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RAPID COMMUNICATION

Treatment of *Helicobacter pylori* in surgical practice: A randomised trial of triple *versus* quadruple therapy in a rural district general hospital

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Abstract

AIM: To compare a lansoprazole-based triple *versus* quadruple therapy for *Helicobacter pylori* (*H pylori*) eradication with emphasis on side effect profile, patient compliance and eradication rate at a rural district general hospital in Wales, United Kingdom.

METHODS: One hundred one patients with *H pylori* infection were included in the study. Patients were randomised to receive triple therapy comprising of lansoprazole 30 mg, amoxycillin 1 g, clarithromycin 500 mg, all *b.d.* (LAC), or quadruple therapy comprising of lansoprazole 30 mg *b.d.*, metronidazole 500 mg *t.d.s.*, bismuth subcitrate 240 mg *b.d.*, and tetracycline chloride 500 mg *q.d.s.* (LMBT). Cure was defined as a negative ^{13}C urea breath test 2 mo after treatment.

RESULTS: Seven patients were withdrawn after randomisation. Fifty patients were assigned to LAC group and 44 to LMBT group. The intention-to-treat cure rates were 92% and 91%, whereas the per-protocol cure rates were 92% and 97%, respectively. Side effects were common, with 56% experiencing moderate to severe symptoms in the LAC group and 59% in the LMBT group. Symptoms of vomiting, diarrhoea and black stools were significantly more common in the LMBT group. Patient compliance was 100% for triple therapy and 86% for quadruple therapy ($P < 0.01$). One-third of patients in both groups were still taking acid-reducing medications at six-month follow-up.

CONCLUSION: One-week triple and quadruple therapies have similar intention-to-treat eradication rates. Certain side effects are more common with quadruple therapy, which can compromise patient compliance. Patient education or modifications to the regimen are alternative options to improve compliance of the quadruple regimen.

Key words: *Helicobacter pylori*; Triple therapy; Quadruple therapy; Side effects; Treatment compliance; Eradication rate

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INTRODUCTION

European studies have shown that quadruple therapy, even though more effective with a cure rate of over 95% by per protocol analysis[1-3], is less popular compared to a standard triple therapy for eradication of *Helicobacter pylori* (*H pylori*) infection. The reasons for this are the complexity of the regimen and also its side effects. Scheduling drugs four or more times a day reduces compliance[4,5]. However, some studies have suggested that quadruple therapy has a similar magnitude of

adherence and adverse effects compared to triple therapies[6,7].

Triple therapies are the mainstay of current treatment but resistance to clarithromycin is reducing its effectiveness. In the presence of resistance to clarithromycin, some studies have shown eradication rate below 80% and even as low as 25%-61% with standard triple therapy containing clarithromycin, amoxycillin and a proton-pump inhibitor[7-11]. Clarithromycin resistance is also increasing in our region[12,13].

Quadruple therapy is used mainly as a second-line therapy after failed eradication with triple therapy[14-18]. Earlier consensus meeting reports including the Maastricht Ⅱ Consensus Report on the management of *H pylori* infection have recommended the use of quadruple therapy for 1 wk as second-line therapy for *H pylori* infection[19-21]. However, updated reports have now recommended quadruple therapy as an alternative first-line eradication therapy[22-24].

The objective of the study was to compare a standard lansoprazole-based triple therapy (HeliClear®) to a lansoprazole-based quadruple therapy as first-line therapy in a surgical practice in a predominantly Caucasian population in North Wales.

MATERIALS AND METHODS

We conducted a prospective randomised trial of patients under the care of an upper gastrointestinal surgeon at Ysbyty Gwynedd, a rural District General Hospital in North Wales. The population served by Ysbyty Gwynedd is predominantly (98.8%) white and there are about 120 new cases of *H pylori* each year from a population of around 180 000. Twenty-four percent of strains were resistant to metronidazole, 7% to clarithromycin and 4% to both. There was resistance to tetracycline in 1 out of 363 isolates and none to amoxycillin[12].

The Local Ethics Committee of the participating hospitals approved the study. From June 2001 to November 2005, 101 patients with diagnosis of *H pylori* infection proven by gastric histology or urease test or culture were included in the study. Two positive tests were required for inclusion. The inclusion and exclusion criteria are shown in Table 1.

Patients were recruited into the trial once they had met the criteria and given fully informed written consent. Patients were recruited from the outpatient departments at one district general hospital and a satellite hospital served by the same team of doctors. The patients received a 7-d course of either a triple regimen (LAC) or a quadruple regimen (LMBT) (Table 2).

Randomisation took place at the hospital pharmacies when the patients collected their medications with a note from the recruiting doctor. The pharmacists dispensed the medications adhering to the order on a random list of therapy regimens.

