Effectiveness differences of ranitidine and omeprazole in prevention of stress ulcer and its effect on pneumonia occurrence and outcome of acute stroke patients

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Abstract. Stress ulcer is one of acute stroke complications. Giving ranitidine or omeprazole may prevent stress ulcer, but may increase the occurrence of pneumonia. Thus, it will affect the outcome of acute stroke. The method was experimental with a randomized control-group pretest - posttest design. This study divided the subjects into two groups, ranitidine 300mg and omeprazole 20mg group. We observed the patients whether stress ulcer or pneumonia occurred during hospitalization. Then, we measured the outcome by the National Institutes of Health Stroke Scale and modified Rankin Scale. There were 32 subjects in this study. Only 1 (3.1%) subject suffered stress ulcer, and 3 (3.1%) suffered pneumonia in ranitidine group. Moreover, 2 (6.2%) subjects suffered pneumonia in omeprazole group. The differences were not significant between the two groups (p = 0.31 and p = 0.54). There was no significant effect and difference effect on the administration of both medications to the outcome at day 14. These results indicate that ranitidine and omeprazole have unequal effectiveness in the prevention of stress ulcer and also have equal effect on the occurrence of pneumonia, and both have no effect on the outcome of acute stroke patients.

1. Introduction
Stoke ranks the fourth among all causes of death, behind diseases of the heart, cancer, and chronic lower respiratory disease. Of all strokes, 87% are ischemic and 10% are intracerebral hemorrhagic strokes, whereas 3% are subarachnoid hemorrhage strokes.[1] In Indonesia, mortality and morbidity caused by stroke are the highest (15.4%), and the prevalence increased from 8.3‰ in 2007 to 12.1‰ in 2013.[2]

Patients who have had stroke are susceptible to many complications. Several complications can arise as a direct consequence of the brain injury itself, from the ensuing disabilities or immobility, or from stroke-related treatments. These events have a substantial effect on the outcome of patients with stroke and often impede neurological recovery. Gastrointestinal bleeding (stress ulcer) and pneumonia are particularly common after a stroke and usually require specific interventions for their prevention and treatment.[3]

In a prospective study by Davenport, et al. in 1996, the frequencies of upper gastrointestinal bleeding in stroke patients (both ischemic and hemorrhagic) were 3% of 613 patients. Half of them were heavy bleeding.[4] In a recent study involving 6,853 ischemic stroke patients, 1.5% suffered gastrointestinal bleeding during treatment.[5] The severity of stroke, history of peptic ulcer, sepsis, renal failure, abnormal liver function is independent predictors of gastrointestinal bleeding in stroke
patients.[3, 6] Mortality of patients with gastrointestinal bleeding was significantly higher than those without gastrointestinal bleeding.[7]

Urinary tract infections and especially pneumonia are serious complications in stroke patients. These complications are reported to occur in 5 - 65% in patients with acute stroke [8], while the frequencies of stroke-associated pneumonia are between 5 - 22%.[9] Pneumonia itself is closely related to the higher risk of mortality in acute phase stroke.[10]

Ranitidine is widely used as a prophylactic of stress ulcer in patients treated in intensive care units. The meta-analysis conducted by Cook et al. in 1996 showed that histamine two receptor antagonists (H2RA) such as cimetidine and ranitidine were more effective than placebo for the prevention of ulcer stress. However, his study could not explain the increased risk of nosocomial pneumonia associated with the use of H2RA.[11,12]

Proton pump inhibitors (PPI) are also widely used for stress ulcer prophylaxis. A meta-analysis of randomized control trial that compared PPI with H2RA for the prevention of stress ulcer and the incidence of nosocomial pneumonia, found that gastrointestinal bleeding in the PPI group significantly lower than in the H2RA group but the incidence of pneumonia between the two groups was similar.[13] Meta-analysis by Alhazzani et al. in 2013, in critically ill patients, found that PPI was more effective than H2RA in preventing upper gastrointestinal bleeding, but there were no differences between the two groups for the incidence of nosocomial pneumonia, mortality and length of stay in the intensive care unit.[14]

2. Method

This study used an experimental method with a double-blind randomized pretest-posttest design. The Health Research Ethical Committee of Sumatera Utara has approved this study, with the letter number: 187/KOMET/FK USU/2014. Subjects were patients who admitted to Haji Adam Malik Hospital with acute stroke, which confirmed by history taking, neurologic examinations, chest X-ray and head computerized tomography (CT) scan. The acute stroke patients fulfilled inclusion and exclusion criteria were randomly divided into two groups, the first group was given ranitidine 300 mg per oral twice daily, and the other was given omeprazole 20 mg per oral once daily. National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) were assessed as the baseline data. NIHSS < 4 = mild, 4-15 = moderate, > 15 = severe and mRS 1-2 = good, 3-6 = bad. We observed the patients for 14 days. During 14 days of observation, we reassessed if there were any occurrences of stress ulcer and pneumonia. NIHSS and mRS were measured for the second times in the 14th days to know the outcome of stroke patients.

