

# Can *Helicobacter pylori* be Eradicated by combination by Fleroxacin and Ascorbic Acid ?

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## ABSTRACT

**Background:** The aim of the treatment for *Helicobacter pylori* (*H. pylori*) infection in any therapeutic context is the eradication of the organism from the fore gut. Triple or quadruple therapy has been widely accepted by many consensus as an eradication treatment in patients with ulcer or *H. pylori* positive dyspepsia, but in our experience, especially in Malang successful eradication with a combination of amoxicillin, clarithromycin, metronidazole and PPI was only found in 15-20% of patients, showing an inadequacy in the use of a combination of triple or quadruple drugs. This failure may be due to multi resistant *H. pylori*. Thus, we must look for another agent for successful eradication. Ascorbic acid is known to play a role in inhibiting *H. pylori* activities.

**Objective:** To evaluate the effect of the fleroxacin and ascorbic acid combination on *H. pylori* dyspeptic patients.

**Design:** Single blind randomized clinical trial.

**Setting:** Out-patients from The Gastro-Hepatologic Clinic, Internal Department Medical Faculty Unibraw/ Dr. Saiful Anwar Hospital, Malang, East Java, Indonesia.

**Patient:** 30 patients were enrolled with a history of more than 3 months of dyspeptic symptoms with prior treatment using amoxicillin 500 t.i.d., metronidazole 500 mg t.i.d., and lansoprazole 30 mg and persistent *H. pylori* after therapy.

**Method:** We administered a combination of fleroxacin 400 mg, ascorbic acid 1000 mg and lansoprazole to patients who had formerly taken amoxicillin, metronidazole and lansoprazole. These drugs were given for 14 days. Evaluation was performed 8 weeks after therapy. The pre-elementary study showed that *H. pylori* strains in Malang, East Java, Indonesia were multi-resistant to many antibiotics.

**Result:** After 2 weeks of treatment and 8 weeks after termination of therapy, 96,6% of patients treated with fleroxacin, ascorbic acid and PPI demonstrated an absence of dyspeptic symptoms. The culture turned out negative and the treatment was found effective in eradicating *H. pylori* in 28 patients (93,3%).

**Conclusion:** Fleroxacin in combination with hexoxaene, ascorbic acid and lansoprazole was efficacious in the treatment of *H. pylori* dyspeptic patients in Malang, East Java, Indonesia.

**Key Words:** Dyspeptic *H. pylori*, eradication, new regimen.

## INTRODUCTION

Since Warren and Marshall found *H. pylori* in patients with chronic gastritis and peptic ulcer in 1983, its presence has been well associated with the development of peptic ulcers. This microorganism is believed to be very strongly associated with several gastroduodenal dis-

eases, from asymptomatic ones to malignancy. Epidemiologic studies demonstrated an association between *H. pylori* and chronic gastritis, peptic ulcer, gastric carcinoma, lymphoma and even coronary heart disease. A study in Malang found positive *H. pylori* culture from the antrum mucous membrane of 69% of patients with

chronic gastritis with a complaint of dyspepsia.

The goal of therapy is to eradicate *H. pylori* from the upper gastrointestinal tract. Eradication is said to have been achieved if no *H. pylori* is found after 4 or more weeks of therapy. Combination therapy using three or four kinds of medicine has been widely accepted by several consensus as the therapy of choice for the eradication of *H. pylori* in patients with ulcer or dyspepsia and positive *H. pylori* findings.

Another important condition is the obvious resistance of *H. pylori* to several antibiotics, especially those recommended. Several studies in Malang demonstrated that the therapeutic success rate using triple or quadruple drugs only amounted to 15-25%. Such failure may have been due to *H. pylori* resistance to several antibiotics. Thus, different regimens, such as ascorbic acid, that is believed to have the ability of suppressing the growth of *H. pylori* must be considered. The antibiotics used must be adjusted to the local situation, bearing in mind differences in the resistance pattern of different geographic areas. Studies conducted by Achmad et al in Malang demonstrated better results with the use of quinolon and gentamycin compared to other recommended agents.

#### AIM OF STUDY

The study aimed to evaluate the effect of combined fleroxacin and ascorbic acid on *H. pylori* associated dyspeptic patients who had undergone unsuccessful conservative therapy using a combination of amoxicillin, metronidazole and lansoprazole.

#### MATERIALS AND METHOD

##### Design

Single blind randomized clinical trial.

##### Patients

We enrolled thirty patients who had suffered from dyspepsia for at least 3 months who had undergone combined therapy of amoxicillin 2 x 1000g, lansoprazole 1 x 30 mg and metronidazole 3 x 500 mg and still demonstrated a positive culture for *H. pylori* from gastric antrum mucous membrane biopsy on 8-week evaluation.

##### Method

The 30 patients were given a combined therapy of fleroxacin 1 x 400 mg, ascorbic acid 1000 mg and lansoprazole 1 x 30 mg for 14 days. The patients were followed up 8 weeks after cessation of treatment. In this follow up, the *H. pylori* status was assessed.

#### RESULTS

On evaluation 8 weeks after termination of therapy, examination and culture demonstrated negative *H. pylori* findings in 28 patients (93.3%), and less or no more complaints of dyspepsia in 29 patients (96.6%).

