Clinical Improvement of Dyspepsia Symptoms Following Eradication Treatment for *Helicobacter pylori*

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ABSTRACT

The prevalence of Helicobacter pylori in patients with peptic ulcer in Indonesia is very high. It ranges between 90-100%. In general, patients with gastritis and peptic ulcer usually have dyspepsia symptoms. The pathophysiology of dyspepsia symptoms caused by Helicobacter pylori has not been clearly understood. However, it is assumed that the symptoms are correlated to various factors including inflammation, apoptosis damage, and increased secretion of gastric acid, atrophy and non-atrophy gastritis as well as the development of peptic ulcer.

The main objective of treatment for Helicobacter pylori infection is elimination of Helicobacter pylori bacteria. Triple therapy has 80% success rate with no significant adverse events and minimal effect in inducing resistance to antibiotics. The success rate of eradication treatment in patients with peptic ulcer is 90%; while an evaluation on improvement of duodenal ulcus following eradication treatment with one month proton pump inhibitor treatment reveals 90% success rate.

***Keywords**: Helicobacter pylori, improvement, dispepsia*

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a main etiology of peptic ulcer, and most studies demonstrate that there is a strong relationship between *H. pylori* infection and gaster lymphoma as well as adenocarcinoma of gaster body and antrum. Eradication treatment of *H. pylori* is strongly assumed that it may reduce the risk of cancer.[1,2,3]

Data of clinical studies in Indonesia show that the prevalence of *Helicobacter pylori* in patients with peptic ulcer ranges about 90-100%.[4] In patients with non-ulcer dyspepsia, the prevalence of *H. pylori* infection is reported between 20-40% with different diagnostic methods, i.e. serology, culture and histopathology.[4] Whereas the incidence of *H. pylori* in dyspepsia patients who had endoscopic examination in multicenter studies of 5 big cities in Indonesia (2003-2004) was 10.2%. A relatively high prevalence was found in Yogyakarta (30.6%) and the lowest was found in Jakarta (8%).[5] This prevalence is lower than the previous study at M. Djamil hospital in Padang, which found *H. pylori* prevalence in patients with dyspepsia was 60% (serology) and 45% (histopathology).[6] An epidemiology study is being conducted recently by the Division of Gastroenterology on the prevalence of *H. pylori* in Jakarta. For temporary moment, the study reveals that the prevalence of *H. pylori* infection is 52.3% of 310 obtained blood samples[7]

H. pylori infection usually causes antral gastritis which increase acid secretion and the risk of duodenal ulcer.[2] Pan-gastritis may occassionally occur, which also may increase the acid secretion.[3] Some studies demonstrate that eradication of *H. pylori* infection causes various different effect, particularly on symptoms correlated to the increased acid secretion. In 1991, the incidence of increased reflux oesophagitis following the eradication treatment was reported for the first time. However, next studies reported different results. Some studies reported improvement of reflux oesophagitis following the eradication treatment. However, a different study reported no improvement.[8]

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Although there is a strong correlation between *H. pylori* infection, chronic gastritis and peptic ulcer, but the correlation between dyspepsia symptoms and gastritis induced by *H. pylori* has not been clearly demonstrated. It is assumed that the symptoms are correlated to inflammation, apoptosis damage, increase gastric acid secretion, atrophy and non-atrophy gastritis, as well as the development of ulcer.

The success rate of eradication treatment by triple therapy is about 80-100%, and in a large-scale randomized study the success rate ranges for 90% of all patients with peptic ulcer.[9] Furthermore, regarding the correlation between the success rate of eradication treatment and ulcer recovery, it is reported that the success rate of primary healing of ulcer after 1 week therapy, which is examined by endoscopy was 80-85%. However, when the PPI treatment was given for one month period, the success rate of duodenal ulcer may increase up to 90%.[2]

The improvement of dyspepsia symptoms in patients with ulcer ranges for 70 -100%. Goggin et al, evaluated dyspepsia symptoms as well as other symptoms correlated to peptic ulcer and they found improvement rate of such symptoms up to 100%. The improvement of symptoms was found after long-term evaluation, with median period of 37 months.[10] On the contrary to the response in patients with ulcer, the response of clinical improvement post-treatment in patients without ulcer varied and ranges for 2-58%.[11] A study by Jaakkimainen et al, reported that there was a correlation between *H. pylori* and dyspepsia symptoms without ulcer and the odd ration was 1.6. In addition, there was an improvement of symptoms post-eradication treatment with odd ratio of 1.9.[12] However, a study by Harvey et al, reported that there was no significant result for improvement of heart burn symptom following two years *H. pylori* eradication treatment with odd ratio of 0.99 (CI = 0.88-1.12), or for the symptoms of gastroesophageal symptom with odd ratio of 1.04 (CI = 0.91-1.19).[8]

