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Cure of peptic gastric ulcer associated with eradication of *Helicobacter pylori*

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Abstract

The effect of *Helicobacter pylori* eradication on ulcer healing and the relapse rate were investigated in a multicentre trial of 239 gastric ulcer patients. Patients with *H pylori* positive gastric ulcer were randomly assigned to one of three groups: (A) 10 days' treatment with metronidazole and eight weeks' treatment with colloidal bismuth subcitrate (CBS) (84 patients); (B) 10 days' treatment with metronidazole placebo and eight weeks with CBS (73 patients); or (C) ranitidine (82 patients). At 12 weeks in 210 patients, gastric ulcer was present in three (9%) of 35 *H pylori* negative patients, and in 45 (26%) of 175 *H pylori* positive patients ($p<0.05$). Results after one year of follow up were available for 205 patients. Between 12 and 52 weeks, two (7%) ulcer relapses occurred in 29 *H pylori* negative patients and in 60 (47%) of 128 *H pylori* positive patients ($p<0.001$). After two weeks of open triple therapy (CBS 120 mg four times daily, amoxicillin 500 mg four times daily, and metronidazole 400 mg three times daily), given to the patients with ulcer relapse, only one (an NSAID user) of 55 successfully treated patients had an ulcer relapse during the one year follow up. Healing of gastric ulcer is rapid and recurrence is infrequent after successful *H pylori* eradication. *H pylori* eradication changes the natural history of the gastric ulcer disease.

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Helicobacter pylori infection is common (>90%) in patients with duodenal ulcer, and eradication therapy has been pivotal in the treatment of this disease. After successful eradication of the infection, the ulcer recurrence rate is extremely low.[1–4] The association of *H pylori* with gastric ulcer is less frequent: the average prevalence of *H pylori* infection was 70% in nine studies comprising 290 gastric ulcer patients.[5] In addition, knowledge of the effect of eradication therapy on the relapse rate of gastric ulcer is relatively limited.[6–12]

To investigate the effect of *H pylori* eradication therapy on the healing and recurrence rates of gastric ulcer, we carried out a prospective, one year, double blind, randomised multicentre trial comparing treatment with colloidal bismuth subcitrate (CBS), metronidazole and CBS, or ranitidine with placebo.

Patients and methods

PATIENT SERIES

A total of 239 *H pylori* positive gastric ulcer patients entered the trial. Nine patients who fulfilled the inclusion criteria refused to participate. The patients were from 20 hospitals, and the mean number of patients from each hospital was 12 (range 1–50).

Inclusion criteria

Patients selected for this study had an endoscopically proved, *H pylori* positive gastric ulcer of 5–30 mm diameter, located more than 2 cm proximal to the pyloric ring. The patients were between 18 and 80 years of age. All were volunteers and their mental and physical condition was such that they were considered to be capable of communicating with the investigator, and of remaining compliant.

Exclusion criteria

The only patients excluded were those known to have taken drugs containing bismuth or metronidazole within four weeks of entry to the study, to have had severe renal impairment, or to have undergone gastric resection.

Patients who had had previous ulcer therapy with H_2 receptor antagonists, omeprazole, or other similar medication had to have a minimum 'wash out' period of one week. Use of antacids or non-steroidal anti-inflammatory drugs (NSAIDs) was not an exclusion criterion, and patients were allowed to take these for relief of pain or other symptoms. Fertile female patients were required to practice contraception during the treatment phase of the study.

H PYLORI DIAGNOSIS

Endoscopy was done after the patients had fasted overnight. Except for specimens of the gastric ulcer, at least three biopsy specimens were taken with sterilised biopsy forceps from both antral and corpus mucosa. One biopsy from both regions was used for a quick urease test (Jatrox). For histology, two formalin fixed biopsy specimens were embedded in paraffin and stained with haematoxylin and eosin and modified Giemsa methods.

H pylori culture was not done as a routine procedure. If the urease test indicated *H pylori*

infection, the patient was randomly assigned to one of the three trial therapy groups. If the test was negative, the patient was not entered until proof of *H pylori* infection had been obtained from histology or culture, or both. Five of 239 *H pylori* positive patients had a negative *H pylori* urease test, and the test was not conducted on one patient. The *H pylori* culture procedure was done in 64 patients; four of these had negative histology but a positive *H pylori* culture.

