A Comparison of Efficacy between Rebamipide and Omeprazole in the Treatment of NSAIDs Gastropathy

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ABSTRACT

Background: Gastropathy represent a disparity of gastric mucosal characterized by sub-epithelial bleeding and erosion. Gastropathy can be induced by non steroidal anti-inflammatory drugs (NSAIDs), alcohol, stressor, and chemical agents with various sign and symptoms. NSAIDs-induced gastropathy is the second most common etiology of gastric ulcer and variceal haemorrhages.

Aims: To investigate the effectivity of rebamipide compare with omeprazole in treatment of NSAIDs-induced gastropathy.

Method: This triple blind randomized study was enrolled from January to June 2004 with 38 subjects who were recruited from outpatient and inpatient clinic in M Hoesin Hospital in Palembang. Subject was divided into two groups. Endoscopic examination was performed in every patients.

Results: There was an improvement of symptom in rebamipide group (78.9%) and omeprazole group (79.0%) after treatment but it didn't have significant difference statistically. Improvement of NSAIDs induced gastropathy after treatment between two groups have significant difference (P = 0.02), and improvement of gradation of gastropathy after treatment has significant difference (P = 0.007).There was no side effect of administration of rebamipide and omeprazole in each group.

Conclusion: Rebamipide as effective as omeprazole in improvement of symptom. Omeprazole is more effective than rebamipide in improvement of NSAIDs induced gastropathy and is as safe as rebamipide in the treatment of NSAIDs induced gastropathy.

***Keywords**: Gastropathy, NSAIDs, rebamipide, omeprazole.*

INTRODUCTION

Gastropathy refers to disorder in gastric mucosa characterized by subepithelial bleeding and erosion. One of the cause of gastropathy is NSAIDs (non steroidal antiinflammatory drugs) aside from other factors such as alcohol, stress or chemical agent. NSAIDs gastropathy may cause varied clinical sign and symptoms from dyspepsia, ulcer, erosion to perforation. In Indonesia NSAIDs gastropathy is 2nd cause of gastropathy after *Helicobacter pylori* and the 2nd cause of upper gatrointestinal bleeding after esophagus variceal rupture.[1]

Many kinds of NSAIDs start from the weakest to the strongest potency to inhibit the prostaglandin synthesis which is the potent mediator in inflammatory process may result in decreased sign of inflammation. However, prostaglandin (PG) specially PGE2 has protective effect for gastrointestinal mucosa mainly the upper one. Inhibiton of PG at one side will reduce the inflamatory process in joints in soft tissues while in the other side will reduce the defense mechanism of gastric mucosa to other insult. This will make the acute lesion on gastric mucosa and duodenum in the mild to severe form.[2] Rebamipide is a new drug which has the potency to protect and resolve gastropathy. Rebamipide has specific mechanism of action as anti free radicals, anti inflammation and also increase secretion of PG.[3]

This study is a triple blind clinical study. Randomization had been used was block randomization by determining the balanced block for every 4 subjects.

This study was conducted in our hospital, rheumatology clinic, Internal Medicine ward from January to June 2004. Sample size involved 38 patients who were divided into 2 groups.

Inclusion criterias were patients whose age 15-65 years old, receiving NSAIDs, had the symptoms of dyspepsia, endoscopic finding in accordance with NSAIDs gastropathy, agreed to participate in the study and sign the informed consent form. The exclusion criteria were reflux esophagitis, pyloric stenosis, pregnancy, on steroid treatment, had chronic disease such as heart disease, hypertension, diabetes, kidney disease, liver disease and malignancy. Rejection criteria were the patients stop using the drugs or died by any cause of death, had complication or severe side effects of trial drug which made the drug had to be stopped and pregnancy during the study period.

Effectiveness Parameter

The effectiveness of therapy was evaluated by endoscopy; decreased grade of lesion and milder clinical symptoms of dyspepsia. To evaluate mucosal disturbance we used Modified Lanza Score (MLS) criteria:[4]

The grading systems according to MLS is as follows:

- Grade 0 : no erosion or bleeding
- Grade 1 : erosion and bleeding in one area or number of lesion ≤ 2
- Grade 2 : erosion and bleeding in one area or there are 3-5 lesions
- Grade 3 : erosion and bleeding in two areas or thereare 6-10 lesions
- Grade 4 : erosion and bleeding > 3 areas or more in gaster
- Grade 5 : there is already gastric ulcer

