The Relationship between Gastric Mucosa Mucous Thickness and Gastroscopic Findings in Patients Receiving Non-Steroidal Anti-Inflammatory Drugs

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ABSTRACT

Non-steroid anti-inflammatory drugs (NSAID) can cause gastropathy and gastric mucosa, especially the mucous may play an important prevention role. This cross-sectional, single group study was conducted to evaluated the difference of mucous thickness in antrum or corpus mucosa and the correlation of gastric mucous thickness to gastropathy. Patients who received NSAID from the rheumatology clinic were studied. Healthy subjects of 14 – 65 years old who never received NSAID were included as normal controls. Piroxicam 20 mg daily was given to the patients for 7 days, then gastroscopy and gastric mucosa biopsy with frozen section were performed. Specimens were stained with haematoxyline eosin and thickness of the mucous layer was measured using ocular micrometer. Thirty-two out of 70 patients participated in the study. All cases had hyperemia on gastroscopy with erosions and ulcer in 32 and 9 cases, respectively. The mean thickness of mucosa in distal antrum, proximal antrum and corpus was 28.5 ± 9, 37.4 ± 13.1 and 43.3 ± 13.1 microns, respectively. There was significant relationship between gastric mucosa mucous thickness with gastroscopic findings. In conclusion, this study confirmed that thickness of gastric mucosa mucous has an important role in preventing NSAID gastropathy and dyspeptic complaints in this kind of patients does not suggest abnormalities of gastric mucosa.

Key Words: *Gastric mucosa mucous thickness, NSAID, gastroscopy.*

INTRODUCTION

Non-steroid anti-inflammation drugs (NSAID), especially salicylie acid are more and more frequently used in the fields of cardiology and neurology. Several NSAIDs are sold over the counter and publically used.[1] The most commonly reported side effects of NSAID are those associated with the gastrointestinal system, especially of the upper gastrointestinal tract. There are also other side effects on the kidneys, hematopoetic system, liver, central nervous system, and skin. The manifestation of disturbance in the protective function of the mucosa can take the form of hyperemia, erosion, ulcer, bleeding, perforation, and obstruction.[1,2,3,4]

Based on the study conducted by Manan C in 1986,[5] and Rani A and Manan C in 1997,[6] at the Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia/Cipto Mangunkusumo Hospital, NSAID users were suffered from acute mucosa lesion in the form of erosion and ulcer in the gaster and duodenum in 70-76.6% cases.

These data suggest a high prevalence of acute mucosa lesion in NSAID users, even despite the use of protective agents such as antacids, H2 receptor antagonist, proton-pump inhibitor, and prostaglandin.[6]

Gastric mucosa lesions due to NSAID are called NSAID gastropathy. NSAID gastropathy is an acute lesion on the mucosa of the upper gastrointestinal tract due to the use of NSAIDs. The term gastropathy is still commonly used since the pathologic mechanism in the formation of such lesions is still unclear, even though prostaglandin plays the most dominant role.[6,7,8,9] One of the most important factors in the formation of gastropathy is the defense system of the gastric mucosa. The defense of the gastric mucosa consists of the pre-epithelial, epithelial, and subepithelial layers. The mucous layer of the gastric mucosa is the initial protective barrier that is very important in protecting the mucosa from destructive substances, such as NSAID.[2] NSAID could inhibit mucous production by inhibiting the production of prostaglandin, thus causing gastropathy.[1,5,7,8,9,10,11]

Nissen CH[11] reported that misoprostol (an analog of prostaglandin E1) could increase the thickness of the gastric mucosa mucous in rats. Clinical studies using misoprostol in NSAID users reduced gastropathy.[11] This study evaluated gastropathy using gastroscopic examination, without evaluating mucous thickness. Studies on the thickness of the gastric mucosa mucous have been conducted in laboratory animals in order to evaluate the results of medication using prostaglandin in portal hypertension gastropathy.[11,12]

NSAID gastropathy has been most commonly reported in the gastric antrum.[2,5,13,14,15] There is still no study report or reference on the thickness of gastric mucosa mucous in humans that could explain why most lesions are located at the antrum. Furthermore, there is still no reference or research that reports a difference in gastric mucosa mucous thickness at the antrum, corpus, and fundus in humans, especially in NSAID users. Based on this data, the author suggests that the gastric mucosa mucous layer is an important pre-epithelial initial protective barrier (cytoprotection).

