Influence of Fucoidan in Mucus Thickness of Gastric Mucosa in Patients with Chronic Gastritis

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ABSTRACT

Background: *Chronic gastritis is commonly found with complains of dyspepsia, which may decrease work productivity. Imbalance between agressive and defensive factors is the cause of chronic gastritis. Therapy is mostly directed to the agressive factors, particularly gastric acid and very few studies are directed on defensive factors. Mucus is the first defense mechanism of gastric mucosa. Fucoidan is a phytopharmaca, which is thought to increase the thickness of gastric mucosa. The objective of this study was to know the thickness of gastric mucosa in patients with chronic gastritis and to evaluate the effect of fucoidan to the gastric mucosa thickness in patients with chronic gastritis.*

Method: *In this double-blinded randomized clinical trial study, 41 patients in the Endoscopy Unit Cipto Mangunkusumo Hospital between October 2009 and October 2010 were enrolled consecutively. Selected patients were divided into 2 groups: a group was given fucoidan and another group was given placebo. Statistical analysis was done using T-test.*

Results: *Of 41 chronic gastritis patients, only 34 patients completed this study. There was difference of mucus thickness of gastric mucosa in patients with chronic gastritis; in the antrum 42.59 µm (± 8.67) and in the corpus 44.28 µm (± 9.64). This study also showed that fucoidan administration increased the mucus thickness in the antrum by 7.42 µm and in the corpus by 7.74 µm compared to placebo significantly.*

Conclusion: *Fucoidan increased the mucus thickness of gastric mucosa in patients with chronic gastritis.*

Keywords: *mucus thickness, chronic gastritis, fucoidan*

ABSTRAK

Latar belakang: *Gastritis kronik seringkali ditemukan dengan keluhan dispepsia yang dapat menurunkan produktivitas kerja. Ketidakseimbangan antara faktor agresif dan defensif merupakan penyebab gastritis kronik. Terapi sebagian besar ditujukan terhadap faktor agresif terutama pada asam lambung. Namun saat ini sedikit sekali penelitian tentang faktor defensif. Mukus merupakan lini pertahanan pertama mukosa lambung yang merupakan faktor defensif, sedangkan fucoidan yang merupakan fitofarmaka diperkirakan dapat menambah ketebalan mukosa lambung. Tujuan penelitian ini yaitu untuk mengetahui ketebalan mukosa lambung pada pasien gastritis kronik dan efek fucoidan terhadap ketebalan mukosa lambung pada pasien gastritis kronik.*

Metode: *Penelitian ini menggunakan desain uji klinik acak tersamar ganda pada 41 pasien di Unit Endoskopi Rumah Sakit Cipto Mangunkusumo pada bulan Oktober 2009 hingga Oktober 2010 secara konsekutif. Pasien yang terpilih dibagi menjadi 2 kelompok yaitu kelompok dengan fucoidan dan plasebo. Analisis statitistik dilakukan dengan menggunakan uji-T.*

Hasil: *Dari 41 pasien gastritis kronik hanya 34 pasien yang mengikuti penelitian hingga selesai. Didapatkan perbedaan ketebalan mukus mukosa lambung pada pasien gastritis kronik di antrum 42.59 µm (± 8.67) dan*

di korpus 44.28 µm (± 9.68). Hasil penelitian juga menunjukkan pemberian fucoidan menambah ketebalan mukus antrum 7.42 µm dan mukus korpus 7.74 µm dibandingkan plasebo secara bermakna.

Kesimpulan: *Fucoidan menambah ketebalan mukus mukosa lambung pada pasien gastritis kronik.*

Kata kunci: *ketebalan mukus, gastritis kronik, fucoidan*

INTRODUCTION

Gastritis is a health problem most commonly found in the clinic, which causes huge health cost and decreases work productivity.[1] Imbalance between agressive and defensive factors in the stomach is the mechanism how gastritis developed. A lot of medicines have been found to be beneficial in overcoming the agressive factors, such as proton pump inhibitors (PPI) and histamine 2 receptor antagonist (H2A). Different with agressive factors, till date there is only few therapy to improve defensive factors. However, there are several agressive factors which influence the mucus thickness, and many medicines are objected to overcome these agressive factors.[2]

Mucus is a sulphate containing polysaccharide which has anti-peptic activity through ionic binding with proteins on the mucosal surface, which are pepsin substrates, and not through enzymatic inhibition.[2] Mucus of the gastric mucosa plays role in the first defense mechanism of the stomach. Therefore, its role is very important before irritant substances reach the epithelial cells of the gastric mucosa. Gastric mucosa is protected from acid and pepsin by mucus, which is a proteoglycan secreted by epithelial cells of gastric mucosal surface. There is no data about the mucus thickness of gastric mucosa in patients with chronic gastritis, which is possibly thinner compared to healthy individuals.