#### DISCUSSION

The 30 patients chosen for this study were patients with chronic dyspepsia with positive *Helicobacter* findings on initial endoscopic examination and culture. Based on the current regimen, the patients received triple drug therapy using a combination of amoxicillin 2 x 1000g, lansoprazole 1 x 30 mg and metronidazole 3 x 500 mg for 14 days and was re-evaluated after 8 weeks with continued presence of *H. pylori*.

Possible causes of failure of eradication of *H. pylori* in these patients:

1. *H. pylori* resistance to antibiotics.
2. A difference in in vivo and in vitro effectivity of the antibiotic, due to thickness of the glycocalyx of the bacteria, bacteria located within/between the epithelial cells of the mucous membrane, reduced bioavailability of the medication in an acidic environment, internalization into epithelial cells and dormant cells.
3. Lack of compliance in the part of the patient
4. Induced resistance to metronidazole, reduced gastric acid secretion and reduced blood flow to the gaster in smokers.

Culture and sensitivity tests demonstrated resistance against amoxicillin and metronidazole. Most probably, failure of therapy based on the results of culture and sensitivity tests are due to the presence of a strain that is multiresistant to antibiotics, specifically towards amoxicillin and metronidazole in Malang.

Based on monthly culture and sensitivity tests conducted in Malang in the year 1999, *H. pylori* has demonstrated sufficient sensitivity towards gentamycin, kanamycin, imipenem and fleroxacin. From these various drugs, fleroxacin was chosen based on the availability of easy to use oral preparation and high tolerance on the part of the patients. Fleroxacin is a broad spectrum antibacterial agent from the fluoroquinolone group that has the ability to eradicate almost all gram negative microorganisms and several gram positive groups. Fleroxacin has a small tendency for drug interaction compared to other fluoroquinolones and has a long half-life, making it possible for single to double daily adminis-

tration. Side effects are usually associated with the gastrointestinal tract, central nervous system and the integumentary system.

A problem that often occurs is a difference in the results of in vivo and in vitro experiments using quinolone agents, where utilization in vivo does not produce as high results as in vitro experiments, due to the possible causes mentioned earlier. However, this study demonstrated promising results, where 93.3% of patients demonstrated eradication of *H. pylori*.

Vitamin C is a water-soluble vitamin. It is found in two forms, namely ascorbic acid and dehydroascorbic acid. Several studies reported that ascorbic acid has the potential to improve body resistance against cancer. This possible anti-carcinogenic effect may be due to its ability to detoxify carcinogens or disturb the carcinogenic process due to its role as an antioxidant or by catching free radical agents and increasing immunocompetency. Ascorbic acid has the ability to reduce nitric acid and prevent the formation of N-nitroso.

The role of ascorbic acid in supporting the therapy of chronic gastritis is associated with its ability in non-specific immune processes to maintain collagen. Collagen is an important component of the natural human barrier and is a component of the basal membrane of epithelial cells, including those of the gastric mucous membrane which are destroyed by *H. pylori*.

The specific role of ascorbic acid in combating *H. pylori* infection is still unknown, but several studies have demonstrated that ascorbic acid has the ability to modify immunity by:

1. Producing antibodies, specifically Ig G and Ig M.
2. Stimulating proliferation of lymphocyte T.
3. Stimulating normal response of slow hypersensitivity.
4. Antimicrobial and antiviral effects.

Based on the complex specific role of ascorbic acid in modifying immunity listed above, an additional dose of ascorbic acid could support therapy against *H. pylori*.

Currently, the body immune system is considered incapable of combating *H. pylori* because the cellular immune response stimulated by this infection is lymphocyte T (CD4) present in the lamina propria, while *H. pylori* is found in the gastric lumen. IgA production that envelops *H. pylori* together with the complement system could not fight *H. pylori* due to the secretion of protease enzyme by the bacteria.

Suppression of the growth of *H. pylori* could also be explained through the role of ascorbic acid as pro-oxi-

dant as well as an antioxidant. As a pro-oxidant, a high dose of ascorbic acid could act as a free radical agent. This pro-oxidant has the ability to suppress the growth of *H. pylori*. Furthermore, ascorbic acid also has the ability to disturb urease production by *H. pylori*. Reduction of urease facilitates destruction of *H. pylori* by macrophages.

Currently, in vitro *Helicobacter pylori* sensitivity studies conducted in Malang have shown resistance towards regimens recommended in Western nations. A combination of high doses of ascorbic acid and an antibiotic, selected based on sensitivity test should be able to combat infection by such *H. pylori*. Further research on a larger sample of patients with chronic gastritis due to *H. pylori* is needed, especially using combination treatment with proton-pump inhibitors (PPI) and certain antibiotics.

## CONCLUSION

- In Malang, patients with dyspepsia with positive *H. pylori* demonstrated a high rate of failure with recommended eradication therapy.
- An alternative form of therapy is a combination of ascorbic acid and fleroxacin which demonstrated promising results, with an eradication rate of 93.3%.

## SUGGESTIONS

- Further investigation should be conducted using a larger sample to evaluate further effects of ascorbic acid and fleroxacin in vivo.
- Culture and sensitivity tests for *H. pylori* should be conducted on a regular basis to illustrate resistance patterns in different geographic areas, so that therapy can be adjusted to the local conditions, taking into consideration the regimen that has been consented to.

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