The grade 4 an 5 were included in this study. Clinical symptoms of dyspepsia are characterized by epigastric pain, heartburn, nausea, vomit, fullness, and anorexia. Dyspepsia is divided into:[5]

- Mild dyspepsia : if the symptoms are well tolerated by patients
- Moderate dyspepsia : if the symptoms are already disturbing but patient can still do normal daily activities
- Severe dyspepsia : if patients cannot do normal daily activities

The improvement conditions by endoscopic findings are divided into 5 categories :

- Mild improvement : decreased one grade level
- Moderate improvement : decreased two grade levels
- Good improvement : decreased grade of dyspepsia ≥ 3 levels
- No improvement : no decreased grade of dyspepsia
- Worsening : increased grade of dyspepsia

MATERIAL AND METHODS

Each patients with NSAIDs gastropathy included in this study had been made individual form containing patient's identity, anamnesis, physical examination, endoscopic examination, laboratory examination. The patients were divided into 2 groups A and B. Group A were given rebamipide 100 mg three times daily and sodium diclofenac 50 mg three times daily for 2 weeks. Group B were given omeprazole 20 mg once daily and natrium diclofenac 50 mg three times daily for two weeks.

During study, observation was done on clinical response and symptoms related to the use of trial drugs. In the end of 2nd week laboratory and endoscopic examination was repeated. The data was collected on research forms. Data was analysed by chi-square test and continuous data analyzed by student *t*-test with significance level of $P < 0.05$.

RESULT

Subject Characteristics

Various ethinic races in South Sumatera from Palembang, OKU, OKI and Sekayu and those from other regions including Padangnese, Bataknese and Javanese. Higher level educations included high school and college. Complete data is shown in table 1.

Table 1. Study Subject Characteristics (N = 38)

Characteristic	Rebamipide Group n (%)	Omeprazole Group n (%)	P
Gender			
Male	6 (31.6)	5 (26.3)	0.72*
Female	13 (68.4)	14 (73.7)	
Mean of Age (x ± SD)	55.79 ± 6.13	56.21 ± 7.13	0.84**
Age Group			0.50*
40-49	3 (15.8)	4 (21.1)	
50-59	10 (52.6)	7 (36.8)	
>59	6 (31.6)	8 (42.1)	
Education			1.00*
High school	8 (42.1)	8 (42.1)	
College	11 (57.9)	11 (57.9)	
Employment status			0.75*
Employed	10 (52.6)	9 (47.4)	
Unemployed	9 (47.4)	10 (52.6)	
Ethnic			0.64*
South Sumatera	17 (89.5)	16 (84.2)	
Outside SouthSumatera	2 (10.5)	3 (15.8)	

Note: * Chi-square, ** t-test

Table 2. Treatment Effect on Laboratory Examination

Characteristic	Rebamipide Group			Omeprazole Group			p
	After X ± SD	Before X ± SD	p**	After X ± SD	Before X ± SD	p**	
Hemoglobin	12.77 ± 1.39	12.71 ± 1.33	0.76	12.97 ± 1.28	12.82 ± 0.87	0.34	0.23
WBC	8,652.63 ± 2,318.37	7,484.21 ± 1677	0.08	8,936.84 ± 2,623.02	7,321.05 ± 1,848.59	0.25	0.77
LED	27.47 ± 20.59	27.63 ± 18.57	0.97	36.47 ± 26.69	26.74 ± 17.17	0.06	0.87
Basophyl	0	0		0	0		
Eosinophyl	2.21 ± 1.87	1.58 ± 1.50	0.30	2.16 ± 2.45	2.53 ± 2.69	0.62	0.18
Netrophyl bar	1.32 ± 0.94	3.63 ± 4.41	0.04	1.53 ± 1.26	1.74 ± 1.36	0.64	0.08
Netrophyl segment	64.42 ± 8.42	62.05 ± 6.61	0.28	66.00 ± 7.83	65.63 ± 5.79	0.84	0.08
Thrombosis	267,157.89 ± 60,676.98	282,368.42 ± 57368.41	0.14	301,473.68 ± 97,917.40	276,842.11 ± 62,338.91	0.10	0.77
BSS	88.00 ± 26.28	86.26 ± 19.07	0.74	92.32 ± 30.77	84.79 ± 14.89	0.16	0.79
BUN	26.37 ± 13.58	21.58 ± 7.71	0.08	31.16 ± 21.60	22.89 ±11.07	0.16	0.67
Creatinine	1.11 ± 0.27	0.98 ± 0.20	0.03	1.05 ± 0.46	0.96 ± 0.31	0.20	0.81
ALT	37.58 ± 10.29	34.47 ± 12.58	0.19	43.16 ± 10.83	37.63 ± 10.91	0.01	0.41
AST	34.00 ± 13.54	27.79 ± 12.61	0.04	38.89 ± 14.13	34.00 ± 14.62	0.09	0.17
Alkaline phosphatase	111.79 ± 48.31	119.26 ± 59.89	0.33	114.47 ± 54.71	104.42 ± 47.24	0.36	0.40