It is reported that fucoidan administered orally is proven to be effective in treating and preventing gastric ulcer in animal studies.[3] Fucoidan polysaccharide is also known to be effective in cell proliferation, particularly in digestive tract and also has some benefits, such as: may resolve inflammation in the stomach (gastritis) as well as ulcer.[4] In the study conducted by Yamamoto which examined the effect of tea containing fucoidan derived from mozuku in patients with gastric ulcer and non-ulcer dyspepsia, improvement in subjective symptoms was found.[5] Many studies have reported that fucoidan administration improved ulcers. However, none evaluated the effect of fucoidan in patients with chronic gastritis, particularly the effect towards mucus thickness. Fucoidan has cytoprotective effect to the gastric mucosa, protecting epithelial cells of the gastric mucosa from irritant substances. This will enable the vascularization of these epithelial cells to have function properly and optimally, predominantly in the mucus production and will lead to increase production of growth factors important for re-epithelialization. Therefore, this clinical study was performed to evaluate the effect of fucoidan to mucus thickness of gastric mucosa in patients with chronic gastritis.

METHOD

This study is a double-blinded randomized clinical trial to evaluate the effect of fucoidan to mucus thickness of the gastric mucosa in chronic gastritis patients between October 2009 and April 2010 in Endoscopy Unit, Cipto Mangunkusumo Hospital. Sample selection was done consecutively. Patients aged 18-60 years old, suffering from chronic gastritis which has been confirmed through endoscopy, and has given informed consent to participate in this study were included.

Exclusion criteria included (1) patients contraindicated to undergo esophagoduodenoscopy (EGD), endoscopy, biopsy, or to consume fucoidan, such as: individuals with hematologic disturbance (e.g. pregnant or lactating women), hypersentive to fucoidan (2) condition which influence mucus thickness and changes of mucus thickness, for example: on medication which may induce gastritis or ulcer, such as: non-steroid anti-inflammatory drugs (NSAIDs), alcoholism, pylori stenosis, history of gastric surgery, renal abnormalities (creatinine > 2 mg/dL), liver disease [abnormal aspartate transaminase (AST)/alanine transaminase (ALT)] > 2 times upper limit of normal values, bilirubin > 2 mg/dL), congestive gastropathy due to cirrhosis, congestive heart failure, consuming gastroprotective medicines, such as teprenon, sucralfate, acid suppressor agents (PPI, H2A), antibiotics, mesalazine (salofalk), and (3) conditions which need to be treated with PPI/H2A, such as erosive or ulcerative esophagitis, peptic ulcer which has been confirmed with endoscopy, and experiencing active gastrointestinal bleeding.

In patients were performed physical examination, laboratory examination, esophagoduodenoscopy, and

gastric biopsy in 4 areas (2 areas in antrum and 2 areas in corpus). Patients were further randomized into 2 groups, fucoidan and placebo groups. Randomization was performed according to block permutation using table. Every patient received 1 tablet daily for 28 days. The reading of mucosal thickness was performed using ocular micrometer in light microscope with enlargement of 10 x 10 to determine the good specimen plate with 1 scale unit in ocular micrometer was equal to 10 micron.[6] Reading of mucus thickness was performed in 4 random areas which has fulfilled criteria mention above and average of the results were taken. This reading was meant to overcome the intraobserver variability. Patient was then given a daily note on the progression of disease, symptoms, and checklist of medicines taken, and rescue drug, antacid, if there were symptoms during the course of the study. Later, re-monitoring was conducted to the patient by repeating the examinations, including physical examination, laboratory examination, esophagoduodenoscopy, and biopsy in 4 areas of the gaster (2 areas in the antrum and 2 areas in the corpus).

