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The effectiveness and cost of lansoprazole and pantoprazole for stress ulcer prophylaxis in intensive care unit

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ABSTRACT

The incidence of bleeding is increased in high risk patients with critical conditions in Intensive Care Unit (ICU). Appropriate prophylaxis medicine is necessary to reduce the incidence of stress ulcer bleeding during hospitalization in ICU which further can minimize the cost of patient care in the ICU. Currently, lansoprazole and pantoprazole are used as a stress ulcers prophylaxis. Nevertheless, there has not been sufficient evidence proving their effectiveness. This study was aimed to compare the effectiveness and cost between iv lansoprazole and iv pantoprazole as a stress ulcer prophylaxis in ICU. In this retrospective observational study, the data were obtained from medical records of all patients admitted to ICU in a District Hospital in Yogyakarta from January 2014 until December 2016. Effectiveness of therapy were obtained from objective data in the medical record by looking at the incidence of major (clinically significant) and minor (overt gastrointestinal) bleeding. Chi-square analysis was performed to analyze the difference of bleeding incidence. The average cost was presented as Expected Monetary Value (EMV), which consisted of the cost of prophylaxis and treatment of bleeding. The difference in average cost was analyzed using independent t-test. A total of 119 patients were included in this study. There were 62 patients in the lansoprazole group and 47 patients in the pantoprazole group. Forty eight patients (77.4%) from lansoprazole group and 35 patients (61.4%) from pantoprazole group did not experience any GI bleeding. There was no statistical difference in the incidence of GI bleeding between the two groups (CI 95%, P-value = 0.057). The EMV of lansoprazole group was higher than pantoprazole group IDR 645.122.57 and IDR 511.629.39 respectively. In conclusion, there was no significant difference regarding the effectiveness between iv lansoprazole and iv pantoprazole as stress ulcer prophylaxis. Costs for the prophylaxis of stress ulcers is lower on the use of pantoprazole compared to lansoprazole.

Keywords: effectiveness, cost, lansoprazole, pantoprazole, intensive care unit (ICU)

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INTRODUCTION

Patients with critical conditions treated in ICU are at risk of developing stress ulcers. Stress ulcers have been reported to increase morbidity and mortality. Previous study had proven that extending the length of stay for 4 and 8 days was associated with an increase in mortality up to 4 times. An endoscopic observation revealed that most of ICU patients (75% - 100%) experienced gastric mucosal disorder a few hours after being admitted to ICU (Burris, 2014; Mutlu et al., 2001; Yazdi and Imantalab, 2015). Another evidence proved that 35 -100% of ICU patients showed positive results in stomach acid test, which is indicated by bleeding event (Spirt and Stanley, 2006).

American Society of Health-System Pharmacists (ASHP) Guideline states that stress ulcer prophylaxis should be prescribed only for high-risk patients, especially for patients in the Intensive Care Unit (ICU). Proton pump inhibitors (PPIs) and histamine-receptor antagonists (H_2RA) are prescribed widely to prevent stress ulcers in clinical practice (ASHP, 1999; Mohamad et al., 2015). Some studies had suggested that PPIs were demonstrably superior and less costly as a stress ulcer prophylaxis compared to H_2RA (Barkun et al., 2013; Udeh et al., 2010).

PPIs were frequently prescribed in ICU for various indications, predominantly for stress ulcer prophylaxis. Such indication accounted for 47% of total PPIs prescription in ICU, while the rest of 20% and 11,5% were indicated for gastrointestinal bleeding and peptic ulcer disease medication, respectively (Heidelbaugh et al., 2010). Administration of PPIs as stress ulcer prophylaxis during inpatient care may affect the total cost of treatment in ICU.

Currently, lansoprazole and pantoprazole, the newer generation of PPIs, are used as a stress ulcers prophylaxis. Nevertheless, there has not been sufficient evidence proving their effectiveness as a stress ulcers prophylaxis compared to older generation, such as omeprazole. Lansoprazole proposed several advantages over pantoprazole. Although classified in the same class, both agents did not share a similar pharmacokinetic profile which may influence their effectiveness. Lansoprazole reaches maximum concentration faster and provides greater bioavailability than lansoprazole as well. However, lansoprazole has a greater clearance compared to pantoprazole (Chubineh and Birk, 2012; Shin and Kim, 2013). Beside that, according to Udeh et al. (2010), lansoprazole required lower acquisition cost per dose in comparison with pantoprazole. Therefore, choosing lansoprazole will be more beneficial in limited healthcare resource conditions.