In this study, measurement of gastric mucosa mucous thickness is conducted using biopsy and a modified method to make the conventional specimen, then the thickness is measured. The cost of examination is fairly inexpensive. This is the first time this technique has ever been used, and it has never been reported in literature. After a standard technique for measuring mucous thickness is found, the study on the correlation between gastric mucosa mucous thickness and gastroscopic findings in NSAID users is performed.

MATERIALS AND METHOD

Design

The design for this study was single group cross-sectional study.

Time and place

The samples were taken at the Rheumatology outpatient clinic and room for endoscopic procedure of the Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia/ Cipto Mangunkusumo Hospital, from August to December 1998.

Sample

The sample was taken consecutively from new out patients receiving NSAID of the Rheumatology out-patient clinic of Cipto Mangunkusumo Hospital, Jakarta.

The cases used are all out patients of the rheumatology out patient clinic who are new users of NSAID that fulfill the criteria for inclusion and exclusion as follows.

Criteria for Inclusion

- All new out patients who have never received NSAID or have not received NSAID in the last week
- Patients of more than 14 and less then 65 years of age
- Willing to participate in the study

Criteria for Exclusion

- Had suffered from dyspepsia in the previous 3 months and was under therapy using H_2 receptor antagonists or proton pump inhibitors
- History of hematemesis melena due to liver cirrhosis and/or portal hypertension
- Took alcohol, drugs (such as corticosteroids) or ate certain foods (spicy, acidy, etc.) and drank substances (e.g. Coffee) that could irritate the gaster and cause dyspepsia in the last week
- Patients with increased body temperature up to subfebrile or febrile suspected due to pancreatitis, cholecystitis, cholelithiasis and acute or chronic hepatitis
- Patients under medication for the eradication of Helicobacter pylori or peptic ulcer prior to use of NSAID in the previous 3 months
- Patients with hypertension, hypotension, acute or chronic renal failure, diabetes mellitus or gastric motility disorder
- Patients unwilling to undergo biopsy for histopathologic analysis
- Positive screening for Helycobacter pylori using micro indol urease (MIU) from specimens of the gastric tissue

Measurement of mucous thickness of gastric mucosa

Biopsy was taken from the distal antrum of the gaster (TM 1), proximal antrum/transitional zone and corpus of the gaster (TM 2) and the corporeal gaster (TM 3). Individual biopsies were taken from the hyperemic region with what was considered the most severe endoscopic abnormality, with a radius of approximately 1 cm from the edges of the erosion or ulcer. Biopsies were taken from the hyperemic regions since the mucous was still intact, since in cases with erosion or ulcer, the mucous layer has been destroyed.[2,12,16]

The thickness of the mucosa mucous is read using an ocular micrometer on the light microscope, using 10 x 10 magnification, 1 unit scale on the ocular micrometer equals 10 microns. If re-measured from 1 scale, measured using a magnification of 10 x 40, 1 scale equals 2.5 microns,[10] according to the criteria for measurement of mucous thickness used at the Department of Anatomic Pathology of the Faculty of Medicine of the University of Indonesia/Cipto Mangunkusumo Hospital.

The results of gastric mucous thickness were measured using the area under the curve (AUC) method with the formula:

$$AUC = \tfrac{1}{2}\,(y^0 + 2y^1 + 2\,y^2 + 2\,y^3 + \ldots\ldots + 2\,y^{11} + 2\,y^{12} + 2\,y^{13} + y^{14})$$

Note: $Y^{0\text{-}14}$ = mucous thickness is read at 15 points throughout

Method

Each patient that fulfills the requirement would undergo 2 phases of examination, which are as follows:

1. Initial examination, consisting of:
   - History taking and filling out questionnaire
   - Physical examination, blood laboratory analysis: hemoglobin, hematocryte, leukocyte, platelet, blood sugar, ureum, creatinine, ALT, AST, total billirubin, routine urinalysis and electrocardiography
2. Advanced examination, consisting of:
   - Endoscopic examination of the upper gastrointestinal tract, and gastric biopsy
   - Microscopic measurement of the thickness of the gastric mucosa mucous layer

All patients were given 20 mg of Piroxicam daily for 1 week. Gastroscopy was performed on all patients using Pentax endoscopic device type EG 3400.

