whitney test for AST drug costs compared with controls; [d]Mann-Whitney test for differences between changes in individual drug costs for cases compared with controls.

manageable. This pilot study, limited by its imperfect randomization, small sample size and uneven distribution of men and women in the intervention and control groups, illustrates some of the difficulties in conducting randomized controlled trials in general practice.[5] However, as most decisions regarding the ongoing management of patients with dyspepsia occur in primary care, it is important that similar but larger randomized controlled studies are conducted within primary care to determine the true benefits and the real costs of *H. Pylori* eradication.

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