Difference on the mucus thickness before and after intervention in each group was analyzed using paired T-test. Difference on the mucus thickness before and after therapy between the fucoidan and placebo group was analyzed using unpaired T-test. All analysis will be using 5% significancy, with 95% confidence interval. Data distribution was analyzed using Kolmogorov-Smirnov test. In addition, analysis at the end of the study was conducted using per protocol principle analysis.

RESULTS

Of 41 patients who fulfilled the criteria and gave consent to participate in the study, 7 patients did not complete the study. There was no adverse effect found in patients who received fucoidan and placebo clinically or in laboratorium. Patients' characteristics were described in Table 1.

From histopathologic examination, 1 (2.4%) patient suffered from *H. pylori* infection in fucoidan group and after 28 days, the infection was negative. Laboratory results of hemoglobin, leukocytes, thrombocytes, ureum, creatinine, AST and ALT were similar in both, fucoidan and placebo group. Besides, in the analysis of mucus thickness variability based on comparing results of mucus thickness reading performed by researcher and an anatomy-pathologist, correlation of 0.954 was obtained.

Table 1. Patients' characteristics

Characteristic	Fucoidan n = 20	Placebo n = 21
Age ± SD (years)	45.25 ± 11.86	40.81 ± 9.55
Sex (%)		
Male	10 (50)	10 (47.6)
Female	10 (50)	11 (52.4)
Ethnics (%)		
Javanese	10 (50)	8 (38.1)
Batak	4 (20)	2 (9.5)
Minangkabau	3 (15)	2 (9.5)
Sundanese	2 (10)	5 (23.8)
Betawi	0 (0)	2 (9.5)
Etc	1 (5)	2 (9.5)
Education level (%)		
Master's degree	1 (5)	1 (4.8)
Bachelor's degree	3 (15)	2 (9.5)
Senior high school	7 (35)	5 (23.8)
Junior high school	4 (20)	3 (14.3)
Elementary school	0 (0)	3 (14.3)
No schooling	2 (10)	1 (4.8)
Etc	3 (15)	1 (4.8)
Occupation (%)		
Government employee	3 (15)	5 (23.8)
Private employee	2 (10)	3 (14.3)
Entrepreneur	2 (10)	5 (23.8)
Student	1 (5)	1 (4.8)
Unemployment	7 (35)	3 (14.3)
Etc	5 (25)	4 (19)
Smoking (%)		
Yes	7 (35)	8 (38.1)
No	13 (65)	13 (61.9)
Diabetes mellitus (%)		
Yes	3 (15)	1 (4.8)
No	17 (85)	20 (95.2)
Hypertension (%)		
Yes	4 (20)	3 (14.3)
No	16 (80)	18 (85.7)
Body mass index (%)		
< 18.5	2 (10)	4 (19)
≥ 18.5	18 (90)	17 (81)
H. pylori infection		
Yes	1 (5)	0 (0)
No	19 (95)	21 (100)
Laboratory examination		
Hemoglobin ± SD (g/dL)	13.3 ± 1.9	13.5 ± 0.9
Leukocyte ± SD (/uL)	8,410 ± 2,170.3	7,623.8 ± 1,861.7
Thrombocyte ± SD (/uL)	335,150 ± 107,631	319,571 ± 72,512
Ureum ± SD (mg/dL)	21.6 ± 7.4	22.0 ± 8.9
Creatinine ± SD (mg/dL)	0.8 ± 0.2	0.8 ± 0.3
AST ± SD (mg/dL)	25.3 ± 10.1	22.5 ± 6.7
ALT ± SD (mg/dL)	25.6 ± 16.9	19.1 ± 11.1

SD: standard deviation; *H. pylori: Helicobacter pylori,* AST: aspartate transaminase; ALT: alanine aminotransferase

There was no significant different on the antrum mucus thickness before initiation of therapy in fucoidan and placebo group (p = 0.17). Differently, there was significant difference of corpus mucus thickness before initiation of therapy in fucoidan and placebo group (p = 0.04) (Table 2).

Table 2. Mucus thickness before initiation of therapy

	μm (SD)	Fucoidan μm (SD)	Placebo μm (SD)	
Antrum	42.59 (8.67)	40.69 (8.91)	44.40 (8.24)	p = 0.17*
Corpus	44.28 (9.64)	41.16 (9.61)	47.26 (8.89)	p = 0.04*

*Unpaired T-test

Antrum mucus thickness before and after therapy in each group showed significant difference. The difference of antrum mucus thickness before and after therapy between fucoidan and placebo group also showed significant difference (Table 3).