A printed chart showing the names of the drugs, the number of pills to take and the time schedule was given to all participants to improve understanding and compliance with treatment.

Table 1 Inclusion criteria and exclusion criteria

	Criteria
Inclusion criteria	Dyspeptic symptoms
	Has recent OGD (duodenal ulcer; gastric ulcer; gastritis or non-ulcer dyspepsia)
	Positive for *H pylori* on histology and culture or CLO test or ^{13}C-urea breath test
Exclusion criteria	Age less than 18 or above 75 yr
	Symptomatic gallstones
	Treated with antibiotic or bismuth-containing drugs during the month prior to inclusion
	Treated with proton pump inhibitor during the week prior to inclusion
	Disturbed gastrointestinal physiology (gastric surgery; vagotomy; Zollinger-Ellison syndrome; chronic ingestion of NSAIDs)
	Concomitant serious disease
	Concomitant medications that may adversely interact with the study drugs (e.g. warfarin, anti-epileptics)
	Pregnancy and breast-feeding
	Childbearing age without adequate contraception
	Allergy to drugs used in the study
	Mental illness
	Heavy drinking or abuse of drugs

Table 2 Regimens used in the trial

Triple therapy regimen (LAC)	Quadruple therapy regimen (LMBT)
Lansoprazole (30 mg *b.d.*)	Lansoprazole (30 mg *b.d.*)
Amoxycillin (1 g *b.d.*)	Metronidazole (400 mg *t.d.s.*)
Clarithromycin (500 mg *b.d.*)	Bismuth subcitrate (240 mg *b.d.*)
	Tetracycline chloride (500 mg *q.d.s.*)

Compliance was evaluated by patient's record of each dosage taken onto the chart during the week of therapy. Any tablet that was not consumed needed to be brought back to the clinic for pill count. The patients were asked to record the reasons for missed dosages. They were also asked to record any side effects and their severity during the therapy. Proton pump inhibitors and other acid-reducing medications were not allowed after treatment. The patients returned for interview at 6 wk after therapy. The efficacy of treatment was evaluated by means of the ^{13}C-urea breath test performed following the standard European protocol at 8 wk following the start of therapy[12]. Patients were reviewed again at 6 mo after therapy to assess symptoms and use of any medications after determining their post therapy *H pylori* status. Patients who tested positive were offered the alternate regimen and retested after a gap of 2 mo.

Statistical analysis

Proportions were compared using Fisher's Exact Test. Quantitative variables were compared using *t*-test and non-parametric variables were compared using Mann–Whitney *U* test. Non-categorical values are given as the mean ± SD. Calculations were performed using the SPSS for Windows statistical package.

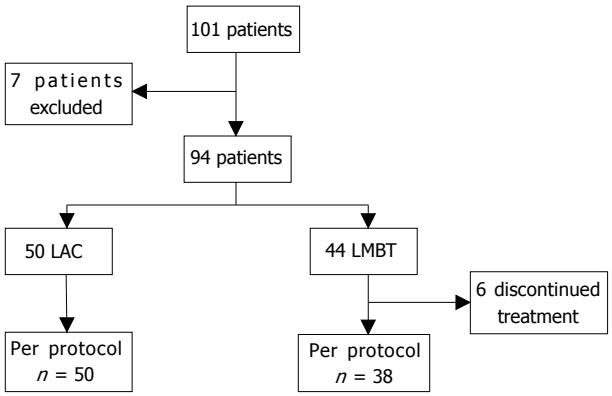

Figure 1 CONSORT flow diagram showing entries and withdrawals from the study.

Table 3 Patient characteristics

	Therapy	
	LAC (n = 50)	LMBT (n = 44)
Age	55.2 ± 10.9	53.7 ± 11.4
Gender (male: female)	26:24	27:17
Active smoking	10 (20%)	16 (36%)
NSAID use	4 (8%)	3 (7%)
Ethanol abuse (> 14 U/wk)	4 (8%)	3 (7%)
Previous therapy with antacids	4 (8%)	8 (18%)
Time between treat-ment and UBT (mo)	2.2 ± 0.7	2.1 ± 0.5
Gastric ulcer	1	1
Duodenal ulcer	3	1
Gastritis	36	33
Duodenitis	6	8
Diagnosis of *H pylori* infection (Urease: Culture: Biopsy)	42:29:45	37:27:44

NSAID: Non-steroidal anti-inflammatory drug; UBT: Urea breath test.

RESULTS

One hundred one patients were randomized into the trial but seven patients were withdrawn from the study after randomization (one because of diagnosis of bronchial carcinoma, one because of diagnosis of gallstones, two withdrew from the study and three were non-compliant to study protocol) (Figure 1).