Note: x = mean, SD = standard deviation

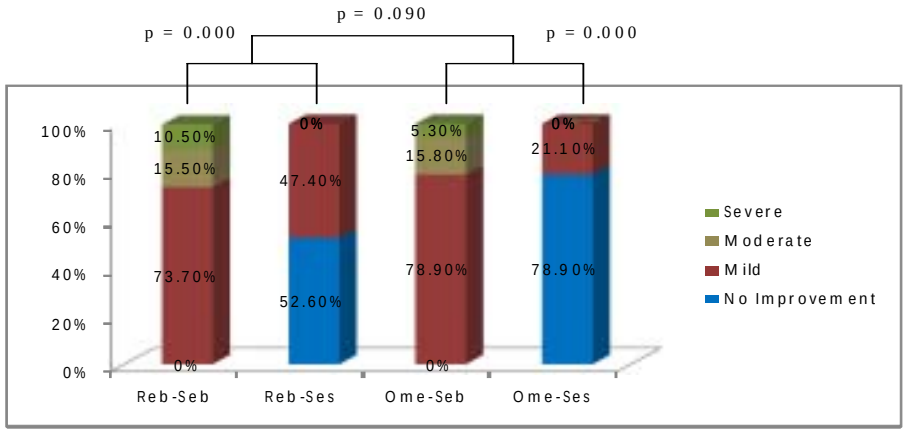

Figure 1. Treatment Effects on Clinical Symptoms of Dyspepsia

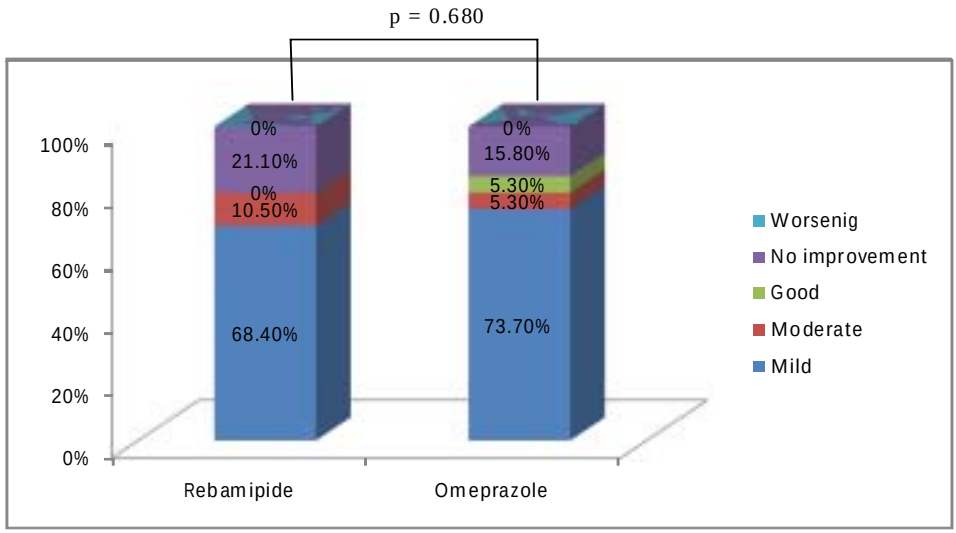

Figure 2. Clinical Improvement after Treatment

Table 3. Improvement of NSAIDs Gastropathy after Treatment

Treatment of NSAIDs Gastropathy	Rebamipide Group n (%)	Omeprazole Group n (%)	p
Mild	4 (21.1)	2 (10.5)	0.02
Moderate	5 (26.3)	3 (15.8)	
Good	3 (15.8)	13 (68.4)	
No Improvement	3 (15.8)	-	
Worsening	4 (21.1)	1 (5.3)	
Total	19 (100)	19 (100)	

Table 4. Decreased Severity of NSAIDs Gastropathy after Treatment (N = 38)