DYSPEPSIA AND *HELICOBACTER PYLORI* INFECTION

In general, patients with peptic ulcer and gastritis usually complain about dyspepsia. Formerly, dyspepsia was defined as a syndrome of some gastro-intestinal disease including nausea, vomiting, bloating, heart burn, belch/a burp, burning sensation, full sensation at epigastric region and rapid satiation.[13] However, by the Rome III criteria in 2006, dyspepsia is defined as a symptom or symptoms found that correlated to gastroduodenal disorder, including epigastric pain, epigastric burning, full sensation or abdominal discomfort after meal and rapid satiation; such symptom(s) should be experienced for 3 months in minimal period of the last 6 months.[14] The pathophysiology of dyspepsia symptoms caused by *Helicobacter pylori* has not been clearly understood. However, it is assumed that the symptoms are correlated to various factors including inflammation, apoptosis damage, and increased secretion of gastric acid, atrophy, and non-atrophy gastritis as well as the development of peptic ulcer.

H. pylori causes continued gastric inflammation. First, the inflammation consists of neutrophils recruitment, followed by lymphocyte T and B, plasma cell, macrophages, in parallel with epithelial cell damage. The host response is mainly induced by bacterial attachment on epithelial cells. The pathogens may be bound on MHC class II molecules of gastric epithelial cells and induce apoptosis.[4] *H. pylori* may cause inflammation at the antrum (antritis) or the body of gaster (corpusitis) or frequently at both (pangastritis). In antritis, there are hypergastrinemia, increased acid production and high risk of duodenal ulcer. Approximately 2-30% antritis will become duodenal ulcer.[4]

Gastritis

In general, the natural history of chronic gastritis induced by *H. pylori* infection may be categorized into non-atrophy chronic gastritis with antrum dominant and multifocal atrophy gastritis. The characteristics of non-atrophy chronic gastritis are moderate to severe inflammation of antrum mucosa; in contrast to mild inflammation or no inflammation at the stomach body. There is no atrophy or metaplasia at the antrum. The patients usually are asymptomatic, but there is a risk of duodenal ulcer development. Multifocal atrophy chronic gastritis has specific characteristics, i.e. inflammation that occurs nearly at all over the mucosa, which is frequently severe, in the form of local atrophy or metaplasia on the antrum and the stomach body. Multifocal atrophy chronic gastritis is a main risk factor of epithelial gastric dysplasia and gastric carcinoma.[15]

Peptic Ulcer

H. pylori that mainly concentrated on the antrum may cause antrum predominant gastritis, which causes cell D damage that may secrete somatostatin, a substance that may inhibit gastrin production. Due to the cell D damage, somatostatin production decreases and therefore the gastrin production will increase which will induce excessive gastric acid production by the parietal cells. Gastric acid will enter into duodenoum that may produce increased acidity and causes duodenitis (active chronic duodenitis), which may lead to duodenal ulcer.[16] Increased acid gastric in duodenum may cause gastric metaplasia, which may become the habitation of *H. pylori*. Moreover, it may produce acid which will further add duodenal acidity. Extreme acidity will inhibit mucus and bicarbonate production which will cause further decrease of

mucosa invulnerability and favor the development of duodenal ulcer.[17]

The development of gastric ulcer induced by *H.* pylori infection is different from duodenal ulcer. *H. pylori* infection may cause chronic pangastritis followed by atrophy of mucosa cells at stomach body and gland, intestinal metaplasia and hypoacidity. This process is influenced by host factors, the duration of infection, (location, inflammation response, genetic), bacterial factors (virulence, bacterial structure, adhesion, porins, urease enzymes, vacA, cagA, etc); environment (gastric acid, drugs, NSAID, gall, and other irritant factor) which finally lead to chronic gastritis such as gastric ulcer.[13]