Although lansoprazole and pantoprazole had been studied previously by Udeh et al. (2010), there were several differences regarding route of administration, research site, and patient condition. Considering the urgency of preventing stress ulcers in high risk patients, increasing demand in minimizing treatment cost, and emerging fact that newer generation of PPIs are frequently prescribed (including lansoprazole and lansoprazole), it is necessary to evaluate the costs and effectiveness of newer generation PPIs. This research was aimed to observe whether there were differences in the effectiveness and cost of using lansoprazole and pantoprazole therapy as stress ulcer prophylaxis.

MATERIALS AND METHOD

We conducted a retrospective cohort study of ICU patients receiving 30 mg lansoprazole given intravenously once daily (Takeda, Prosogan®, city, state, Indonesia) or 40 mg pantoprazole generic given intravenously once daily as a stress ulcers prophylaxis at Hospital in Yogyakarta. This study was approved by Ethics Committee (approval number : 00527 / KKEP / FKG-UGM / EC / 2016), Faculty of Medicine, Universitas Gadjah Mada, Indonesia.

Population

The study population comprised patients admitted to ICU and received lansoprazole or pantoprazole as a stress ulcer prophylaxis. Patients were eligible for this study if they fulfilled inclusion criteria as follow : (1) Adult patient, ≥18 years - 65 years old, having at least one of the following risk factors (a) Use of mechanical ventilation > 48 hours, (b) Coagulopathy (INR> 1.5; PTT > 2x controls; Platelet <50 thousand) and two factors risk of (a) Hypotensive shock, (b) Sepsis shock,

(c) Liver failure / kidney failure / heart failure, (d) spinal cord injury, (e) Liver/kidney transplantation, (f) Burns> 35% body surface area, (g) Trauma: Post-major, post-natal, post chemotherapy, (h) Head Injury (GCS ≤ 10), (i) History of gastric ulceration / bleeding in 1 year before entering the hospital, (j) ICU Stay> 1 week, (k) Corticosteroid therapy (> 250 mg or similar); (2) Received lansoprazole or pantoprazole for at least 1 day or 24 hours during the hospitalization in the ICU. Patients were excluded if they received a combination of gastric acid suppressants therapy other than pantoprazole and lansoprazole or if they were diagnosed with any of these conditions : hematemesis, melena, gastritis or ulcer when admitted to ICU.

Data collection

Data were obtained from patient medical records and hospital billing system between January 2014 and December 2016. Following data were retrieved from patient medical records: (1) Patient diagnoses at admission and during hospitalization in ICU, (2) patient characteristics such as type sex, age, length of stay, GCS scale, type and number of risk factors, (3) agent used for stress ulcers prophylaxis, including dose and route of administration (4) Any medication to treat other underlying disease or comorbid (5) presence/absence of bleeding (overt gastrointestinal bleeding /minor bleeding and clinically significant gastrointestinal bleeding/major bleeding).

Medication costs were retrieved from the hospital billing system. Medication cost consisted of drug and non-drug costs directly related to stress ulcer prophylaxis and management of ulcer/bleeding. Components of drug costs consisted of prophylaxis drug costs (lansoprazole and pantoprazole) and drug costs to cure bleeding events such as sucralfate, vitamin K, tranexamic acid, and parenteral nutrition. While non-drug costs component included the cost of medical devices such as syringes and transfusion costs.