Stroke was defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[15] Stress ulcer was defined as gastrointestinal tract bleeding in proximal from Treitz ligament, characterized by hematemesis, melena or presence of blood or coffee-like fluids in the nasogastric tube.[16] Pneumonia was confirmed by recommended diagnostic criteria for definite and probable stroke-associated pneumonia in patients not receiving mechanical ventilation based on the center for disease control criteria.[17]

Inclusion criteria in this study were those with acute ischemic or hemorrhagic stroke (onset of stroke ≤ 7 days) and agreed to follow this study (have signed the informed consent). While the exclusion criteria in this study were patients who already suffered from stress ulcer and pneumonia before admission to hospital, patients with liver and renal dysfunction, patients with the history of allergic to ranitidine or omeprazole, Glasgow Coma Scale ≤ 8 and patients with lacunar infarction stroke.

3. Results

3.1. Demographic characteristics of subjects
The whole characteristic of subjects is shown in table 1.
Table 1. Demographic characteristics of subjects.

| Variable               | Total (N=32) | Ranitidine 150 mg | Omeprazole 20 mg |
|------------------------|--------------|-------------------|------------------|
| N (%)                  | 32 (100)     | 16 (50.0)         | 16 (50.0)        |
| Sex (%)                |              |                   |                  |
| Male                   | 21 (65.6)    | 10 (31.2)         | 11 (34.4)        |
| Female                 | 11 (34.4)    | 6 (18.8)          | 5 (15.6)         |
| Age (years)            | 59.3 ± 5.4   | 61.4 ± 4.8        | 57.3 ± 5.4       |
| Type of Stroke (%)     |              |                   |                  |
| Ischemic               | 19 (59.4)    | 9 (56.3)          | 10 (31.2)        |
| Haemorrhagic           | 13 (40.6)    | 7 (43.8)          | 6 (18.8)         |
| NIHSS-baseline         | 13.9 ± 8.0   | 15 ± 8.0          | 12.8 ± 8.0       |
| mRS-baseline           | 3.9 ± 1.0    | 3.9 ± 0.9         | 3.9 ± 1.1        |

3.2. The difference of effectiveness of ranitidine and omeprazole in prevention of stress ulcer in acute stroke patients

In this study, there was 1 (3.1%) patient who received ranitidine had stress ulcer while none was found among those who received omeprazole (0.0%). However, by using Chi-Square test, the differences between these two groups were not significant (p = 0.31).

Table 2. The difference of effectiveness of ranitidine and omeprazole in the prevention of stress ulcer in acute stroke patients.

| Drugs       | Stress Ulcer | p*   |
|-------------|--------------|------|
|             | Yes (%)      | No (%)|
| Ranitidine  | 1 (3.1)      | 15 (46.9) |
| Omeprazole  | 0 (0.0)      | 16 (50.0) |
| Total       | 1 (3.1)      | 31 (96.9) |

*Chi-Square test

3.3. The difference of effect of ranitidine and omeprazole on pneumonia occurrences of acute stroke

From 32 acute stroke patients who participated in this study, there was 3 (9.3%) patients suffered pneumonia. Two (6.2%) of them were found among those who received omeprazole. While among those who received ranitidine, there was only one patient suffered pneumonia (3.1%). However, by using Fisher test, the difference in both group was not significant (p = 0.54).

Table 3. The difference of effect of ranitidine and omeprazole on pneumonia occurrences of acute stroke patients.

| Drugs      | Pneumonia | p*   |
|------------|-----------|------|
|            | Yes (%)   | No (%)|
| Ranitidine | 1 (3.1)   | 15 (46.9) |
| Omeprazole | 2 (6.2)   | 14 (43.8) |
| Total      | 3 (9.3)   | 29 (90.7) |

*Fisher test
3.4. The difference of effect of ranitidine and omeprazole on outcome of acute stroke patients
Wilcoxon statistical tests were used to show the effect of ranitidine and omeprazole on the outcome (NIHSS and mRS) of stroke, with no significant changes in NIHSS and mRS at 14th day in each group (Table 4).