Data processing and analysis

The data collected are processed using a personal computer. Endoscopic findings and gastric mucous thickness are analyzed using Pearson correlation (bivariate analysis) using SPSS software (Statistical Package for Social Sciences) 7.5 for Windows.

RESULTS

From August to December 1998, 70 patients were selected. There were thirty-seven patients that could fully participate in the whole study up to endoscopic examination and examination of gastric mucosa mucous thickness. Samples were taken after a significant correlation between mucous thickness and gastroscopic findings was established. The average age was 46.2 years (SD 11.9), with an age ranging from of 16 to 64 years. There were 14 men (37.8%) and 23 women (62.2%).

SAMPLE CHARACTERISTICS

In this study the gastroscopic abnormalities found were mostly of severe degree, found in 17 cases (45.9%), followed by mild degree in 13 cases (35.1%) and others as seen in the following table.

In this study the site of gastroscopic abnormalities is mostly located at the antrum, in the form of hyperemia in all cases (100%), erosion in 32 cases, and ulcer in 9 cases out of the 10 ulcer cases. The 32 patients with erosion 21 suffered from mild erosion (56.8%), 5 cases (13.5%) from moderate erosion and 6 cases (16.2%) from severe erosion.

Table 1. Gastroscopic Findings of the Antrum and Corpus

Type of lesion	Antrum	%	Corpus	%
Hyperemia	37/37	100	18/37	48.6
Erosion	32/37	86.5	16/37	43.2
Ulcer	9/37	24.3	1/37	2.7
Bleeding	0/37	0	0/37	0

In this study the most common dyspeptic complaint was mild dyspepsia in 23 cases (62.2%), followed by 11 cases without complaints (29.7%). Thus, all 34 cases (91.9%) demonstrated only mild dyspepsia or no dyspeptic complaints. Out of the 9 cases with ulcer in the antrum, 5 cases had no complaints of dyspepsia, 4 cases had mild complaints of dyspepsia. In this study, the complaints of dyspepsia were not related to the degree of gastroscopic findings.

In this study, the most common complaint for dyspepsia is heartburn found in 15 cases, followed by a feeling of gas in the stomach in 14 cases, epigastric discomfort in 11 cases, nausea in 10 cases, anorexia in 6 cases and vomiting in 2 cases.

The mean thickness of the gastric mucosa mucous at the distal antrum (TM 1) calculated using the AUC method was 40 square micrometers (SD 12.9). The calculated mean thickness of gastric mucosa mucous at the distal antrum (TM 1) was 28.5 micrometers (SD 9.0). The mean thickness of the gastric mucosa mucous at the proximal antrum (TM 2) calculated using the AUC method was 52.5 square micrometers (SD 18.4). The calculated mean thickness of gastric mucosa mucous at the proximal antrum (TM 2) was 37.4 micrometers (SD 13.1). The mean thickness of the gastric mucosa mucous at the corporeal antrum (TM 3) calculated using the AUC method was 60.8 square micrometers (SD 18.4). The calculated mean thickness of gastric mucosa mucous at the corporeal antrum (TM 3) was 43.3 micrometers (SD 13.1).

