

Primary care

Randomised controlled trial of *Helicobacter pylori* testing and endoscopy for dyspepsia in primary care

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Abstract

Objective To determine the cost effectiveness of a strategy of near patient *Helicobacter pylori* testing and endoscopy for managing dyspepsia.

Design Randomised controlled trial.

Setting 31 UK primary care centres.

Participants 478 patients under 50 years old presenting with dyspepsia of longer than four weeks duration.

Interventions Near patient testing for *H pylori* and open access endoscopy for patients with positive results. Control patients received acid suppressing drugs or specialist referral at general practitioner's discretion.

Main outcome measures Cost effectiveness based on improvement in symptoms and use of resources at 12 months; quality of life.

Results 40% of the study group tested positive for *H pylori*. 45% of study patients had endoscopy compared with 25% of controls. More peptic ulcers were diagnosed in the study group (7.4% v 2.1%, $P=0.011$). Paired comparison of symptom scores and quality of life showed that all patients improved over time with no difference between study and control groups. No significant differences were observed in rates of prescribing, consultation, or referral. Costs were higher in the study group (£367.85 v £253.16 per patient).

Conclusions The test and endoscopy strategy increases endoscopy rates over usual practice in primary care. The additional cost is not offset by benefits in symptom relief or quality of life.

Introduction

The NHS spent £1.1bn on managing dyspepsia in 1998,¹ and 450 000 patients had endoscopy. If endoscopy is reserved for patients who test positive for *Helicobacter pylori*, it should maximise the yield of peptic ulceration (for which eradication therapy is effective²⁻³) and reduce overall endoscopy workload. Patients negative for *H pylori* can be given empirical acid suppression treatment.

Two non-randomised studies in secondary care have examined this "test and endoscopy" strategy. A retrospective cohort study found that positive *H pylori* test results were highly predictive of peptic ulcer and suggested that screening out negative patients could

have reduced endoscopy workload by 23%.⁴ A controlled before and after study found that test and endoscopy was as effective in reducing dyspeptic symptoms as the previous practice of endoscopy in all patients referred.⁵ However, the study did not follow up the whole screened cohort, and the control group consisted only of patients negative for *H pylori* who had had endoscopy. The groups are not therefore representative. Furthermore, all the patients examined in these two studies had been referred for endoscopy by their general practitioner. The test and endoscopy strategy has not been investigated in a randomised controlled trial, and there are no studies based in primary care.

Near patient testing allows general practitioners to base their initial management on the results of tests.⁶ However, there are few outcome studies of near patient tests in clinical decision making.⁷ A recent systematic review of *H pylori* tests in primary care showed that the Helisal rapid blood test has variable performance in primary care, with a sensitivity of 77-92% and a specificity of 56-69%.⁸ However, when the test was evaluated in the population local to our trial, the sensitivity was 89% and specificity 84%.⁹ Analysis with a Markov model suggested that the test would be cost effective.¹⁰ We therefore used the test in this study to determine the cost effectiveness of the test and endoscopy strategy in primary care.

Participants and methods

Participants

All patients aged 18-49 years who consulted their general practitioner with dyspepsia of more than four weeks duration were eligible for the trial. We excluded patients who had had endoscopy or a positive barium meal examination in the past three years, who were unable to give informed consent, or who were unfit for endoscopy. Dyspepsia was defined as epigastric pain or heartburn with or without nausea and bloating.¹¹

Randomisation and concealment of allocation

We randomised patients individually using sealed, opaque, sequentially numbered envelopes. The randomisation schedule was done on a 60:40 basis (study: control) and used a computerised random number sequence without blocking or stratification. We kept a log of numbers issued to practices.

Interventions

Patients were randomised to “test and endoscopy” or to usual management. The Helisal test (Cortecs Diagnostics, Deeside) was done by the general practitioner or practice nurse. Endoscopies on patients with positive results were carried out according to usual practice at open access services at six local hospitals. Patients with negative results were not referred for endoscopy but received empirical acid suppressing drugs chosen by their general practitioner.

