A PLACEBO CONTROLLED TRIAL OF BISMUTH SALICYLATE IN HELICOBACTER PYLORI ASSOCIATED GASTRITIS

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ABSTRACT

In a placebo controlled prospective clinical trial of bismuth salicylate in helicobacter pylon associated gastritis, 52 adult patients were randomly allocated to treatment with bismuth salicylate or placebo. Helicobacter pylon were totally cleared in 77% patients in bismuth group but none in placebo group ($P < 0.001$). Resolution of gastritis ($P<0.001$) and improvement of symptoms ($P < 0.01$) were significantly better in patients where H. pylori infection cleared as compared to patients where the infection persisted (JPMA 40:154, 1990).

INTRODUCTION

Helicobacter pylori, a new organism first isolated by Marshall, has been implicated for acid peptic disease and is increasingly being reported from different parts of the world. Two self inoculation experiments performed in healthy human volunteers in order to fulfill Koch's postulates have demonstrated the histological development of gastritis after ingestion of H. pylori which strongly supported a pathogenic role of this bacterium as did heighten humoral and cellular immune responses in H. pylon associated gastritis as compared to non-bacterial gastritis.[1] The significance of the infection with this bacteria in causing dyspeptic symptoms however remains largely unsettled. The aim in this study was to assess the therapeutic benefit of antimicrobial treatment aimed at elimination of Helicobacter pylori from antral mucosa in a population of patients undergoing endoscopy for dyspeptic symptoms.

PATIENTS AND METHODS

In a placebo controlled randomised study 52 patients presenting with dyspeptic symptoms i.e. upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting or other symptom referable to the proximal alimentary tract were included in the study. Only those patients were included who had histological antral gastritis and were positive for H. pylori, with special stains either on culture or on histology. All patients with endoscopically confirmed gastric or duodenal ulcer were excluded. Patients were randomised.in such a manner that 26 patients in eachgroup received either placebo or bismuth salicylate. The drug was provided in an identical bottle containing either placebo or bismuth salicylate 500 mg/5ml, enough to last for 3 weeks, to be taken orally at a dose of 5m1 thrice a day half an hour before meals. The patients after completion of the treatment were reassessed for the symptoms and endoscoped within two days after completion of treatment. The endoscopic appearances of antral mucosa were noted and an antral biopsy taken to assess the histological and bacterial status after the completion of treatment. The improvements in symptoms, histological grade and bacterial status both by bismuth salicylate and placebo were analysed by CM Square test.

i. Histological assessment of gastritis

Histological assessment of gastritis included: Grade 0-normal, Grade 1 increased mononuclear cells, Grade 2-increased cells with expansion of lamina propria, and Grade 3 - polymorph infiltration in addition to features noted in grade 2 gastritis.

ii. Histological assessment of bacteria in tissues

The number of bacteria were also graded from 0 to 3 + Grade 0- no bacteria, Grade 1- occasional bacteria, Grade 2- scattered bacteria in most high power fields or occasional groups of numerous bacteria, Grade 3 numerous bacteria in most high power fields.

iii. Assessment of symptoms

Questions were asked regarding symptoms like epigastric pain, flatulence, nausea and vomiting, loss of appetite and heartburn. After treatment patients were asked if they were same, better, or worse. Improvement or worsening of each symptom over the three weeks of treatment was added as +1 or -1 respectively. The symptom scores were added for each patient giving a possible score ranging from-S to + 5.

iv. Statistical analysis

Statistical analysis was done by $X.^2$ test. Results were considered significant when the P value was <0.05.

RESULTS

Fifty two patients entered the clinical trial, half of the patients received bismuth salicylate and the other half placebo. There was no significant difference between the two treatment groups with respect to age, sex and presenting symptoms. There were 38 males and 14 females whose ages ranged between 15 to 60 years.

Clearance of H. pylon in the two treatment groups

In the bismuth group H. pylon were cleared completely (grade 0) in 20 out of 26 patients and did not clear in any of the 26 patients receiving placebo (P <0.001) (Table-I).