Table 2. Thickness of gastric mucosa mucous

Thickness of gastric mucosa mucous	Mean AUC $(\mu m)^2$	SD $(\mu m)^2$	Mean AUC (μm)	SD (μm)
Distal antrum (MT 1)	40	12.9	28.5	9.0
Proximal antrum (MT 2)	52.5	18.4	37.4	13.1
Corpus (MT 3)	60.8	18.4	43.3	13.1

Note: AUC= area under the curve, SD=standard deviation, MT=mucous thickness

Table 3. Correlation Between Gastroscopic Findings and Thickness of Gastric Mucosa at the Distal Antrum (Using Pearson Correlation-r)

Type of abnormality	Hyperemia	Erosion	Ulcer	MT 1
Hyperemia	1.000	0.392**	0.258	0.004
Erosion	0.392**	1.000	0.167	0.126
Ulcer	0.258	0.167	1.000	-0.52
MT 1	0.004	0.126	-0.52	1.000

Note:
MT 1 = mucous thickness at the distal antrum
* = correlation considered significant at 0.05 (1-tailed)
** = correlation considered significant at 0.01 (1-tailed)

Table 4. Correlation Between Gastroscopic Findings and Thickness of Gastric Mucosa at the Proximal Antrum (Using Pearson Correlation-r)

Type of abnormality	Hyperemia	Erosion	Ulcer	MT 2
Hyperemia	1.000	0.392**	0.258	-0.361*
Erosion	0.392**	1.000	0.167	-0.161
Ulcer	0.258	0.167	1.000	-0.82
MT 2	-0.361*	-0.161	-0.82	1.000

Note:
MT 2 = mucous thickness at the proximal antrum
* = correlation considered significant at 0.05 (1-tailed)
** = correlation considered significant at 0.01 (1-tailed)

Table 5. Correlation Between Gastroscopic Findings and Thickness of Gastric Mucosa at the Corporeal Antrum (Using Pearson Correlation-r)

Type of abnormality	Hyperemia	Erosion	Ulcer	MT 3
Hyperemia	1.000	0.779**	-0.145	-0.404*
Erosion	0.779**	1.000	-0.119	-0.180
Ulcer	0.145	-0.119	1.000	-0.21
MT 3	-0.404**	-0.180	-0.21	1.000

Note:
MT 3 = mucous thickness at the corporeal antrum
* = correlation considered significant at 0.05 (1-tailed)
** = correlation considered significant at 0.01 (1-tailed)

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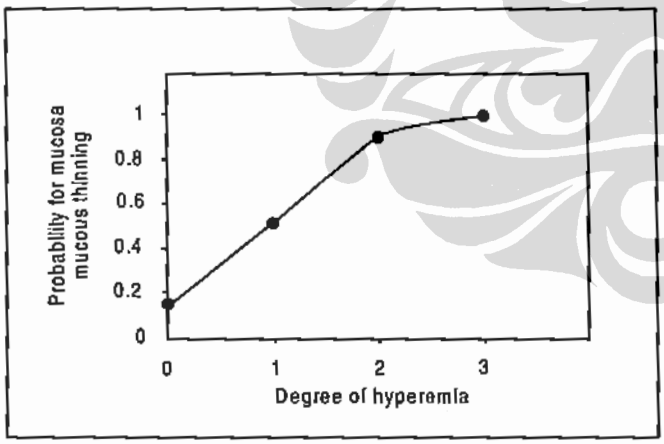
From the tables above, we can see:

1. There is no significant correlation between gastroscopic findings and the thickness of the gastric mucosa mucous at the distal antrum (see Table 3).
2. The analysis reached an r of –0.361, and p = 0.014 with a significant correlation between gastroscopic findings of hyperemia and TM 2 (thickness of the proximal antrum mucous) at p <0.05. The analysis suggest that the thicker the gastric mucosa mucous, the lower the degree of hyperemia, which was proven to be a significant correlation for the proximal antrum (see Table 4).
3. The analysis reached an r of –0.404, and p = 0.007 with gastroscopic findings of hyperemia and TM 3 (thickness of the corporeal antrum mucous) significantly correlated at p <0.05. The analysis suggests that the thicker the gastric mucosa mucous, the lower the degree of hyperemia, which was proven to be significant for the corporeal antrum (see Table 5).