NSAIDs Gastropathy	Rebamipide Group			Omeprazole Group			
	After X ± SD	Before X ± SD	p	After X ± SD	Before X ± SD	p	p
Degree 0	0	0	0.004	0	6 (31.6)	0.000	0.007
Degree 1	0	1 (5.3)		0	5 (26.3)		
Degree 2	0	4 (21.1)		0	5 (26.3)		
Degree 3	0	6 (31.6)		0	1 (5.3)		
Degree 4	12 (63.2)	5 (26.3)		12 (63.2)	1 (5.3)		
Degree 5	7 (36.8)	3 (15.8)		7 (36.8)	1 (5.3)		

DISCUSSION

Treatment effects on clinical symptoms of dyspepsia

The result of this study showed lower clinical response compare to those study conducted by Keiji et al., Hawkey et al., and Yeomans et al.[5-7] This might be due to shorter period of time (only 2 weeks), while other study observed for trreatment in 4-8 weeks. The sample size in this study was also smaller compare to the other ones.

Improvements of NSAIDs gastropathy after Treatment

Clinical improvements of NSAIDs gastropathy would be better if the patients stop using NSAIDs. To maintain high cure rate, anti secretory agents to neutralize the gastric acid is needed, so the restitution process could go well.[1,3,8]

The combination of rebamipide and PPI was superior to PPI alone ($P < 0.05$) was reported by Tsukamoto et al. Miwa T also reported ulcer healing by rebamipide and ranitidine was 90% compare to ranitidine alone which only reached 77 % ($P < 0.05$).[9] The high response rate was also reported by Higuchi et al., the cure rate was 100% for group of omeprazole + rebamipide and omeprazole + amoxicillin, 96% for omeprazole alone.[10]

Other researchs were conducted to study the protective effect of rebamipide like one had been reported by Naito et al.[4] He observed protective effect of rebamipide to indomethacin compare to placebo. Clinical symptoms of dyspepsia were found in 43% patients and 80% in the placebo group. In the therapy group, grade 1 gastropathy NSAIDs was found in 86%, grade 2 was 14%. In the placebo group NSAIDs gastropathy grade 1 was found in 30%, grade 2-4 was 40% and grade 5 was 30% ($P < 0.05$).

Damman[11] reported rebamipide had decreased number of lesions in the antrum as much as 96% in therapy group and 77.3% in placebo group ($P = 0.015$). If the observation of lesion was done thoroughly including corpus, antrum and duodenum bulbus, rebamipide had decreased number of lesions to 141.5% and 115.2% in placebo group ($P = 0.058$).

The treatment effects of rebamipide in this study was not superior compare to other study because it was conducted in shorter period of time (2 weeks) and the sample size were also smaller than those in other studies. Aside from that, the high cure rate might be due anti secretory used. Protective effect of rebamipide was more prominent than cure rate on gastric mucosal lesion due to NSAIDs. In the omeprazole group decreased degree of NSAIDs gastropathy before and after treatment was significant ($P = 0.00$). This result was not different from study conducted by other researchers: Yeomans et al., Djojoningrat, Langman et al., Hawkey et al., and Agrawal et al.[5,7,12,13,14] In group of omeprazole the worsening of NSAIDs gastropathy was also observed in 5.3%. This was caused by individual difference of gastric acid level for each patient.[8,13] In high level of gastric acid, the antisecretory treatment like PPI was very beneficial for the patients in ulcer healing process.[8,15,16] In neutral or low level gastric acid level, the antisecretory treatment would not be very beneficial. In this case, cytoprotective drugs such as rebamipide, prostaglandin analog, cetraxate could be used to increase defensive factors for optimizing healing process.[8,15,16]

Comparison of Adverse Effect

In all patients who were given rebamipide, we observed no adverse effect like hypersensitivity, rash, pruritus, drug eruption, constipation, diarrhea, vomit, menstrual disturbance or edema. The same was also observed in omeprazole group, like reported by other studies.[17-19]

CONCLUSION

Rebamipide and omeprazole were both effective in decreasing clinical symptoms of dyspepsia. The differences in decreased symptoms was not different significantly between both groups ($P = 0.09$). Omeprazole was more effective in gastropathy NSAIDs than rebamipide ($P < 0.05$). Rebamipide and omeprazole were considered safe because no adverse event occurred during the study.

SUGGESTION

Further studies on protective effects iof rebamipide on gastric mucosal lesion due to NSAIDs gastropathy are required. Omeprazole may be used for NSAIDs gastropathy treatment.

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