Patients randomised to the control arm of the trial were managed according to the practitioner’s usual management strategy. This allowed outpatient referral to a specialist gastroenterologist but excluded initial referral to open access endoscopy. Patients in whom initial management failed could be referred for endoscopy after six weeks.

Outcomes

The main outcomes were effectiveness (assessed by symptoms) and costs of managing dyspepsia. We measured symptoms at recruitment and 15-18 months using the Birmingham dyspepsia symptom score, a postal measure previously validated in the local population.¹² We calculated the costs of dyspepsia from a health service perspective. We assessed use of resources in primary and secondary care for 12 months after randomisation by abstracting data from primary care case records. All data were double entered, and we verified inconsistencies by referring to the original case records.

We used a questionnaire derived from a validated measure for patients with peptic ulcer disease to measure quality of life in terms of pain, emotion, and social function.¹³ Patient satisfaction was assessed by a validated measure of satisfaction with the primary care consultation¹⁴ supplemented with additional questions relating to secondary care and endoscopy.

Analysis

We analysed data by intention to treat. A sample of 430 patients would detect differences of 2 units (SD = 4) in the dyspepsia score, 9 units (SD = 22) in the pain dimension of the quality of life, and 8 units (SD = 20) in the emotion and social dimensions, and would detect a reduction in general practice consultation rates from 3 to 1 a year (SD = 3). These estimates were based on a power of 90% at the 5% significance level and assumed 25% loss to follow up. Ethical approval was obtained from all local research ethics committees.

We recorded numbers of endoscopies, barium meal examinations, and primary care consultations from each patient’s notes. Drugs prescribed, including those for eradication of *H pylori*, were recorded as defined daily doses of drug per patient. Table 1 shows the unit costs for management, which we obtained from national reference sources for 1998.

Secondary analyses included comparison of procedure, rates of diagnosis, and use of services in the first year after randomisation; changes in quality of life; and patient satisfaction. We compared use of resources per patient using *t* tests¹⁸ and changes in symptom and quality of life scores from baseline to 18 months using two sample *t* tests. We identified variables relating to response rates using multiple logistic regression analysis and included them in analysis of covariance models

Table 1 Unit costs of care for dyspeptic patients used in economic analysis

Procedure	Mean cost (£)
Attendance at accident and emergency ¹⁵	98
Barium meal examination ¹⁶	246
Test for campylobacter-like organisms*	15
Dilation of oesophagus ¹⁶	323
Endoscopy ¹⁶	246
Helico G ELISA test*	2
Helisal rapid blood test†	17
Histology for <i>H pylori</i> *	8
Outpatient appointment ¹⁵	63
Primary care consultation ¹⁵	17
Prescribing costs ¹⁷	Individual defined daily doses

*Public Health Laboratory Service. †Cortecs Diagnostics.

to assess their effect on symptom and quality of life scores. Data were analysed with SAS (version 6.12).

Results

The 31 participating practices had a registered population of 195 700. Four hundred and seventy eight patients entered the trial; 285 were randomised to “test and endoscopy” and 193 to usual management. The patients were recruited over three years from May 1995 at a mean rate of 2 per 1000 registered practice population per month. Full details of ascertainment and recruitment by practice have been reported.¹⁹

Figure 1 shows the trial profile. Full data on use of resources were collected for 475 patients (99%). Records for three patients could not be traced. We obtained evaluable symptom scores and quality of life scores from 290 (61%) patients. Two hundred and seventy three (57%) patients returned satisfaction questionnaires. The baseline characteristics of the patients entered into the analysis were similar in the two randomised groups (table 2).