Based on the analysis of gastric mucosa mucous thickness at the 3 locations of biopsy, only in 2 of the areas of biopsy, the proximal antrum and corpus. There was proven a significance for hyperemic gastroscopy findings. For further analysis on the reliability of this data, the degree of reliability was evaluated using step-wise multivariate regression analysis. Based on step-wise multivariate regression analysis, the following findings were demonstrated:

The probability for mucosa mucous thinning and the degree of hyperemia at the proximal antrum was as follows:

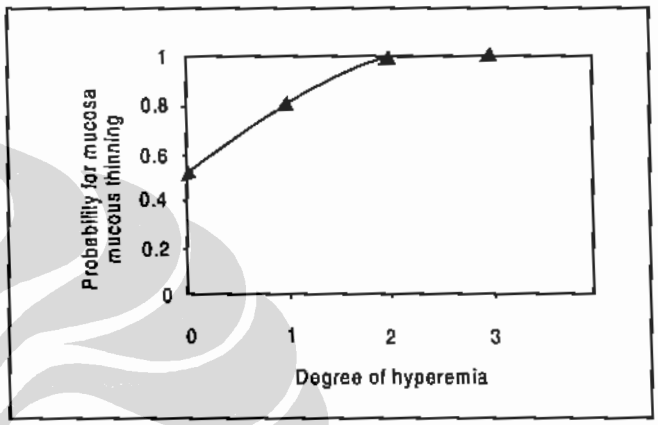


Note: Degree of hyperemia:
0= normal mucosa;
1= mild;
2= moderate;
3=severe

Figure 1. Graph of the probability of mucosa mucous thinning correlated with the degree of hyperemia at the proximal antrum

In the probability graph above, p = 0.155 for the normal mucosa (degree of hyperemia 0). P = 0.514 for mild hyperemia (degree of hyperemia 1), p = 0.896 for moderate hyperemia (degree of hyperemia 2), and p = 1 for severe hyperemia (degree of hyperemia 3) correlated with thinning of the mucosa mucous of the proximal gaster.

The probability for mucosa mucous thinning and the degree of hyperemia at the corpus was as follows:



Note: Degree of hyperemia:
0= normal mucosa;
1= mild; 2= moderate;
3=severe

Figure 2. Graph of the probability of mucosa mucous thinning with the degree of hyperemia at the corporeal antrum

In the probability graph above, p = 0.525 for the normal mucosa (degree of hyperemia 0). P = 0.804 for mild hyperemia (degree of hyperemia 1), p = 0.987 for moderate hyperemia (degree of hyperemia 2), and p = 1 for severe hyperemia (degree of hyperemia 3) correlated with thinning of the mucosa mucous of the corporeal gaster.

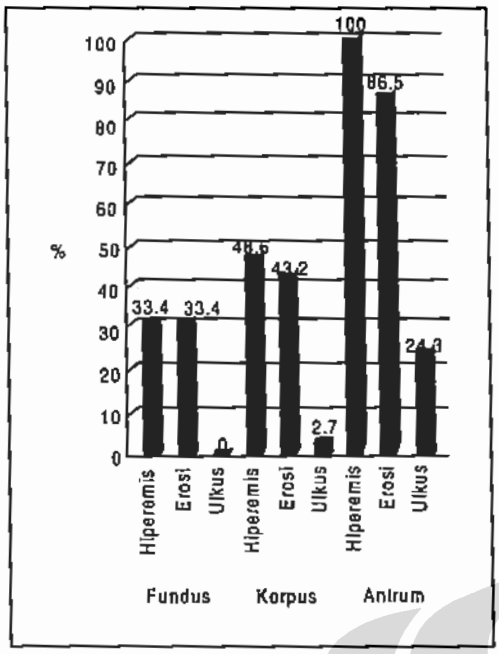


Figure 3. Gastroscopic findings of gastric mucosa

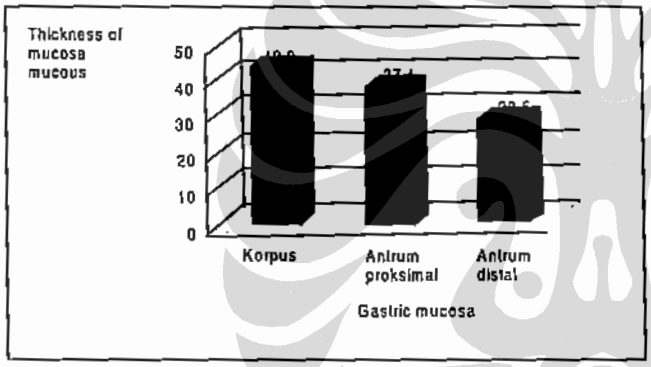


Figure 4. Graph of mean thickness of the mucosa mucous at the distal, proximal and corporeal antrum

In figure 3, we see the most severe gastroscopic lesion in the antrum. In figure 4, we see that the thinnest gastric mucosa mucous is located at the distal antrum.