SITE AND SIZE OF THE ULCERS

Most ulcers (175 (77%) of 227) were located at the angulus area or near it at the lesser curve; 40 (18%) occurred in another part of the corpus and 12 (5%) at the greater curve of the gastric antrum. The exact ulcer location was unknown in two patients. The mean ulcer size, 112 mm^2 (13–706), was similar in all three study groups.

TREATMENT DESIGN

The outcome in the *H pylori* positive or negative patients was compared by endoscopy and *H pylori* assessment at weeks 12, 33, and 52. The 'end points' were a symptomatic or asymptomatic ulcer relapse at scheduled control endoscopies or at any endoscopy before week 52. Compliance was determined at weeks 4 and 8 when all patients returned their allocated medication.

Two study trials

Trial 1 was the original blind intervention based on controlled dual treatment. After endoscopic diagnosis of an active gastric ulcer and confirmation of the presence of *H pylori* infection, the patients were randomly assigned to three groups. The treatment groups were: (A) 10 days with metronidazole 400 mg three times daily and eight weeks with colloidal bismuth subcitrate (CBS) 2 tablets twice daily (84 patients); (B) 10 days' metronidazole placebo and eight weeks' CBS 2 tablets twice daily (73 patients); or (C) eight weeks' ranitidine 75 mg 2 tablets twice daily (82 patients). CBS and ranitidine were taken on an empty stomach, 30 minutes before a meal and at bedtime.

Trial 2 was added to the protocol later and used for 94 *H pylori* positive patients, of whom 16 had an ulcer at week 12, and 78 between weeks 12 and 52. This open two weeks' triple therapy consisted of CBS 120 mg four times daily, amoxicillin 500 mg four times daily, and metronidazole 400 mg three times daily.

Confounding factors

Of the patients entered, 49% consumed alcohol and of these 6% drank more than 200 g/week; 57% of patients were smokers. Forty two (19%) patients had taken acetosalicylic acid and 35 (16%) NSAIDs more than once per week. The mean age of the patients was 59 (range 33–78) years and the male:female ratio was 1·06 (123:116). The three study groups were similar and there was no statistical significance in demographic or personal characteristics between the patients in the treatment groups.

Withdrawals and drop outs

Of the 239 patients entered, 205 were available for the trial. Ten of the remaining 34 patients had gastric malignancy, six withdrew, six dropped out, six were excluded for protocol violations, and four were treatment failures because of ineffective pain relief. Adverse reactions were reported in eight patients, so much so that two of them had to leave the study: one developed exanthema and the other nausea and depression. Patient compliance was good, except for 12 (5%) patients who were not available for efficacy analysis (six drop outs, four treatment failures, and two adverse reactions).

ETHICS

The study, which was approved by the ethical committees of the local hospitals, began on 1 March 1990. Patient inclusion ended on 1 March 1992. Patients were informed and aware of the study design and treatment.

STATISTICS

The χ^2 and Kruskal-Wallis tests were used for statistical analysis.

Results

ERADICATION RESULTS AND ONE YEAR FOLLOW UP (TRIAL 1)

The presence of gastric ulcer in 210 patients at the 12 week control is presented in Table I. The results showed that the eradication (or clearance) of *H pylori* ($p<0·05$) improved the healing of gastric ulcers. In the active treatment group A (dual therapy), 28 of 72 patients (39%) were *H pylori* negative at 12 weeks; in group B (CBS+metronidazole placebo) seven of 65 patients (11%) and in group C (ranitidine+metronidazole placebo) none of 73 patients were *H pylori* negative at 12 weeks. The differences between groups A and B and A and C were highly significant ($p<0·001$). The difference between groups B and C was also significant ($p<0·02$). The healing rates of gastric ulcer in the three trial groups (A, B, and C) were 83% (60/72), 85% (55/65), and 64% (47/73), respectively. The difference in healing rates was significant for groups A and B compared with group C ($p<0·02$).