If gastritis induced by *H. pylori* infection occurs predominantly in the stomach body, gastric acid secretion will decrease and the long-term risk of gastric cancer will be greater. Severe or extensive inflammation of the stomach body will disturb or inhibit parietal cells which lead to hypo - or achlorhydria and it is usually accompanied by mucosa atrophy of the stomach body, a premalignant lesion for gastric cancer. In contrast, we assume that the level of gastric acid secretion, which may be affected by genetic factors, has a role on different predomination of gastritis induced by *H. pylori* infection. If the secretion of gastric acid is augmented, gastritis will predominantly occur at antrum. While low secretion will cause gastritis that occur predominantly at thestomach body. Both will lead to different illness.[4]

A study conducted in rodents (mongolian gerbils) found a significant increase of activity score, gastritis inflammation and gastrin serum lelvel, and there was a significant result of reduced gastric acid secretion 6 and 12 weeks after *H. pylori* inoculation. We assume that it is mediated by IL-1b, which is induced by *H. pylori*.infection.[17] The effect of *H. pylori* elimination on gastric acid secretion has been studied by Feldman M et al, that demonstrated the effect of *H. pylori* eradication treatment on the stomach of healthy subjects. The study has demonstrated that *H. pylori* elimination treatment may reduce the gastritis score of stomach body and antrum, reduce pepsin secretion up to 30%, and inhibit secretion of non-parietal cells for 35%, without affecting the secretion of parietal cells.[18]

EVALUATION FOLLOWING THE *HELICOBACTER PYLORI* ERADICATION TREATMENT

The main objective of treatment for *H. pylori* infection is elimination of *Helicobacter pylori* bacteria.[19] Triple therapy has 80% success rate with no significant adverse events and minimal effect in inducing resistance to antibiotics. The incidence of reinfection following eradication treatment is quite low, i.e. 3.0 - 7.0% in developed countries and 6-14% in developing countries.[1]

Evaluation of successful *H. pylori* eradication should be conducted in 4 weeks following the eradication therapy and the best test for evaluation is by using ^{13}C Urea breath test (UBT). The success rate of eradication therapy in a large-scale randomized study is about 90% of all patients. The study also demonstrated that low-dose triple therapy with amoxycillin-clarithromycin/nitroimidazole-proton pump inhibitor treatment was very effective with minimal adverse effect and it is a standard regimen for *H. pylori* eradication treatment.[20,21] A study by Kuipers et al, in patient with *H. pylori* infection and clinical manifestation of reflux oesophagitis found 88% success rate of *H. pylori eradication* in a group treated by triple therapy compared to the group treated by PPI only (24%).[22] Wu et al, found 98% success rate following eradication treatment of triple therapy in patients with reflux oesophagitis. Moreover, Manes reported 94% success rate of eradication treatment in patients with dyspepsia symptom.[23,24] Rosengren and Polson who evaluated eradication treatment in one month following triple therapy by using ^{13}UBT found that the success rate of eradication treatment was up to 100% in patients with duodenal ulcer.[25]

The effectiveness of dual therapy with amoxycillin and omeprazole treatment is very low; therefore, such therapy is not recommended anymore. Koelz et al, reported *H. pylori* eradication of 52% and improvement of dyspepsia symptom by using dual therapy (amoxicillin and omeprazole) compared to the control group that used omeprazole only in 6 months following the eradication treatment with no significant difference.[26] The result is similar to previous study, i.e. a study by Behrens et al, that demonstrated different effectiveness of eradication treatment by using dual therapy compared to triple therapy. They found 52% eradication by using dual therapy (omeprazole and amoxicillin) and 83% eradication by using triple therapy (omeprazole + amoxycillin + clarithromycin). They also concluded that high-dose omeprazole treatment did not affect the eradication result, i.e. there was no significant difference of eradication result between subjects who had omeprazole treatment with 1 mg/kgBW/day and 2 mg/kgBW/day dose.[27]

As have been proven by various studies, *H. pylori* infection may induce progressive change of inflammation in gastric mucosa, which may lead to gastric cancer. Mera R et al, who evaluated long-term cohort study up to 12-years period, found that there is histopathological improvement in patients who had *H. pylori* eradication treatment. Such improvement was demonstrated by decreased histopathology score.