Table 4. The effect of ranitidine and omeprazole on outcome of acute stroke patients.

| OUTCOME   | Alteration | n (%) | p  |
|-----------|------------|-------|----|
| Ranitidine: | NIHSS      |       |    |
|           | Improved   | 3 (9,4) | 0,95 |
|           | Worsened   | 6 (18,7) |     |
|           | Constant   | 7 (21,9) |     |
|           | mRS        |       |    |
|           | Improved   | 2 (6,3)  | 0,26 |
|           | Worsened   | 5 (15,6) |     |
|           | Constant   | 9 (28,1) |     |
| Omeprazole: | NIHSS      |       |    |
|           | Improved   | 2 (6,3)  | 0,12 |
|           | Worsened   | 8 (25,0) |     |
|           | Constant   | 6 (18,7) |     |
|           | mRS        |       |    |
|           | Improved   | 0 (0,0)  | 0,50 |
|           | Worsened   | 8 (25,0) |     |
|           | Constant   | 8 (25,0) |     |

*aWilcoxon test

While the differences in NIHSS and mRS between the two groups were assessed by Chi-Square and Fisher statistical tests and also showed no significant differences (Table 5).

Table 5. The difference of effect of ranitidine and omeprazole on outcome of acute stroke patients.

| OUTCOME            | Ranitidine 150 mg | Omeprazole 20 mg | p   |
|--------------------|-------------------|------------------|-----|
| NIHSS at admitted  |                   |                  |     |
| Mild-Moderate      | 7 (21.9)          | 8 (25.0)         | 0.72a |
| Severe             | 9 (28.1)          | 8 (25.0)         |     |
| NIHSS at day-14    |                   |                  |     |
| Mild-Moderate      | 7 (21.9)          | 8 (25.0)         | 0.72a |
| Severe             | 9 (28.1)          | 8 (25.0)         |     |
| mRS at admitted    |                   |                  |     |
| Good               | 2 (6.3)           | 2 (6.3)          | 0.70b |
| Bad                | 14 (43.7)         | 14 (43.7)        |     |
| mRS at day-14      |                   |                  |     |
| Good               | 4 (12.5)          | 6 (18.8)         | 0.45a |
| Bad                | 12 (37.5)         | 10 (31.2)        |     |

aChi-Square test
bFisher test

4. Discussions

4.1. Demographic characteristics of subjects
From 32 acute stroke patients who enrolled in this study, there were 21 (65.65%) males and 11 (34.4%) females with the average age were 59.3 ± 5.4 years. Moreover, 19 (59.4%) subjects were diagnosed as an acute ischemic stroke, while 13 (40.6%) subjects were diagnosed as an acute hemorrhagic stroke. The baseline of NIHSS was moderate while the mRS was considered as bad.
4.2. The difference of effectiveness of ranitidine and omeprazole in prevention of stress ulcer in acute stroke patients

This study found that there was 1 (3.1%) patient who received ranitidine had stress ulcer during the hospitalization while none of those who received omeprazole had stress ulcer, but the difference was not significant. This finding is similar to the study of Pongprasobchai et al. 2009 and Alhazzani et al. 2013 (but their studies were showing significant result).[13, 14] Proton pump inhibitor can reduce the production of gastric acid more than 90% while H2RA only reduces it to 70%, this may explain why there was no stress ulcer among those who received omeprazole.

Moreover, in this study, the statistic test did not show any significant results between the two groups, it is because in this study the subjects was not critically ill patients as in the studies of Pongprasobchai et al. 2009 and Alhazzani et al. 2013.[13, 14] Putative mechanisms underlying stress ulcer include reduced gastric blood flow, mucosal ischemia and reperfusion injury, all of which frequently occur in the critically ill.[18]

4.3. The difference of effect of ranitidine and omeprazole on pneumonia occurrences of acute stroke

A meta-analysis from Messori et al. 2000 found a significant increase in the risk of pneumonia in the ranitidine group versus Sucralfate (p = 0.08) in patients treated in the intensive care unit.[12] In this study, the occurrence of pneumonia was more frequent in the omeprazole group. The explanation is that PPI reduces gastric acid secretion more than 90% (while ranitidine does not reduce as much as 90%), thus reducing the pH of the gastric.

Reduction of gastric pH, may trigger bacterial growth in the gaster such as streptococcus, staphylococcus, micrococcus and enteric bacteria. Increased gastric bacteria may trigger bacterial colonization/migration to the lungs during aspiration.[19] This result was not significant, it was because the subjects were generally with better awareness (GCS ≤ 8 were excluded) than the Messori et al. 2000 study. Thus, aspiration was less common. Aspiration is one of the causes of pneumonia in stroke patients.[9]

4.4. The difference of effect of ranitidine and omeprazole on outcome of acute stroke patients

Several clinical studies have searched the effect of acid-neutralizing drugs administration and its outcomes on critically ill patients, which treated in intensive care units. A meta-analysis study by Shan et al. 2013, which looked for an association between antacids and hospital-acquired pneumonia in critically ill patients and found that no significant difference between antacid and groups in mortality.[20] Alhazzani et al. 2013 also found no difference in mortality and length of stay in the intensive care units between groups who received PPI or H2RA.[14]

5. Conclusions

This study results indicate that ranitidine and omeprazole have an equal effectiveness in the prevention of stress ulcer and have equal effect on the occurrence of pneumonia, and both have no effect on the outcome of acute stroke patients. We should consider the risks and benefits of giving stress ulcer prophylaxis drugs in patients with acute stroke and it is necessary to consider acid neutralizing agents for the prevention of stress ulcer with fewer incidences of pneumonia.