Fifty patients were assigned to the LAC group and 44 to the LMBT group. The demographic and clinical characteristics of the groups were comparable (Table 3).

Compliance and side-effects

Compliance was excellent in the LAC group with all the patients completing the 7-d therapy. In contrast, 6 patients (14%) in the LMBT group failed to complete the treatment ($P < 0.01$). In spite of this three had a negative breath test.

Four out of the six patients had attributed moderate/severe nausea as the reason for discontinuing treatment. One had severe diarrhoea and another had nausea, vomiting and diarrhoea.

Side effects were reported by vast majority of patients in both groups, 45 patients (90%) in the LAC group and 42 patients (95%) in the LMBT group.

Table 4 Incidence of side effects n (%)

	Therapy		*P*-value
	LAC (n = 50)	LMBT (n = 44)	
Nausea	11 (22)	20 (45)	< 0.05
Vomiting	0 (0)	9 (20)	< 0.01
Diarrhoea	14 (28)	25 (57)	< 0.01
Headache	12 (24)	19 (44)	
Dizziness	9 (18)	11 (25)	
Blurred vision	5 (10)	6 (14)	
Itching	5 (10)	5 (11)	
Rash	1 (2)	2 (5)	
Dry mouth	27 (54)	19 (43)	
Sore mouth	4 (8)	0 (0)	
Glossitis	2 (4)	1 (2)	
Black tongue	6 (12)	6 (14)	
Black stool	5 (10)	35 (80)	< 0.01
Taste disturbance	23 (46)	14 (32)	
Arthralgia	3 (6)	1 (2)	

Table 5 Severity of side-effects (n)

	Therapy	
Severity	LAC	LMBT
None	5	2
Mild	17	19
Moderate	25	13
Severe	3	10
Total	50	44

Severity score: 1 = mild, does not cause any concern; 2 = moderate, but not bad enough to discontinue treatment; 3 = severe or incapacitating, forced to discontinue treatment.

The most frequent symptoms in the LAC group were dry mouth (54%) and taste disturbance (46%). Patients in the LMBT group experienced significantly more nausea (45%), vomiting (20%), diarrhoea (57%) and black stool (80%) (Table 4).

Each symptom was graded as mild, moderate or severe. In the LAC group, mild symptoms were observed in 17 patients (34%), moderate symptoms observed in 25 patients (50%) and severe symptoms observed in 3 patients (6%). In the LMBT group, mild symptoms were observed in 19 patients (43%), moderate symptoms observed in 13 patients (30%) and severe symptoms observed in 10 patients (23%) (Table 5, $P < 0.05$). Despite most of the patients experiencing some side effects, none were severe enough to require hospitalization.

^{13}C-urea breath test

All 94 patients returned for a ^{13}C-urea breath test 2 mo after eradication therapy. Four patients (8%) from the LAC group and four patients from LMBT (9%) had positive results indicating failure of *H pylori* eradication. Three of the four patients had an incomplete quadruple therapy (Table 6).

All the eight patients who tested positive with ^{13}C-urea breath test had the alternate regimen. Three of four patients, who had initially LAC and then LMBT therapy, were negative on the second breath test.

Table 6 ^{13}C-urea breath test results *n* (%)

	Therapy		*P*-value
	LAC (*n* = 50)	LMBT (*n* = 44)	
Returned for UBT	50 (100)	44 (100)	-
Completed therapy	50 (100)	38 (86)	< 0.01
UBT result	46 negative, 4 positive	37 negative, 1 positive	
Not completed therapy	0 (0%)	6 (14)	< 0.01
UBT result	-	3 positive, 3 negative	-
Intention-to-treat cure rate	92% (46/50)	91% (40/44)	
Per-protocol cure rate	92% (46/50)	97%(37/38)	

UBT: Urea breath test.

Table 7 Symptomatic outcome at 6-mo follow-up *n* (%)

	Therapy	
	LAC (*n* = 50)	LBMT (*n* = 44)
Follow-up at 6 mo	46 (92)	40 (91)
Persistent symptoms	4 (8)	7 (16)
Recurrent symptoms	17 (34)	9 (20)
Repeat eradication therapy	1 (2)	1 (2)
Long-term acid-reduction therapy	17 (34)	14 (32)

Six-month follow-up

Eighty-six patients (91.5%) returned for a 6-mo follow-up. Over one-third of patients had recurrent or persistent symptoms and remained on long-term acid-reduction therapy (with proton-pump inhibitors, H_2-antagonist or other antacids) even after successful eradication (Table 7).