TABLE I. Correlation of grades of Gastritis and H. pylori status before and after treatment with Bismuth and Placebo.

	Before Treatment				After Treatment			
Grades	0	1	2	3	0	1	2	3
			Bismuth Treated					
Histology	–	–	7	19	8	13	4	1
H. pylori	–	–	9	17	20	3	3	0
			Placebo Treated					
Histology	–	–	15	11	–	–	11	15
H. pylori	–	–	10	16	–	–	10	16

Improvement of histological gastritis in the two treatment groups

In the bismuth group 19 patients had grade 3gastritis and 7 had grade 2 gastritis before starting treatment. After completion of treatment, gastritis was completely resolved to grade 0 in 8 cases. Of the remaining 18 patients, 13 had grade 1 gastritis, 4 grade 2 gastritis and 1 grade 3 gastritis. In the placebo group none of the patients showed any improvement in histological grade (Table-I). Of 20 patients who cleared the organism, 8 showed complete resolution of gastritis, while in rest of 32 patients in whom H. pylon were not cleared, none showed complete resolution of gastritis (P <0.001; table 1).

Improvement of symptoms in the two groups

TABLE-II. Correlation of symptom score and number of patients after completion of treatment in the two groups.

Symptom score	Number of Patients	
	Bismuth treated (26)	Placebo treated (26)
–5	0	0
–4	0	0
–3	0	0
–2	0	0
–1	1	3
0	6	14
+1	3	8
+2	5	1
+3	8	0
+4	2	0
+5	1	0

Table-II shows symptom scores before and after treatment in the two groups. Of the 26 bismuth treated patients, symptoms improved in 19 patients as compared to 9 out of 26 patients treated with placebo ($P < 0.01$). Out of 24 patients who showed improvement in H. pylon grades, 18 (75%) showed improvement in symptoms. Of 28 patients who did not show improvement in H. pylon grades, 10 (35.7%) showed improvement of symptom ($P < 0.01$) (Table-III).

TABLE III. Correlation between improvement in symptoms and improvement of H. pylori grades in 52 patients.

Improvement in symptoms		Improvement in H. pylori grade	
		Improved	Not Improved
Improved (28)	Bismuth 19 Placebo 9	18	10
Not Improved (24)	Bismuth 7 Placebo 17	6	18
Total (52)		24	28

Note: Improvement in H.pylori grades was seen only in Bismuth treated patients.

DISCUSSION

Placebo controlled clinical trial of bismuth salicylate was carried out to see the effect on the inflainmed gastric mucosa associated with H. pylori infection, after the bacilli were eradicated or decreased in number. The trial also enabled to evaluate the clinical significance of the H. pylori associated gastritis which was achieved by evaluating the improvement in symptoms in patients showing improvement in H. pylon grades. H. pylon sensitivity to bismuth has been established[1]. Bismuth is the drug of choice because it is absorbed in very little quantity, can attain high concentration locally in the stomach, can penetrate the gastric mucus thusreaching the deep seated bacilli and is stable in the acidic environment of the stomach. Results of the present clinical trial confirm the strong correlation between the presence of H. pylori in the gastric antrum and histologically proven gastritis. Clearance of H. pylon was strongly associated with resolution of gastritis, than observed in patients with persistent infection. Some other workers also have performed studies, successfully using bismuth salts and other antimicrobial agents in the treatment of H. pylon associated gastritis[2,3]. These reports show improvement of histological gastritis with the eradication of H. pylon. As in two other clinical trials reported[4,5] symptomatic response to treatment was difficult to assess. The two previous clinical trials although showed greater improvement of symptoms in patients cleared of H. pylon however this did not reach statistical significance in either. The results of the present clinical trial role of H. pylon in causing gastritis and dyspeptic symptoms and showed a significant improvement in symptoms with clearance of H. pylon.

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