Research outcomes

The clinical outcome of the analysis was gastrointestinal bleeding events. Stress ulcer prophylaxis was considered a success if the patient did not experience either overt gastrointestinal bleeding or clinically significant bleeding. Overt gastrointestinal bleeding/minor bleeding was characterized by hematemesis, melena, hematochezia or reddish/blackish-brown residue inside the nasogastric tube (NGT). While clinically significant bleeding/major bleeding was defined as occurrence of minor bleeding followed by at least one condition : systolic or diastolic blood pressure suddenly fell 20 mmHg or more within 24 hours of bleeding, started using vasopressor or increased vasopressor dose by 20%, decrease hemoglobin (Hb) level at least 2 g/dL, needed transfusion of 2 units of PRC or more (Krag et al., 2016). The economic outcome was the average cost for each treatment group. The average costs were presented as Expected Monetary Value (EMV). EMV was calculated for both treatment groups.

Analysis

Chi-Square test was used to analyse effectivity of stress ulcer prophylaxis. Cost analysis were carried out by looking at the details of medication costs directly on patients receiving care at the ICU. A decision tree scheme was constructed to present the costs of lansoprazole versus pantoprazole during the hospitalization in ICU. In each treatment group, patients were categorized into those experiencing bleeding and those without bleeding. EMV was calculated by multiplying an outcome probability in specific treatment group and the costs related to the outcome. Independent t-test was performed to compare the average cost between the two groups. SPSS 22 was used to perform statistical analysis. A two-tailed P-value of 0.05 was considered statistically significant in this study.

RESULT AND DISCUSSION

Patient Characteristics

From the beginning of the study, it was discussed that lansoprazole and pantoprazole were chosen because they were the most widely used PPIs class in ICU. A total of 119 patients met

eligibility criteria and were included in the analysis, of whom divided into 62 patients in the lansoprazole group and 57 patients in pantoprazole. The baseline characteristics of 119 patients included sex, length of stay in ICU, Glasgow Coma Scale (GCS) scale, the total of risk factors, and the type of bleeding risk factors during the hospitalization in ICU are shown in Table 1.

Table 1. Characteristics of patients with high risk of bleeding in ICU

Characteristic	Patients (n=119)		P Value
	Lansoprazole (n=62) n(%)	Pantoprazole (n=57) n(%)	
Gender			
Man	44 (71)	34 (59.6)	0.194
Woman	18 (29)	23 (40.4)	
Age (Year)			
18-30	1 (1.6)	2 (3.2)	
31-40	3 (4.8)	3 (4.8)	0.592
41-65	58 (93.5)	52 (91.2)	
Age (mean ± SD)	57.26 ± 9.243	55.98 ± 9.539	0.220
ICU Stay (day)			
≤ 7	49 (79)	32 (56.1)	0.007*
> 7	13 (21)	25 (43.9)	
GCS Scale			
≤ 10	4 (6.5)	10 (17.5)	0.061
> 10	58 (93.5)	47 (82.5)	
Number of Risk Factors			
1-2	39 (62.9)	24 (42.1)	
3-4	22 (35.5)	29 (50.9)	0.016*
> 4	1 (1.6)	4 (7.0)	
Risk Factors			
CHF	41 (66,1)	35 (61.4)	0.592
Sepsis	20 (32.3)	31 (54.4)	0.015*
CKD	22 (35.5)	21 (36.8)	0.878
Corticosteroid use	18 (29)	15 (26.3)	0.741
Trauma	4 (6.5)	7 (12.3)	0.273
Coagulopathy	4 (6.5)	6 (10.5)	0.423
Mechanic ventilator	3 (4.8)	4 (7.0)	0.615
HF	6 (9.7)	3 (5.3)	0.363
Hipotension	8 (12.9)	2 (3.5)	0.065
History of bleeding	0 (0)	1 (1.8)	0.297

*statistically significant (P≤0.05)
GCS : Glasgow Coma Scale
CHF : Chronic heart failure
CKD : Chronic kidney Disease
HF : Heart Failure

Most of the characteristics between the two groups were balanced, except length of stay, number of risk factors, and sepsis (P≤0.05). Most patients in both groups stayed in ICU for less than 7 days. However, the proportion of those who stayed in ICU for less than 7 days in the pantoprazole group was higher than lansoprazole group. Patients in the pantoprazole group seemed to have more risk factors than those in the lansoprazole group. Patients in the pantoprazole group predominantly had

more than 2 risk factors. Furthermore, there were more patients who suffered from sepsis in the pantoprazole group than those in the lansoprazole group.