DISCUSSION

This study has shown that a lansoprazole–based quadruple therapy is as effective as triple therapy in a predominantly white population in the UK (intention-to-treat rate: 91% *vs* 92% respectively). The resistance to clarithromycin (7%) is beginning to diminish the effectiveness of the triple therapy (92% per protocol eradication) whereas metronidazole resistance (24%) did not affect quadruple therapy (97% per protocol eradication)[25].

Side effects are common in both regimens occurring in around 90% of patients. However, severe side effects occurred more frequently with quadruple therapy (23% *vs* 6%) and this reduced compliance.

Four out of the six patients taking quadruple therapy stopped because of nausea and vomiting, which was probably due to metronidazole. Replacing metronidazole with amoxycillin should reduce these side effects and increase compliance[26]. Interestingly, dry mouth was noticed more in the triple therapy group even though lansoprazole was the most likely cause.

The intention-to-treat cure rate of quadruple therapy (LMBT) was comparable to triple therapy (LAC) in spite of lower compliance. Educating patients about the possible common side effects and the importance of complete eradication should provide a very high cure rate as the per protocol cure rate was 97% for quadruple therapy.

Quadruple therapy is very cost effective and should be considered as a first-line therapy especially when there are economic constraints. Lansoprazole-based quadruple therapy costs £17 as against £38 for the triple therapy for a one-week course[27]. The difference of £21 per treatment can be relieved from economic burden for the health service to treat this common condition.

Patients have to be warned that about one sixth of them will have persistent symptoms and about third of them will develop recurrent symptoms with a similar proportion needing long-term treatment with a proton-pump inhibitor, H_2-antagonist or other antacids.

Modified seven-day quadruple therapy, by reducing the frequency of tetracycline chloride and bismuth subcitrate from four times to three times daily, has also been tried successfully as a first-line treatment with cure rate and compliance rate of over 90%[2]. Bateson has shown that a twice-daily quadruple therapy using lansoprazole, tetracycline, clarithromycin and metronidazole is effective (95.5% eradication rate) in UK patients with duodenal ulcer but this pre-dated resistance to clarithromycin and metronidazole[28]. Amoxycillin has been shown to improve eradication in resistant patients and perhaps a trial of a twice-daily quadruple therapy substituting amoxycillin for metronidazole should be considered[26]. Other approaches to the problem of antibiotic resistance include a sequential therapy that substituted amoxycillin with tinidazole during the first 5 d of a 10-d triple therapy with pantoprazole, amoxycillin and clarithromycin, which has been shown to achieve a significantly higher eradication rate[29]. Pretreatment sensitivity testing has been confirmed to be cost effective by significantly improved eradication in a study that used omeprazole and two antibiotics chosen based on susceptibility testing, compared to omeprazole, clarithromycin and metronidazole standard triple therapy[30].

Recent randomised studies that compared triple therapy with quadruple therapy as a first-line treatment option for *H pylori* and some reports showed superior eradication rates with the quadruple therapy[6,31,32] whereas others have shown no difference[33,34]. Quadruple therapy is becoming the standard treatment as resistance to clarithromycin, and to a lesser extent metronidazole, is reducing the efficacy of triple therapies. The side effects may be reduced by replacing metronidazole with amoxycillin but patients should be better educated about the side effects in order to improve compliance and cure rates.

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COMMENTS

Background

The treatment for *Helicobacter pylori* (*H pylori*) is becoming less effective as the organism is becoming resistant to the commonly used antibiotics in triple

therapies. Quadruple therapies were less popular because of their side effects but still have good eradication rates.

Research frontiers

This study compares lansoprazole-based triple and quadruple therapy for *H pylori* infection in white Caucasians in rural Wales, an area with low resistance to Clarithromycin and moderate resistance to metronidazole.

Innovations and breakthroughs

Both regimens had high eradications rates (> 90%) showing that resistance has not yet significantly affected this UK population. Even better rates (97%) can be achieved with quadruple therapy if patients are able to complete the full course. Patients need to be educated about the side effects and importance of completing the course to achieve the higher eradication rates.

Applications

Quadruple therapies provide a cost effective and highly successful treatment for *H pylori*. The side effects and compliance may be improved by substituting amoxycillin for metronidazole-an area for future research.

Terminology

Triple therapy is a regimen of a proton pump inhibitor and two antibiotics. Quadruple therapy is a regimen of a proton pump inhibitor, a bismuth compound and two antibiotics.

Peer review

The authors compared lansoprazole-based triple and quadruple therapy in the eradication of *H pylori*. They found that both regimens were equally effective and that quadruple therapy was less costly even though 6 patients had to discontinue treatment because of side effects. This is an important study.

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