Table 3. Effect of fucoidan to antrum mucus thickness

	Before µm (SD)	After µm (SD)	Δ µm	
Fucoidan (n=16)	39.10 (9.03)	51.52 (8.93)	12.42	p < 0.001*
Placebo (n=18)	44.51 (8.78)	49.51 8.10)	5.00	p = 0.002* p = 0.001**

*Paired T-test; **Unpaired T-test; Δ: the difference of antrum mucus thickness before and after therapy

The difference in corpus mucus thickness before and after therapy showed significant difference between fucoidan and placebo group (Table 4). Based on the difference of mucus thickness in antrum and corpus before and after therapy, significant difference was exhibited (Figure 1).

Table 4. Effect of fucoidan to corpus mucus thickness

	Before µm (SD)	After µm (SD)	Δ µm	
Fucoidan (n = 16)	38.75 (8.93)	49.96 (7.56)	11.21	p < 0.001*
Placebo (n = 18)	47.29 (9.54)	50.76 (7.40)	3.47	p = 0.08* p = 0.007**

*Paired T test; **Unpaired T-test; Δ: the difference of corpus mucus thickness before and after therapy

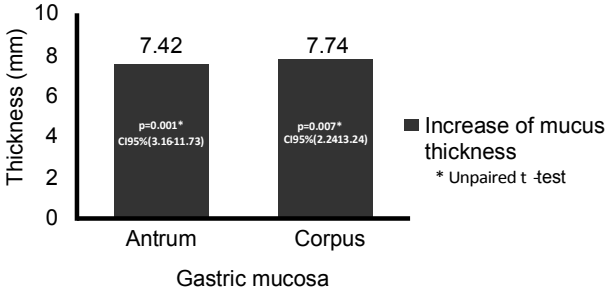

Figure 1. Fucoidan effect to mucus thickness of gastric mucosa

DISCUSSION

This study included chronic gastritis patients with similar characteristics between fucoidan and placebo group, in terms of sex, ethnics, occupation, and educational status. Demography characteristics in this study was similar to the study performed by Antono et al, on mucus thickness in patients with NSAIDs gastropathy and the study conducted by Jhuffrie et al on the effect of fucoidan towards gastric ulcer.[6,7]

In the mucus thickness variability based on the comparison of reading results of mucus thickness by researcher and an anatomy-pathologist, correlation of 0.954 (very good) was acquired. Therefore, the interobserver variability was very small which showed that the reliability of the measurement was high. In this study, interim analysis was performed due to limited time and cost, and also due to suspicion of improvement in endoscopic appearance in some patients and no significant improvement in the other patients by using smaller significant value (p = 0.02).

Mucus thickness in the antrum was thinner compared to the corpus in patients with chronic gastritis. This is in concordance with the study of Antono et al, on mucus thickness in patients with NSAIDs gastropathy and also in line with histology theory of gastric mucosa in the corpus, in which epithelial cells were thicker and mucus cells were more abundant compared to antrum.[7,8] Methods used in this study was similar with the methods used in the study conducted by Antono.[7] However, in the study conducted by Allen et al, to mice, the mucus thickness of the antrum was thicker compared to the corpus.[9] Data on mucus thickness of the antrum has been reported in the study conducted by Allen and Bickel et al. However, there was no previous data on mucus thickness in patients with chronic gastritis.[10,11] Data from the study held by Jordan et al found that mucus thickness in normal individual was 144 µm, however using a different method from the method used in this study, in which modified staining of schif periodic/alcian blue was used, reported that this method was better compared to the conventional method used in this study. This is because the continuity and integrity of the mucus would be better seen.[12] Compared to normal patients, mucus thickness in patients with chronic gastritis in this study was thinner. This is in accordance with the theory that in patients with chronic gastritis, there is inflammation of gastric mucosa which may disrupt the function of epithelial cells of the gastric mucosa in producing mucus.[8]

There are many medicines available to treat peptic ulcer, such as H2A, PPI, and sucralfate. From these medicines, studies are mostly directed to agressive factors and very few studies are directed to defensive factors. Before ulcer is developed, repeated stress to the epithelial of gastric mucosa occur.[3] Several medicines are directed to overcome the agressive factors in the development of peptic ulcer and very few medicines are used to modify defensive factors. Mucus is the first defense mechanism in the stomach, which potentially prevents the development of peptic ulcer. Misoprostol, a prostaglandin analog, is also a potent medicine to inhibit gastric acid and stimulate

the development of gastric mucus. However, this medicine has many side effects, such as pain, abdominal cramping, and diarrhea.[13] Conversely, fucoidan is believed to increase the mucus of gastric mucosa with no side effects.