References

[1] Go A S, Mozaffarian D, Roger V L, Benjamin E J, Berry J D, Borden W B, et al. 2013 Heart disease and stroke statistics 2013 update: A report from the american heart association Circulation 127 e6-e245

[2] Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan R I 2013 Riset kesehatan dasar – riskedas

[3] Kumar S, Selim M H and Caplan L R 2010 Medical complications after stroke Lancet Neurol. 9 105–18
[4] Davenport R J, Dennis M S and Warlow C P 1996 Gastrointestinal hemorrhage after acute stroke Stroke 27 421-4
[5] O'Donnell M J, Kapral M K, Fang J, Saposnik G, Eikelboom J W, Oczkowski W, et al. 2008 Gastrointestinal bleeding after acute ischemic stroke Neurrol. 71(9) 650-5
[6] Cook D J, Fuller H D, Guyat G H, Marshall J C, Leasa D, Hall R, et al. 1994 Risk factors for gastrointestinal bleeding in critically ill patients NEJM 330(6) 377-81
[7] Alhazzani W, Alshahrani M, Moayyedi P and Jaeschke R 2012 Stress ulcer prophylaxis in critically ill patients: review of the evidence Pol. Arch. Med. Wewn. 122(3) 107-14
[8] Vermeij F H, Reimer W J, Man P D, Oostenbrugge R J, Franke C L, Jong G D, et al. 2009 Stroke-associated infection is an independent risk factor for poor outcome after acute ischemic stroke: data from the Netherlands stroke survey Cerebrovasc. Dis. 27 465–71
[9] Harms H, Halle E and Meisel A 2010 Post-stroke infections – diagnosis, prediction, prevention and treatment to improve patient outcomes Eur. Neurol. Rev. 5(1) 39–43
[10] Hoffmann S, Malzahn U, Harms H, Koennecke H C, Berger K, Kalic M, et al. 2012 Development of a clinical score (A2DS2) to predict pneumonia in acute ischemic stroke Stroke 43 00-00
[11] Cook D J, Reeve B K, Guyatt G H, Heyland D K, Griffith L E, Buckingham L, et al. 1996 Stress ulcer prophylaxis in critically ill patients: Resolving discordant meta-analysis JAMA 275(4) 308-14
[12] Messori A, Trippoli S, Vaiani M, Gorini M and Corrado A 2000 Bleeding and pneumonia in intensive care patients givenranitidine and for prevention of stress ulcer:meta-analysis of randomised controlled trials BMJ 321 1103–6
[13] Pongprasobchai S, Samruay K S and Nopmaneemuratslers C 2009 Proton pump inhibitors for the prevention of stress-related mucosal disease in critically-ill patients: ameta-analysis J. Med. Assoc. Thai. 92(5) 632-7
[14] Alhazzani W, Alenezi F, Jaeschke R Z, Moayyedi P and Cook D J 2013 Proton pump inhibitors versus histamine2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: asymtomatic review and meta-analysis Crit. Care Med. 41 0–0
[15] Sacco R L, Kasner S E, Broderick J P, Caplan L R, Connors J J, Culebras A, et al. 2013 An updated definition of stroke for the 21st century: astatement for healthcare professionals from the American heart association/american stroke association Stroke 44 2064-89
[16] Adi P 2009 Pengelolaan saluran cerna bagian atas Buku ajar ilmu penyakit dalam edisi V vol 1, ed A W Sudoyo, B Setiyohadi, et al. (Jakarta: Interna Publishing) pp 447-52
[17] Smith C J, Kishore A K, Vail A, Chamorro A, Garau J, Hopkins S J, et al. 2015 Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in stroke consensus group Stroke 46 2335-40
[18] Plummer M P, Blaser A R and Deane A M 2014 Stress ulceration: prevalence, pathology and association with adverse outcomes Crit. Care 18 213
[19] Giuliano C, Wilhelm S M and Kale-Pradhan P B 2012 Are proton pump inhibitors associated with the development of community-acquired pneumonia? Exp. Rev. Clin. Pharmacol. 5(3) 337-44
[20] Shan L, Li X, Liu K, Sun M N, Yao Z X and Li L D 2013 Relationship between antacid therapy and hospital acquired pneumonia in critically ill patients: a meta-analysis Chin. Crit. Care Med. 25(6)