Ulcerogenic drug use profile

During treatment at the ICU, the patient received medications to overcome medical problems. Of the drugs received by the patients, there were ulcerogenic drugs. These drugs are well known for their potency to induce gastrointestinal bleeding (Yasuda et al., 2015). The researcher would emphasized the use of stress ulcer prophylaxis drugs and ulcerogenic drugs. The proportion of ulcerogenic drugs prescribing between the two groups are illustrated in Table 2.

Table 2. Comparison of the number of patients receiving ulcerogenic drugs between the lansoprazole group and pantoprazole group

Ulcerogenic agent	Lansoprazole	pantoprazole	P-value
Corticosteroid	21	20	0.889
Analgesic NSAIDs	21	24	0.355
Antiplatelet	26	26	0.686
Anticoagulant	10	8	0.750

NSAIDs : Non Steroid Anti-Inflammation Drugs

Several types of ulcerogenic drugs in this study were corticosteroid (prednisolone and dexamethasone), Nonsteroidal Anti-inflammatory Drugs/NSAIDs (antalgic injection (Sanofi Aventis, Novalgin®, ketorolac and diclofenac potassium), antiplatelet (aspirin and clopidogrel) and anticoagulant (fondaparinux sodium). (Tambahkan referensi bahwa obat-obat ini bersifat ulserogenik) It could be inferred from the table that the proportion of ulcerogenic drugs prescribing in both groups was well balanced and proven statistically (P>0.05).

Clinical outcome

The patient medical record was used in order to observe the bleeding incidence encountered by the patients during their hospitalization in ICU. The proportion of patients experiencing minor and major bleeding events in the ICU are illustrated in Table 3 below.

Table 3. Proportion of bleeding events in lansoprazole and pantoprazole group

Group	No Bleeding (n,%)	Bleeding		P-Value
		Minor Bleeding	Major Bleeding	
lansoprazole	48 (77.4)	1 (1.6)	13 (21)	0.057
pantoprazole	35 (61.4)	5 (8.8)	17 (29.8)	

As mentioned in Table 3, fewer patients had minor or major bleeding when lansoprazole was used as a stress ulcer prophylaxis. A total of 48 of 62 patients (77.4%) in the lansoprazole group did not experience bleeding and 35 of 57 (61.4%) patients in the pantoprazole group did not experience bleeding. According to statistical analysis, it could be interpreted that there was no difference regarding effectiveness of lansoprazole and pantoprazole as a stress ulcer prophylaxis (P=0.057) even though a higher percentage of both major and minor bleeding was observed in pantoprazole group. Thus, we also examined the other factors to find out what might influence the clinical outcome.

Several factors affecting the effectiveness difference between lansoprazole and pantoprazole in preventing bleeding incidence did exist in this study. This difference was due to some of the patient characteristics proportions mentioned in Table 1, such as length of stay, sepsis, the number of risk factors and ulcerogenic drugs. Table 4 shows the association between these characteristics and bleeding events.

Table 4. Effect of patient characteristics on bleeding events

Characteristics	No Bleeding n (%)	Bleeding n (%)	P-Value
ICU Stay			
- > 7 days	19 (50)	19 (50)	0.001*
- ≤ 7 days	64 (79)	17 (21)	
Sepsis	31 (37.3)	20 (55.6)	0.065
No sepsis	52 (62.7)	16 (44.4)	
Number of Risk factors			
- 1-2	49 (77.8)	14 (22.2)	0.030*
- 3-4	32 (62.7)	19 (37.3)	
- > 4	2 (40)	3 (60)	
Ulcerogenic Drugs			
- Kortikosteroid	11	30	0.556
- NSAIDs	16	29	0.326
- Antiplatelet	9	43	0.007*
- Antikoagulan	2	16	0.055

*Statistically significant (P value ≤0,050)
NSAIDs : Non Steroid Anti-Inflammation Drugs

According to Table 4, the length of stay in ICU and the number of risk factors had a P-value <0,05. Therefore it could be concluded that length of stay in ICU and number of risk factor significantly predisposed the clinical outcome (bleeding occurrence) (P value=0.001 and P value=0.030 respectively), whereas sepsis had no effect on the clinical outcome.