The existence of significant difference on mucus thickness between fucoidan group and placebo in the antrum and corpus showed the presence of significant effect of fucoidan towards mucus thickness of gastric mucosa. This effect is acquired through the cytoprotective effect and increase growth factor production on epithelial cells of the gastric mucosa.[14] With the presence of cytoprotective effect, the epithelial of mucosal surface may function optimally in producing mucus. Similarly, the presence of growth factors will enhance epithelial regeneration, so that mucus production by new epithelial cells will be better.[13] Sucralfate also has cytoprotective effect, but has no effect in increasing growth factor production in the epithelial cells of gastric mucosal surface and effect towards the thickness of mucus of gastric mucosa.

Study on fucoidan and clinical symptoms of dyspepsia has been performed previously by Jhuffrie et al, which concluded that fucoidan was able to improve dyspepsia symptoms in patients with gastric ulcer.[6] Mechanism of symptoms improvement in that study was unclear. One of the hypotheses is that it increased the mucus thickness, and thus, the mucus thickness which was thought to be thinner than normal people would increase and would approximately achieve the normal mucus thickness and protected gastric mucosa.

There is no data on the value of mucus thickness which will exhibit dyspepsia symptoms. Through data collection on mucus thickness in chronic gastritis patients, it was predicted that with mucus thickness of < 50 μm, dyspepsia symptoms will be exhibited. Previous studies in normal individuals found that the thickness of gastric mucus was > 100 μm.[10,11,12] Nevertheless, a particular study to find the relationship between mucus thickness and dyspepsia symptoms is needed, in order to show the thickness of mucus which exhibit dyspepsia symptoms.

Although there was an increase of mucus thickness after administration of 100 mg fucoidan for 28 days, the mucus thickness has not reach the mucus thickness in normal individuals.[12] Possibly, the administration of fucoidan in longer term will improve the mucus thickness similar to normal individuals, not only in chronic gastritis patients but also in patients with mucus thickness disturbance, such as in patients with NSAIDs induced gastropathy, *H. pylori* infection, or peptic ulcer. Yet, further studies are needed to prove it.

Increase of mucus thickness induced by fucoidan may play role in preventing peptic ulcer. Nevertheless, particular study is needed for further evaluation. Besides preventive factors, fucoidan may also improve subjective dyspepsia symptoms, such as in the study performed by Jhuffrie et al.[6] Currently, a study is conducted to determine the effect of fucoidan towards dyspepsia symptoms and improvement in endoscopy appearance in chronic gastritis patients.

Different with the study conducted by Jhuffrie et al, which used omeprazole, this study was performed to patients who were given fucoidan without administration of any other medicine, so that the direct effect of fucoidan could be seen without the influence of other medicines.[6] However, in this study, the exclusion factors were many and was held in single centre with limited sample. Thus, it can be assumed that generalization of this study can only be done in patients with chronic gastritis, without liver function disturbance, heart failure, and others according to the selection criteria. In implementation to chronic gastritis patients in Indonesia, generally there should be multicentre study with the same study design and methods, to be assumed as representation of chronic gastritis patients in Indonesia.

CONCLUSION

Thickness of mucus in the antrum and corpus in patients with chronic gastritis was thinner compared to normal patients. Thus, administration of fucoidan may increase the thickness of mucus in antrum and corpus in patients with chronic gastritis in Cipto Mangunkusumo Hospital.

SUGGESTION

As a complementary to this study, further study is needed, including multicentre study to acquire the mucus thickness data, the effect of fucoidan towards mucus thickness in patients with chronic gastritis, standard mucus thickness which will exhibit dyspepsia symptoms. Besides, this further study is expected to represent the population of patients with chronic gastritis in Indonesia.

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