Combination of PPI with a Prokinetic Drug in Gastroesophageal Reflux Disease

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ABSTRACT

Aim: *to evaluate the efficacy of combination of PPI with prokinetic drug compared to PPI mono therapy in GERD patients with high frequency scale for the symptoms of GERD (FSSG) score.*

Methods: *sixty dyspeptic patients having heartburn and/or regurgitation were recruited during the period of July 2010 – April 2011 in this double blind clinical trial. By randomization, they were divided into two groups; group A was given omeprazole 2x20 mg and domperidone 3x10 mg for 2 weeks, while another group was only given omeprazole 2x20 mg. The FSSG score was performed before treatment and after 2 weeks of treatment.*

Results: *there were 20 (33%) males and 40 (67%) females. The mean total score of FSSG was 25.3±8.2 at pretest, and 19.3±9.7 at posttest, with improvement of 6.1±4.9. The FSSG score in group A after treatment (19.3±11.3) was significantly lower than before treatment (26.7±8.9, p<0.001) as well as in group B (from 23.9±7.3 to 19,3±7.9, p<0.001). The mean improvement score in group A was 7.5±5.9, while in the group B was of 4.6±3.3, and this difference was statistically significant (p=0.02)*

Conclusion: *combination of omeprazole with domperidone in GERD patients with high FSSG score is more superior compared to omeprazole monotherapy.*

Key words: *GERD, FSSG, omeprazole, domperidone.*

INTRODUCTION

Dyspepsia syndrome and gastroesophageal reflux disease (GERD) are prevalent in the community throughout the world.[1] Gastroesophageal reflux disease (GERD) is defined as a pathological condition when the amount of gastric contents reflux into the esophagus exceeds the normal limit, with a variety of symptoms caused.[2,3]

The prevalence of GERD in Asia, including Indonesia, is relatively lower compared to Western countries. In United States, nearly 7% of the population have a heartburn complaint, and 20-40% of them are estimated to suffer from GERD. Prevalence of esophagitis in the West ranged from 10-20%, while in Asia only 3-5%, with the exception of Japan and Taiwan (13-15%).[3,4] There is no gender predilection on GERD, in which men and women have the same risk, but the incidence of esophagitis in males was higher (2:1-3:1), likewise the incidence of Barrett's esophagitis is also higher (10:1).[2] GERD can also occur in all age groups, but the prevalence increases in ages over 40 years.[2]

Typical clinical symptoms of GERD are heartburn (burning sensation in the chest accompanied by pain) and regurgitation (sour and bitter taste on the tongue).[1,4.5] The 2004 National Consensus for Gastro-esophageal Reflux Disease (GERD) treatment in Indonesia[4] has agreed on the basic standards of diagnosis is the upper gastrointestinal endoscopy. However, endoscopic examination of the upper gastro-intestinal tract is not easy to be implemented as the facilities and experts are not always available and it is often less comfortable for patients. Besides, repeating the procedure of the endoscopic examination for the purpose of treatment's evaluation is not practical to do. Hence, there is a scoring system that has been developed for the screening and evaluation of GERD therapy.[6] Currently, a scoring

system called the Frequency Scale for the Symptoms of GERD (FSSG) has been developed in Japan to evaluate GERD symptoms. This questionnaire is specific to GERD, which contains 12 questions consisting of seven questions for reflux score and five questions to score the dysmotility or dyspeptic.[7] FSSG score has been validated against the endoscopic findings in Japan with the cut-off score (cut points) at 8, showed sensitivity of 62%, specificity 59% and accuracy of 60%.[8,9] Ndraha (2010) had measured FSSG score from 129 dyspeptic patients with heartburn and regurgitation, and found that the symptoms of dyspeptic/dysmotility was more dominant than symptoms of reflux, while the mean FSSG score was 17.6±6.9.[10]

The National Consensus 2004 for Gastro-esophageal Reflux Disease (GERD) treatment in Indonesia[4] had mentioned that proton pump inhibitor (PPIs) is the most effective agent to treat GERD, compared to antacids, prokinetics, and H2 receptor blockers. PPI works by blocking the final step in the H+ ion secretion by the parietal cell. They have few adverse effects and are well tolerated for long-term use. PPI should be given for 8 weeks as initial treatment in GERD.[2] Due to the superiority and efficacy of PPI, treatment of GERD should be started with PPI. However, in some cases, PPI monotherapy cannot completely resolve symptoms in all cases of GERD, and combination therapy with prokinetic will further improve symptoms for some GERD patients.[7]

Miyamoto et al found that high score FSSG is one of the factors related to failure of PPI mono therapy, in addition to female gender, alcohol consumption and obesity. Thus, GERD with a high FSSG score requiring PPI combination therapy with pro-kinetic drug for a more satisfactory outcome.[7] Therefore, it is important to prove that in GERD population with a high mean FSSG score, combination therapy of PPI with pro-kinetic drug is more superior compare to PPI only.