The score was 3.77 (95% CI 3.68-3.86) before treatment and after 6 year treatment, the score was decrease, i.e. 0.13 lower than previous score, and 12 year following treatment the score was 0.59 lower compared to previous data.[28] The other study also concluded that there was significant decrease on activity and inflammation in the antrum and stomach body ($p < 0.001$), as well as significant improvement of atrophy gastritis in the stomach body ($p < 0.001$) excluding the antrum.[22]

The correlation between *H. pylori* and gastric cancer has been proven in a lot of studies. A study by *Helicobacter and cancer collaborative group* reported a relative risk of 5.9 for non-cardiac gastric cancer incidence in patients with *H. pylori*. Such risk is higher than previous meta-analysis study which reported OR of 2.0-3.1.[29] Moreover, regarding the evaluation of ulcer recovery, it is found that the success rate of primary healing of ulcer following one week PPI treatment was 80-85%, after being examined by endoscopy. However, when the PPI treatment was given for one month period, the success rate of duodenal ulcer may increase up to 90%.[2] Goggin et al, found 100% recovery rate of duodenal ulcer in all subjects.[10]

Improvement of Dyspepsia Symptoms

In patients with dyspepsia, detection on *H. pylori* infection is extremely suggested. We recommend UBT diagnostic test, which is the best non-invasive method. Manes et al,[24] reported a very significant dyspepsia symptom in patients who had *H. pylori* detection test before having treatment. The study compared a group of patients with dyspepsia symptoms who directly had PPI and omeprazole treatment (group A) and a group of patients with dyspepsia symptom who had *H. pylori* examination before treatment by using UBT (group B). In group B, if the *H. pylori* is negative, the patients only had omeprazole treatment, while in patients with positive *H. pylori* will had eradication treatment by using triple therapy. The study concluded a significant difference of dyspepsia symptoms in group B patients. There was a significant difference of the patients' visit in 12 months follow up, i.e. approximately 231.5 vs. 139.3 with $p < 0.001$. This also may reduce the number of patients who should undergo endoscopy examination, i.e. the patient who still has dyspepsia symptoms after treatment will have endoscopy examination for further diagnosis. Hence, it will reduce treatment cost either by the patients or government.[18] The evaluation of cost effectiveness is very important because there is a high cost for UBT examination and eradication treatment. Duggan et al, reported a relatively high eradication rate (97%) in patients with *H. pylori* infection, but the treatment is quite expensive, i.e. £62.63 for every patient.[30]

Clinical response following therapy in patients without ulcer ranges about 2-58%.[11] However, several studies reported different results. A meta-analysis in patients without ulcer found that there was 73% improvement of dyspepsia symptoms following eradication treatment with negative *H. pylori* result compared to 45% subjects that remained positive following the eradication treatment.[31] A study by Jaakkimainen et al, reported there was a correlation between *H. pylori* and non-ulcer dyspepsia symptoms with odd ratio of 1.6, and there was improvement of symptoms following the eradication treatment with odd ratio of 1.9.[11] A study by Lane et al, in patients with dyspepsia at primary health care unit concluded that there was only 35% who still had dyspepsia symptoms following 2 year *H. pylori* eradication treatment. However, there was no different quality of life in patients who had eradication treatment compared to the placebo. The other study also reported the number of patient who should be treated to cure a patient (NNT = number needed to treat) was 15.[32]

The effect of *H. pylori* eradication treatment in patients with functional dyspepsia is still debated. Talley NJ evaluated patients with functional dyspepsia who were infected by *H. pylori*. Eradication of *H. pylori* was found in 85% patients. However, after 12 month follow up, the improvement of dyspepsia symptoms was not significantly different between the treatment group and the control group, i.e. 24% vs. 22%. The study concluded that there was no valid evidence that *H. pylori* eradication will improve functional dyspepsia symptoms following 12 months therapy.[33]

Chiba et al, studied the success rate of *H. pylori* eradication treatment and improvement of dyspepsia symptom in patients with dyspepsia without differentiating functional and organic dyspepsia. They found 80% success rate of *H. pylori* eradication treatment and 54% improvement of dyspepsia symptoms. The study found NNT value for a patient cure of 7.[34]

Different result in this study may be caused by different observation period for those patients. Some investigators assume that there is a different improvement of dyspepsia symptom in patients observed after 12 months eradication treatment and before 12 months eradication treatment. There is higher incidence of dyspepsia improvement in patients who are observed more than 12 months. This may be due to incomplete gastritis recovery following *H. pylori* eradication

before 12 months period.[28] Goggin et al, evaluated dyspepsia symptoms as well as other symptoms correlated to peptic ulcer and found improvement of such symptoms up to 100%. All subjects showed ulcus

recovery and disappeared symptoms after long-term evaluation with median period of 37 months (ranged 26 - 62 months).[10] Rosengen & Polson who evaluated improvement of dyspepsia symptoms in patients with duodenal ulecer found 88.2% improvement of dyspepsia symptoms after 1-month therapy. However, after 4 months therapy, two subjects experienced dyspepsia symptoms and the other two subjects still occasionally consumed antacids or anti-H_2 receptor although they did not have any dyspepsia symptom again. Thus, the percentage of dyspepsia improvement reduced in the fourth month, i.e. only 76.5%.[25]