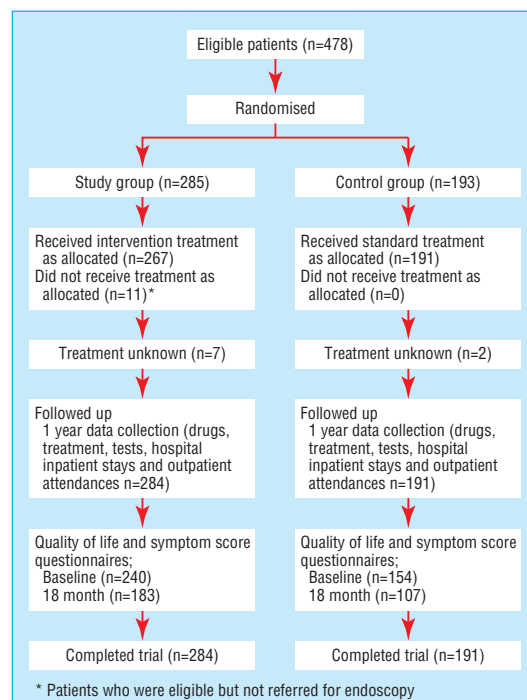


Fig 1 Trial profile

* Patients who were eligible but not referred for endoscopy

Table 2 Baseline characteristics of participants. Values are numbers (percentages) of participants unless stated otherwise

	Study (n=284)	Control (n=191)
Mean (SD) age (years)	36.9 (8.4)	37.1 (7.2)
Men	165 (58)	106 (55)
Smokers	126/276 (46)	75/182 (41)
Taking non-steroidal anti-inflammatories at study entry	7/284 (2)	6 (3)
Previous confirmed diagnosis of ulcer	13/280 (5)	13 (7)
Previous barium meal examination	50/281 (18)	26 (14)
Previous endoscopy	38/280 (14)	28 (15)
Endoscopy in past 3 years	6/280 (2)	2 (1)
Mean (SD) quality of life scores:		
Pain	57.1 (20.8)	54.2 (20.6)
Emotion	57.4 (18.2)	56.7 (18.1)
Social	69.0 (19.5)	67.2 (20.1)
Total	60.3 (15.2)	58.8 (16.2)
Mean (SD) symptoms score	10.1 (3.8)	10.6 (3.9)
Epigastric pain more than once a month	202/238 (85)	130/152 (86)
Heartburn more than once a month	161/238 (68)	103/152 (68)
Epigastric pain and heartburn more than once a month	149/238 (63)	92/152 (61)

Patients for whom accurate historical data could not be attained are excluded from comparisons of previous investigations.

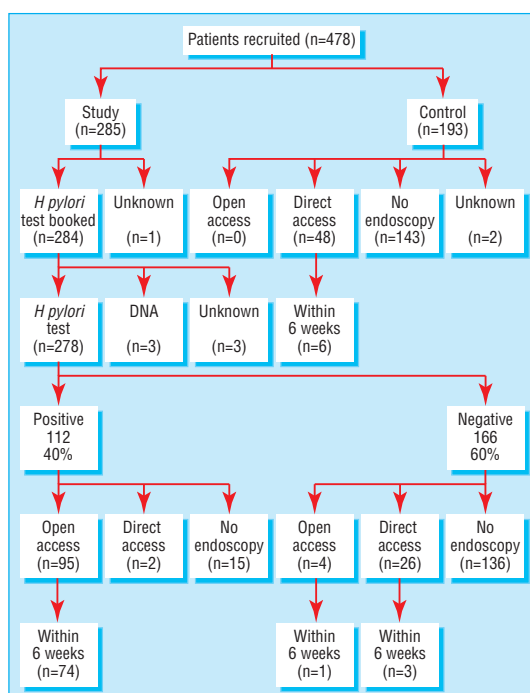


Fig 2 Numbers of participants having open and direct access endoscopy in study and control groups

Table 3 Diagnostic findings in patients who had endoscopy

Diagnosis at endoscopy	No (%) in study group (n=127)	No (%) in control group (n=48)	Difference in % (95% CI)	χ^2 (df=1)	P value
Normal	48 (38)	17 (35)	3 (-4 to 18)	0.1	0.7
Duodenal ulcer	17 (13)	3 (6)	7 (-2 to 16)	1.8	0.2
Gastric ulcer	4 (3)	1 (2)	1 (-4 to 6)		0.99†
Oesophagitis	22* (17)	15 (31)	-14 (-29 to 1)	4.1	0.04
Duodenitis	24 (19)	3 (6)	13 (3 to 22)	4.3	0.04
Gastritis	26 (20)	11 (23)	-3 (-16 to 11)	0.1	0.7
Gastric cancer	0	0	—	—	—

*Includes one patient with diagnosis of Barrett's oesophagus.