The aim of this study was to know the efficacy of combination of PPI with pro-kinetic drug compared to PPI mono therapy in high FSSG score GERD patients.

METHODS

This study used double blind clinical trial design, with the population of all outpatients who visited Department of Internal Medicine Koja hospital in the period of July 2010 – April 2011. Samples were taken by using non probability sampling, that is consecutive sampling.

The inclusion criteria were the presence of heartburn (burning sensation in the chest accompanied by pain) and / or regurgitation (acid taste and bitter to the tongue). Patients would be excluded if they refused to participate in the study or could not speak Indonesian. Data were taken from all patients who met the inclusion criteria and the FSSG score was obtained.

All 60 patients who fulfill the inclusion criteria divided into 2 groups using Randomized Block Design, named group A (30 subjects) and group B (30 subjects).

One group has been given omeprazole 2x20 mg and domperidone 3x10 mg for 2 weeks, while another group was only given omeprazole 2x20 mg. Both the study participants and the investigator did not know the treatment received by each group, until the code was opened at the end of study. After 2 weeks, their FSSG score was measured again.

All the data were recorded in the entry form, and further organized using descriptive statistics, presented as mean ± SD for numerical data, and proportion (%) for the categorical data. To analyze the improvement of FSSG score before and after treatment between those two groups, statistical analysis for this trial was independent student t-test.

RESULTS

This study had been done on patients with dyspepsia with heartburn or regurgitation, or both. There were 60 patients, 20 (33%) males, 40 (67%) females. After randomization, 30 people were put into group A (received combination omeprazole and domperidone) and the other into group B (omeprazole only). The mean age of 42.3 ± 13.1 years, 45% in the age group of < 40 years and 43% in 40-60 years. Only 7% patients were aged over 60 years. Body mass index (BMI) of most patients (70%) was normal, overweight (BMI 25-30 kg/m^2) was found in 12.5% patients, 15% met the criteria of underweight (BMI <18.5 kg/m^2), and only 1 patient (2.5%) who met the criteria of obese (BMI > 30 kg/m^2).

Frequency scale for the symptoms of GERD (FSSG) score that was conducted on 60 patients, revealed the mean of pretest score being 25.3 ± 8.2, posttest score 19.3 ± 9.7, improvement score (the gradient of pretest and posttest) 6.1 ± 4.9, as could be seen in **Table 1**.

Statistical analysis using paired t test, revealed that the FSSG score in group A after treatment (19.3±11.3) was significantly lower than before treatment (26.7±8.9, p<0.001). The same result was found in group B, with FSSG score after treatment reduced significantly (from 23.9±7.3 to 19.3±7.9, p<0.001).

The gradient score in each group, called

improvement score, was compared using unpaired t test. The mean improvement score in the group A was 7.5±5.9, while in group B was of 4.6±3.3, and this difference was statistically significant (p=0.02) as shown in **Table 2** and **Figure 1**.

Table 1. Characteristics of 60 study subjects

Variables	Total Subjects (% or SD)	Group	
		A (% or SD)	B (% or SD)
Number of Subjects (%)	60 (100)	30 (50)	30 (50)
Gender			
- Male	20 (33)	14 (47)	6 (20)
- Female	40 (67)	16 (53)	24 (80)
Age (years)	42.3±13.1	44.3 (12.2)	40.4 (13.9)
Age group			
- <40 years	27 (45)	11 (37)	16 (53)
- 40-60 years	26 (43)	15 (50)	11 (37)
- >60 years	7 (12)	4 (13)	3 (10)
BMI (kg/m2)			
- <18.5 = underweight	6 (15)	3 (15)	3(15)
- 18.5-24.9 = normal	28 (70)	15 (75)	13 (65)
- 25.0-29.9 = preobese	5 (12.5)	2 (10)	3 (15)
- ≥30 = obese	1 (2.5)		1 (5)
FSSG score			
- Pretest	25.3±8.2	26.7(8.9)	23.9(7.3)
- Posttest	19.3±9.7	19.3 (11.3)	19.3 (7.9)
- Improvement score	6.1±4.9	7.5 (5.9)	4.6 (3.3)

Table 2. Results of the mean improving of FSSG score in group A and group B

Variables	Before (mean+SD)	After (mean+SD)	Different (mean+SD)	p value
FSSG score in group A	26.7±8.9	19.3±11.3	7.5±5.9	<0.001
FSSG score in group B	23.9±7.3	19.3±7.9	4.6±3.3	<0.001
Mean improvement score			2.9±1.2	0.02