TABLE I *Gastric ulcer and* Helicobacter pylori *status in 210 patients at the 12 week control*

	H pylori *positive* *No (%)*	H pylori *negative* *No (%)*	*Total*
Ulcer present*	45 (26)	3 (9)	48
Ulcer healed	130 (74)	32 (91)†	162
Total	175	35	

*The index 'ulcer not healed' or ulcer relapsed (including three duodenal ulcers). †$p<0·05$ χ^2 (corrected).

TABLE II *One year follow up results for 157 gastric ulcer patients. Relation of the number of cumulative relapses to the* Helicobacter pylori *status (48 patients with an ulcer at 12 weeks follow up excluded)*

	H pylori *positive* No (%)	H pylori *negative* No (%)	*Total*
Ulcer relapse	60 (47)	2 (7)	62
No ulcer relapse	68(53)	27 (93)*	95
Total	128	29	157

*p<0·001 χ^2 (corrected).

The influence of *H pylori* eradication on the cumulative rate of gastric ulcer relapses between 12 and 52 weeks is presented in Table II. In six (17%) of 35 patients, a negative *H pylori* status at 12 weeks became *H pylori* positive. By 52 weeks, 60 of 128 *H pylori* positive patients had had an ulcer relapse, whereas two of the 29 *H pylori* negative patients had had a relapse (p<0·001). The cumulative ulcer recurrence rates in the 52 week follow up were 41% (28/68), 52% (33/64), and 67% (49/73) for the three trial groups (A, B, and C) respectively. The difference in the cumulative ulcer relapse rates was significant between groups A and C (p=0·003).

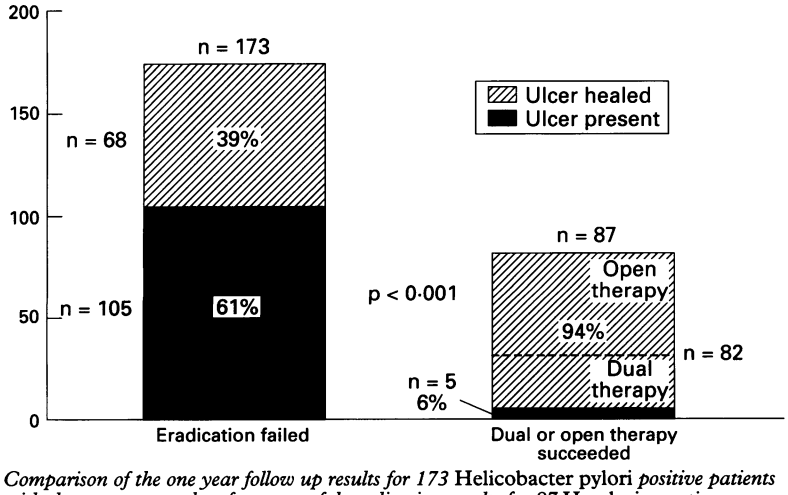
RESULTS OF TRIAL 2

A total of 94 patients with ulcer relapse received open triple therapy. *H pylori* eradication was successful in 65 of them (69%). Of these, 55 *H pylori* negative patients were followed for 12 months and only one patient (an NSAID user) had an ulcer relapse.

The combined data on the one year follow up for trials 1 and 2 were available for 205 patients and are presented in the Figure. The cumulative relapse rate was 6% in patients with successful eradication of *H pylori* and 61% in those in whom eradication failed (p<0·001).

Discussion

H pylori gastritis and peptic digestion play important roles in the natural history of peptic ulcer disease. We found that gastric ulcers heal more rapidly and ulcer relapses are less frequent after successful *H pylori* eradication. These results strongly support a dominant role for *H pylori*, not only in duodenal ulcer but also in gastric ulcer.



Comparison of the one year follow up results for 173 Helicobacter pylori *positive patients with the one year results after successful eradication results for 87* H pylori *negative patients (31 patients from the first year of follow up together with 55 relapsed patients after successful open triple therapy).*

These data confirm our earlier promising preliminary results[7 8] and observations in other series[9–12] of gastric ulcer patients. This trial shows further that *H pylori* eradication strategy is a feasible procedure and applicable in all kinds of hospitals. Diagnosis of *H pylori* and its treatment and control are readily available routines.