DISCUSSION

In this study, the most commonly found gastroscopic abnormality is found in the antrum, in the form of 100% hyperemic mucosa, erosion in 32 cases (86.5%) and ulcer in 9 out of 10 cases (27%), 7 of them at the prepyloric antrum. Such findings are similar to the results of studies by Manan,[5] Ivey,[13] Graham,[14] Silvoso,[15] Lanza et al,[17] and Eliakim et al,[18] using aspirin (regular tablet, buffer and enteric-coated), naproxen, indomethasine, piroxicam, and ibuprofen for 1-2 weeks. All of those researches reported a hyperemic antrum in 76-100% cases, multiple erosions in the antrum in 40-100% cases, depending on the dose of medication. The ulcers are most commonly found in the pre-pyloric antrum (10-31% cases). Acute gastroscopic lesions are most commonly found on the first to 14th day.[17] Gastroscopic lesions are most commonly found in the antrum, perhaps due to its anatomic position as the lowest part of the gaster.[8] Oral medication would directly fall to the antrum and stop for a while before entering the duodenum. Another possible cause is that the longest contact between the NSAID and the gastric mucosa occurs at the antrum.[2] A longer contact time would increase topical irritation, thus causing further destruction of the mucosa.[1,2] There has not been a study that directly associates the thickness of the gastric mucosa mucous and the gastroscopic findings in NSAID users.

This study aimed to determine the correlation between the thickness of the gastric mucosa mucous and the gastroscopic findings at the antrum and corpus. Three biopsy locations were analysed, the distal antrum (TM 1), the proximal antrum (TM 2), and the corpus (TM 3). This study found a significant correlation between the thickness of the mucosa mucous and the gastroscopic findings of hyperemia at the proximal antrum. The thicker the mucosa mucous of the proximal antrum (TM 2), the milder the hyperemia (see Table 4). There was also a significant correlation between the thickness of the mucosa mucous and the gastroscopic findings of hyperemia at the corpus, in which the thicker the mucosa mucous of the corpus (TM 3), the milder the hyperemia (see Table 5).

Research on the thickness of gastric mucosa mucous has only been reported in laboratory animals, where the thickness could be directly measured.[11,12] Theoretically, the mucous layer is the initial barrier of the upper gastrointestinal tract against foreign objects that enter the intestinal lumen, protecting the cells under it from digestion and contact with chemical substances.[2] There have not been any reports on studies on the thickness of gastric mucosa mucous thickness in NSAID users. In this study, the most common location of gastroscopic lesions is the antrum (100%). The lesions at the corpus are usually milder, even to the point of remaining normal (19 cases). On the other hand, the mucous at the antrum tends to be thinner than that in other parts of the gaster, in accordance with the degree of the gastroscopic lesions observed. This suits the theory of gastric mucosa histology at the corpus, which has a thicker layer of epithelial cells and more abundant mucous cells (75%) compared to the antrum. Theoretically, the author suggests

that the mucous layer at the corpus is thicker than that of the antrum (see Table 2). Thus, the mucous protection at the corpus is better than that of the antrum,[11] which explains why most gastroscopic lesions are located at the antrum.