DISCUSSION

Most patients studied in this study were females (67%). Some authors in Western countries reported that gender differences did not influence the incidence of GERD.[2] However, this study found that female patients with GERD are dominant compared to male. Mantynen (2002) examined 3378 patients with GERD, and got the ratio of male: female was 1: 1.3. 11 In Japan, Miyamoto studied 163 patients with GERD, 99 (60.7%) were

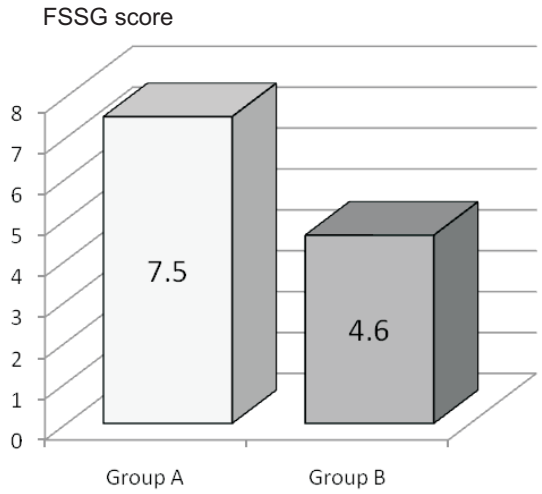

Figure 1. Results of the mean improving of FSSG score in both groups (p= 0.02)

women. According to Miyamoto, female gender is a factor associated with failure of PPI mono therapy.[7] Thus, from the point of gender, this study showed that probability of failure of PPI mono therapy is higher. Gender predominance of female in this study was also more in line with Asian populations.[12]

Body mass index (BMI) of most patients (70%) was normal, overweight (BMI 25-30 kg/m^2) was found in only 12.5 patients, 15% met the criteria of underweight (BMI <18.5 kg/m^2), and there is only 1 patient (2.5%) who met the criteria of obese (BMI >30 kg/m^2). These findings were not in accordance with the literature that states obesity is a major risk factor in GERD.[2,5,13]

Malekzadeh et al reported some significant risk factors for the occurrence of GERD, such as obesity, high fat diet, too much eating, spicy food, smoking, tight clothing, emotional stress, regular fast food, tea and coffee, pregnancy, drugs, and habit of lying down immediately after eating. Among these factors, it is considered that obesity and high fat diet plays an important role in GERD.[5] This lack of conformity may have been obtained because the study sample was small, or because of confounding factors in this study such as age, smoking, alcohol, educational level, and the use of NSAIDs, were not controlled.

The mean FSSG score pretreatment in this study was quite high, that was 25.3 ± 8.2. According to the study of Miyamoto et al, this high score became a factor associated with failure of PPI mono therapy. In his study, Miyamoto et al found that a group that failed with PPI monotherapy had a mean FSSG score of 17.4, and then that group was given a combination therapy of PPI with prokinetic.[7] Miyamoto proposed that pretreatment FSSG scores can be used to predict

the need for the addition of a prokinetic agent to PPI therapy prior to treatment Japanese physicians usually add prokinetic agent to the standard dose of a PPI instead of doubling the dose of the PPI for cases refractory to PPI monotherapy.

Combination PPIs with prokinetics will improve the effect of PPIs. PPIs are unstable at a low pH, dysmotility will slow down gastric emptying, resulting in retention of PPIs. Retention of PPIs inside the stomach for a long time may result in an impaired acid suppressive effect, so rapid transit of the PPIs to the upper intestine will be of benefit.[7] The result of this study do supports this theory. This study showed there was an improvement in FSSG score after treatment in group A (which was given omeprazole and domperidone) as well as in group B (omeprazole monotherapy). Both improvements, were statistically significant (group A $26.7\pm8.9 \rightarrow 19.3\pm11.3$, $p<0.001$; group B $23.9\pm7.3 \rightarrow 19.3\pm7.9$, $p<0.001$). However, in group A the improvement was higher than in group B ($7.5\pm5.9 \rightarrow 4.6\pm3.3$, $p=0.02$). It proves that giving prokinetic together with PPI will have better results than giving PPI only. Based on this, it was recommended to consider the combination therapy, especially in high FSSG score patients.

CONCLUSION

Combination of omeprazole with domperidone in GERD patients with high FSSG score is superior compared to omeprazole monotherapy. The result of this study suggests the use of combination therapy of PPI and prokinetic in GERD patients, especially with high FSSG score. Further studies are needed to assess more about the efficacy and side effects of drugs, with a better research design, larger sample size and longer duration of treatment.

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