†Fisher's exact test.

Interventions and diagnostic findings

The Helisal test gave positive results in 40% (112/278) of patients (fig 2). The expected prevalence of *H pylori* in this population was 30%.¹² We used the test performance and the observed numbers of positive and negative results to calculate underlying prevalence and predictive values. With a sensitivity of 89% and a specificity of 84%, a positive rate of 40% reflected an underlying prevalence of 33%.⁹ On this basis, 27% of positive results and 6% of negative results would be false.

Overall, 127 (45%) of the study group had endoscopy compared with 48 (25%) of the control group. Figure 2 shows the numbers of patients who had open access endoscopy, consultant booked endoscopy, and no endoscopy. Fifteen patients who were positive for *H pylori* did not have endoscopy, of whom one refused, nine did not attend, and five were not referred. Of the 166 patients who were negative for *H pylori* in the test group, 30 (18%) had endoscopy during the 12 month follow up. Only one of these patients had open access endoscopy within six weeks. No control patients were inappropriately managed by test and endoscopy.

Among the patients who had endoscopy, significantly more peptic ulcers were detected by the test and endoscopy strategy than by standard management (21 (7%) v 4 (2.1%), $\chi^2 = 6.4$, df = 1, P = 0.011). Compared with the control patients, fewer patients in the study group had oesophagitis (17% v 31%, $\chi^2 = 4.1$, df = 1, P = 0.04) and more had duodenitis (19% v 6%, $\chi^2 = 4.3$, df = 1, P = 0.04; table 3).

Outcomes and costs

Symptoms and quality of life scores in the test and control groups significantly improved by 18 months. There was no evidence of a difference in the size of improvement between the groups (table 4). Non-respondents were more likely to smoke and were younger than respondents (smoking odds ratio = 1.63, 95% confidence interval 1 to 2.65; age 0.96, 0.93 to 0.99), but no difference in sex or baseline symptoms was observed. Analysis of covariance found that age and smoking had no significant effect on symptoms or quality of life. No significant differences were observed in the satisfaction questionnaire.

There were no significant differences in the use of drugs for dyspepsia between the groups (table 5). The numbers of outpatient attendances, general practice consultations, or regimens for eradication of *H pylori* did not differ significantly between the groups (table 6). Mean total costs were £367.85 for test and endoscopy and £253.16 for usual management. This increased cost of £114.69 per patient was not associated with any significant difference in effects. The test and endoscopy strategy was thus less cost effective than usual management.

Discussion

In contrast to non-randomised studies in secondary care,^{4 5} our study shows that the test and endoscopy strategy increased endoscopy referral rates by almost twofold over usual practice. Some of the increase in referral was due to the choice of non-invasive test. However, even if a carbon-13 urea breath test had been

used, at least 92 patients would have been referred (33% of the total would test *H pylori* positive) compared with the 69 (25%) expected from the rate in the control group.

We found that test and endoscopy did not improve dyspeptic symptoms or quality of life compared with usual management. The number of questionnaires returned was lower than expected, but the numbers returned were still large enough to detect the predefined differences with adequate power (80%). As the trial was subject to 39% attrition on the symptom and quality of life scores, the possibility of bias needs to be considered. Logistic regression analysis for the effect of differential follow up by age and smoking status had no significant effect on the result.

Investigation of dyspeptic patients by test and endoscopy increased the use of resources without producing benefit. Contrary to expectation, there was no fall in primary care consultations for dyspepsia or outpatient attendance in the test and endoscopy group. Most patients investigated had non-ulcer dyspepsia, and the number of peptic ulcers was too small to detect an effect of *H pylori* eradication. The low prevalence of treatable disease in patients under 50 means that relatively expensive methods of case finding such as endoscopy are not cost effective. Empirical prescribing is therefore the best treatment. In older patients, however, who have a greater frequency of treatable disease, a primary care based randomised controlled trial has shown that initial endoscopy may be cost effective compared with empirical management.²⁰

Although acid suppression is effective for undiagnosed dyspepsia, especially reflux symptoms,²¹ treatment with these drugs misses the opportunity to cure an important minority of patients with recurrent peptic ulcer disease due to *H pylori*. Eradication of *H pylori* may also have a small but important effect in non-ulcer dyspepsia, possibly by preventing the development of ulcers in susceptible patients.²² It is unclear whether a strategy to test for *H pylori* and then eradicate is cost effective as an initial management strategy in primary care. Future trials should evaluate the cost effectiveness of this strategy compared with empirical prescribing. Until then, near patient testing for *H pylori* is probably unwarranted in patients under 50.