Unlike dyspepsia symptoms, some investigators observe different correlation between *H. pylori* and reflux oesophagitis. Beil et al, conducted a study on parietal cells of rats. The study demonstrates that from the isolated parietal cells, *H. pylori* and MOA (*H. pylori* fatty acid cis 9,10-methyleneoctadecanoic) augments the potency of omeprazole 1.8 times in inhibiting the acid production but *H. pylori* do not affect the potency of omeprazole in inhibiting the activity of H^+/K^+-ATPase.[35] This study is supported by Koike et al in Japan which concluded that the incidence of reflux erosive oesophagitis is more frequently occur in patients without *H. pylori* infection or gaster hyposecretion. *H. pylori* infection in reflux oesophagitis case usually occurs without gaster hyposecretion. Hence, it is assumed that *H. pylori* may inhibit the development of reflux oesophagitis by inducing gastric hypoacidity.[36] Some studies also indicated no significant difference on clinical improvement of reflux oesophagitis in patients following eradication treatment. A study by Harvey et al, reported that there was no significant result either for heartburn symptom following two year *H. pylori* eradication treatment with odd ratio 0.99 (CI = 0.88-1.12), or gastroesophageal reflux with odd ratio 1.04 (CI = 0.91-1.19).[8]

Recent epidemiology studies in western countries tend to demonstrate increased incidence of reflux oesophagitis (about 25-40%) in accordance with decreased incidence of duodenal ulcer induced by *H. pylori*. This data is also supported by low prevalence of *H. pylori* in patients with *GERD* (about 5-10%), which is assumed to be lower than the prevalence of *H. pylori* in control population.[37,38] The prevalence of *H. pylori* in patients with *GERD* reported by Raghunath et al, was 38.2% compared to 49.5% in the control group. The estimation value of OR was 0.59 (CI = 0.51-0.66).[38] Although a lot of studies have demonstrated that there is no correlation between *H. pylori* infection and the incidence of *GERD*, but in most patients *H. pylori* eradication does not induce the development of *GERD*. A prospective study indicated GERD recurrent rate of 83% after one year follow up and there was no significant different of recurrent rate in patients who had eradicated *H. pylori*, persistent *H. pylori* infection or patients with negative *H. pylori* status prior to the study. [39]

H. pylori Treatment in Healthy Population

Although chronic *H. pylori* infection has been demonstrated to cause gaster atrophy and intestinal metaplasia, which are significant risk factors for the development of gastric cancer, but recent guidelines do not recommend eradication treatment for asymptomatic patients. Vaira D et al, examined 169 blood sample donor infected by *H. pylori* without dyspepsia symptoms. Upon subjects' permission, an eradication treatment was given and after 8 year follow up the concluded that *H. pylori* eradication treatment may inhibit the development of dyspepsia symptoms, i.e. 83% patients at the end of the trial remained asymptomatic (147 of 169 patients remained asymptomatic), and only 13 patients had dyspepsia symptoms subsequently (i.e. 12 patients with positive *H. pylori* status and 1 patient with negative *H. pylori*). [40]

CONCLUSION

Helicobacter pylori infection is a main etiology of peptic ulcer incidence and urease test, which is directly conducted, for specimen biopsy taken by gastroscopy is a gold standard examination to establish the diagnosis of *H. pylori*; while the gold standard non-invasive examination is *urea breath test* (UBT). The success rate of eradication treatment in patients with peptic ulcer is 90% and the best non-invasive diagnostic test to evaluate successful eradication treatment is UBT examination. In addition, evaluation of ulcer recovery following eradication treatment with 1-month PPI therapy reveals duodenal ulcer recovery up to 90%.[2] In patients without ulcer, the clinical response ranges about 21-58%. However, the correlation between improvement of dyspepsia symptom and successful eradication treatment has not been clearly demonstrated. Clinical improvement of dyspepsia symptoms usually occurs in 12 months following the eradication treatment. There is no correlation between successful eradication treatment and clinical improvement of reflux oesophagitis symptoms.

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