The frequency of *H pylori* infection in gastric ulcer patients varies considerably in published reports; it is 70% on average. In recent data from Helsinki University Central Hospital, the *H pylori* infection rate was 92% in 170 consecutive gastric ulcer cases (unpublished results). The low number of *H pylori* positive peptic gastric ulcers (with chronic gastritis) in some studies can be explained, at least partly, by diagnostic failures. Some problems in diagnosis of *H pylori* also occurred in our study. Intestinal metaplasia in association with a small quantity of colonising bacteria in focal areas of the gastric mucosa may bias the *H pylori* diagnosis. For reliable diagnosis, several biopsies (also from the corpus) and other diagnostic methods should be used.

Accurate assessment of *H pylori* infection in peptic ulcer is essential, because the appropriate therapy may differ for negative and positive gastric ulcer patients. There is a subgroup of NSAID induced gastric ulcers that occurs in association with normal gastric mucosa and is not related to *H pylori*.[13] Gastric ulcer patients with *H pylori* gastritis also commonly use NSAIDs. However, the ulcerogenic role of NSAIDs in these patients can be evaluated only after eradication of *H pylori*.[14] The same can be concluded from our results. One third of our patients took acetosalicyclic acid or NSAIDs before the beginning of the trial, and we did not prohibit use of NSAIDs during the follow up. However, most did not show ulcer relapse when *H pylori* was eradicated, suggesting a minor ulcerogenic role of NSAIDs when compared with that of *H pylori*. On the other hand, in the course of the one year follow up of 87 patients with successful *H pylori* eradication, two of the five with ulcer relapses were NSAID users.

The dual therapy used was safe. Compliance was also good; only two patients dropped out because of side effects and four because of ineffective therapy. Our primary objective was not completely fulfilled because the dual therapy was not as effective as had been expected when the trial was planned. We therefore extended the study with an open triple trial for patients who had unhealed ulcers at 12 weeks' control or had ulcer relapse during the follow up. After successful *H pylori* eradication, only one of the 55 patients had a new ulcer relapse after one year.

Our results show that *H pylori* eradication is an important issue in attempts to achieve permanent gastric ulcer healing. We believe that even though the ulcerogenic mechanisms in *H pylori* positive gastric ulcer are not clear,

successful eradication of *H pylori* will change the natural course of gastric ulcer as it does in duodenal ulcer disease.

The following members of The Finnish Gastric Ulcer Study Group participated in the study: K Seppälä, E Kivilaakso, K Höckerstedt, *Helsinki University Central Hospital*; P Sipponen, *Department of Pathology, University of Helsinki*; T U Kosunen, *Department of Bacteriology and Immunology, University of Helsinki*; E Vaittinen, *Malmi City Hospital, Helsinki*; J Lehtola, S Niemelä, *Oulu University Central Hospital*; R Julkunen, E Janatuinen, *Kuopio University Hospital*; A-L Karvonen, P Pikkarainen, *Tampere University Hospital*; E Pehkonen, M Rasmussen, S Kyrönpalo-Kauppinen, *Tampere City Hospital of Hagtanpää*; E Toivanen, *Central Hospital of Kanta-Häme, Hämeenlinna*; E Kiviniemi, *Central Hospital of Lappi, Rovaniemi*; T Jääskeläinen, *Central Hospital of Länsi-Pohja, Kemi*; I Krekelä, *Central Hospital of Päijät-Häme, Lahti*; P Jauhonen, *Central Hospital of Kainuu, Kajaani*; M Sotka, *District Hospital of Hyvinkää*; S Nyyssönen, *District Hospital of Jokilaakso, Jämsä*; M Honkala, *District Hospital of Raahe*; K Marenk, *District Hospital of Valkeakoski*; V Tuunanen, *District Hospital of Selkämeri, Kristiinankaupunki*; C J Lindström, S Meyer, *District Hospital of Länsi-Uusimaa, Tammisaari*; B Isomaa, *District Hospital of Malm, Pietarsaari*; O Suhonen, *District Hospital of Lohja*.

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