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Table 4 Improvement in symptom and quality of life scores from baseline at 18 months

Score	Mean (SD) change from baseline at 18 months		Mean (95% CI) difference in change	P value*
	Study	Control		
Symptom	3.8 (4.8)	3.5 (4.5)	0.3 (-0.9 to 1.5)	0.61
Quality of life:				
Pain	16.9 (25.3)	14.3 (21.5)	2.5 (-3.5 to 8.6)	0.41
Social	9.6 (18.4)	10.3 (17.3)	0.7 (-3.9 to 5.2)	0.78
Emotion	5.4 (18.6)	7.2 (18.0)	1.8 (-2.8 to 6.4)	0.44

* t test.

Table 5 Mean (SD) defined daily doses of drugs for dyspepsia in study and control groups

Type of drug	Study	Control	Difference (95% CI)	P value*
Antacid	8.0 (19.9)	6.2 (12.9)	0.3 (-0.9 to 1.5)	0.26
H ₂ receptor antagonist	33.5 (66.6)	35.7 (82.4)	2.5 (-3.5 to 8.6)	0.75
Proton pump inhibitor	39.4 (80.0)	45.5 (100.5)	-0.7 (-5.2 to 3.9)	0.48
Prokinetic	3.5 (14.4)	4.6 (15.3)	-1.8 (-6.4 to 2.8)	0.43
Total	84.3 (112.8)	92.1 (127.0)	0.61 (0.47 to 0.75)	0.49

* t test.

Table 6 Mean (SD) use of resources per patient

	Study	Control	Difference (95% CI)	P value*
Endoscopy	0.59 (0.76)	0.28 (0.49)	0.31 (0.19 to 0.43)	<0.0001
Barium meal examination	0.06 (0.23)	0.05 (0.25)	0.004 (-0.04 to 0.05)	0.86
Outpatient appointment	0.23 (0.82)	0.21 (0.63)	0.01 (-0.13 to 0.15)	0.87
Inpatient episode	0.02 (0.26)	0.01 (0.1)	0.01 (-0.02 to 0.05)	0.40
<i>H pylori</i> test	1.35 (0.78)	0.74 (0.73)	0.61 (0.47 to 0.75)	<0.0001
GP consultation	3.26 (2.73)	3.30 (2.67)	0.03 (-0.46 to 0.53)	0.89
<i>H pylori</i> eradication	0.20 (0.45)	0.28 (0.52)	-0.07 (-0.16 to 0.01)	0.11

* t test.

Contributors: BCD, SW, and FDRH designed and managed the study. BCD, AW, and VR recruited the practices. Data were collected and entered by VR and LR. BCD, AW, and LR coded the data, and AR analysed the data. BCD did the economic analysis. All authors contributed to writing the paper. BCD is the guarantor.

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What is already known on this topic

Patients younger than 50 without *H pylori* infection are unlikely to have treatable disease detected at endoscopy

Such patients can be managed by acid suppression and reassurance alone

Test and endoscopy (referral of patients testing positive for *H pylori* in primary care) has been recommended as a way to reduce endoscopic workload

What this paper adds

Applying a test and endoscopy strategy increased the endoscopy referral rate from 25% to 40%
The strategy produced no significant differences in symptoms or quality of life compared with usual management

The increased costs of this strategy cannot be justified

Astra Foundation supplied the Helisal tests. BCD holds a NHS research and development national primary care career scientist award. LR holds a NHS Executive, West Midlands new blood fellowship.

Competing interests: None declared.

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