The thickness of the gastric mucosa mucous layer could act as a protection against various destructive substances including NSAID, as proven in in vitro studies on the effects of the prostaglandin E1 analog (misoprostol) on gastric mucosa protection in rats. In this study, the thickness of the mucous increased to twice its original size at the insoluble gel layer (the layer of mucous that strongly binds to the mucosa) and increased to three times its original size at the soluble mucous layer (the dynamic and mobile mucous that acts as a lubricant). The prostaglandin E1 analog was proven to be able to significantly reduce lesions at the gaster compared to cimetidin and sucralfat.[11] Based on the data above in NSAID users, the author suggests that the thicker the gastric mucosa mucous layer, the milder the gastroscopic abnormalities. With a thicker gastric mucosa mucous, there is less contact between the gastric mucosa epithelium and the NSAID, thus preventing destruction of the gastric epithelial cells. Besides the thickness of the mucosa mucous, the quality of the mucous glycoprotein structure (serine, treonine, proline, and olygosaccharide chain) also plays a role in keeping it intact.[8,19] Furthermore, many other factors also play a role, such as prostaglandin, secretin, gastrin, and cholecystokinin, which stimulate mucous secretion.[7] The influence of these factors on mucous thickness has not been subject of research, since it is difficult to determine. Thus, it is still unclear whether a thicker mucous would directly correlate with a better quality of gastric mucosa mucous. As in the study on the analog effects of prostaglandin E1 on mucous thickness,[11] a thicker mucous layer would have a significant correlation in reducing NSAID gastropathy. Based on this data, the author suggests that a thicker layer of gastric mucosa mucous is a manifestation or final product of the complete preepithelial protective function.

Endoscopic findings of erosion or ulcer, and hyperemia could not be the basis of establishing the diagnosis of NSAID gastropathy.[5] Histologically, hyperemia is one of the criteria of NSAID gastropathy,[20] while in the case of erosion and ulcer, histopathologically there is no intact mucous layer.[13,16,17,20] Thus, mucous biopsy is performed in the most severe hyperemic area at the side of the lesion. The hyperemic area around the lesion still has an intact mucosa, including its mucous layer.[16] This result was tested using step-wise multivariate regression analysis. In accordance with testing of the degree of reliability against the predicted thinning of the mucosa mucous layer of the proximal antrum and the corpus, the higher the degree of hyperemia, the thinner the mucosa mucous layer of the proximal antrum and corpus (see figures 1 and 2). Gastroscopically, this study demonstrates a positive correlation between hyperemia and erosion, where the higher degree of hyperemia is associated with more erosion (see table 4, 5 and figure 3). With these correlation analysis, there is no significant correlation between the gastroscopic findings and the mucosa mucous thickness at the distal antrum. If analyzed further, the gastroscopic findings at the distal antrum were more severe than that of the proximal antrum. In this region, the motility is higher and the mucous layer thinner than in the proximal antrum.[11] There are fewer mucous cells that produce mucine at the distal antrum than at the proximal antrum and corpus, only 20% of mucous cells in the gaster.[8] Similar findings were reported by Silvoso,[15] who mentioned that most gastroscopic lesions, from hyperemia to ulcer, are located at the distal antrum. In this study the mucosa mucous layer of the distal antrum is most thin compared to other locations (see table 2). Based on these data the author suggests that a thin layer of mucosa mucous is one of the main reasons for a more severe gastroscopic abnormality, (see table 1, figures 3 and 4).

In this study, complaints of dyspepsia were not related to the severity of gastroscopic findings. Seen from 9 cases of ulcer at the antrum, 5 cases (13.5%) without complaints, and 4 cases (10.8%) with mild dyspepsia. This is in accordance with studies by Ivey,[13] Graham,[14] and Silvoso,[15] where ulcers, erosions, and bleeding could occur without any complaints. Thirty percent of gastric ulcers occur without any complaints.

CONCLUSION AND SUGGESTIONS

Conclusions

1. There is a significant correlation between the thickness of gastric mucosa mucous and gastroscopic findings in NSAID users.
2. The thicker the gastric mucosa mucous layer, the milder the gastroscopic lesion.
3. Gastroscopic lesions are most commonly found in the antrum.
4. Complaints of dyspepsia in NSAID users do not signify the presence of gastric mucosa abnormalities according to gastroscopic examination.

Suggestions

1. Use of NSAID should be limited to precise indications, and drugs with the least side effects should be chosen.
2. Bearing in mind that this was the first time the technique of gastric mucosa mucous biopsy using frozen section was used, further studies need to be conducted using a larger number of samples for standardization of this novel technique.

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