In this study, the length of stay in ICU was categorized into those who stayed in ICU for less than 7 days and those who stayed in ICU more than 7 days. A higher incidence of bleeding was reported in patients whose length of stay was more than 7 days. Therefore, extending the length of stay in ICU until more than 7 days was related to increased risk of bleeding (P=0.001). These findings was consistent with the result of a former study conducted by Khoshbaten et al. (2006) and Kerama et al. (2014),. This study stated that the average length of stay of those who experienced major bleeding (26,67% of total patients observed) was longer than those without major bleeding. In addition, Reyes and Ramírez (2014) and Mohebbi (2009) stated that the length of stay more than 7 days in ICU were associated with a high risk of bleeding. Therefore, the magnitude of bleeding incidence in the pantoprazole group was possibly affected by a high proportion of patients staying in ICU for more than 7 days.

Major and minor risk factors were never found separated with any patient condition in ICU. During the study, the subjects, on average, had 2-4 risk factors each patient. The researcher classified the patients into 3 categories based on the number of risk factors. According to Table 4, it could be inferred that the more risk factors the patients had, the higher the percentage of bleeding event. This association was proven with statistically significant (P=0.030). Thus, further subgroup analysis was necessary to ensure the impact of stress ulcer prophylaxis type and bleeding event in each level of risk factor.

In this study, Sepsis had no effect on the increased risk of gastrointestinal bleeding. This is different with the research conducted by Yang et al. (2018), which stated that sepsis is an important risk factor for gastrointestinal bleeding in patients with acute coronary syndrome (ACS).

Some patients from both lansoprazole and pantoprazole groups were treated using medicines that might affect the incidence of gastric bleeding. Table 4 shows the effect of the use of ulcerogenic medicines on bleeding events in patients treated with lansoprazole and pantoprazole.

According to Table 4, the sum of patients experiencing bleeding was higher than those without bleeding regardless of the type of the ulcerogenic drugs. Based on statistic analysis, most of the

ulcerogenic drugs did not significantly affect bleeding event except antiplatelet (P=0.007). Similar finding was established in a study conducted with Pipilis et al. (2014). This research stated that the use of antiplatelet, as well as increasing age, was one of gastrointestinal bleeding risk factors. Another research found that a dose-dependent gastrointestinal bleeding was related to the use of aspirin. The risk of gastrointestinal bleeding event was doubled if 300 mg aspirin was administered as an antiplatelet (Lanas et al., 2006). However, the proportion of antiplatelet drug prescription between the two groups was not significantly different (P-value = 0.587) so that both groups had the same bleeding risk due to antiplatelet use.

Economic outcome

Cost analysis was carried out by directly looking at the details of medical costs of patients treated in ICU. Each of stress ulcer prophylaxis and ulcer/bleeding costs was a combination of drug and non-drug components. Drug costs represented prophylaxis drug costs (lansoprazole and pantoprazole) and drug costs to cure bleeding events such as sucralfate, vitamin K, tranexamic acid, and parenteral nutrition. Meanwhile, non-drug costs component included the cost of medical devices such as syringes and transfusion costs. The difference in the average cost required in the therapy groups of lansoprazole and pantoprazole can be seen in the Table 5.

Tabel 5. The difference in the average cost required in the therapy groups of lansoprazole and pantoprazole in ICU

Cost	Average Cost ±SD (Rp)		P Value
	Lansoprazole (n=62)	Pantoprazole (n=62)	
Prophylaxis drug costs	IDR573,181.52 ± 224,427.21	IDR 284,280,93 ± 160,843.74	0.000*
Medical Device Cost	IDR 17,409.52 ± 6,816. 62	IDR 22,188,95 ± 12,494.63	0.011*
Subtotal	IDR **590,591. 05 ± 231,243. 83**	IDR **306,469,88 ± 173.160,51**	
Drug costs to cure bleeding events	IDR 219,895. 64 ± 239,834.63	IDR 345,594,23 ± 583,148.27	0.935
Non-drug costs to cure bleeding events	IDR 27,229.09 ± 19,442. 40	IDR 240,585. 71 ± 480,260. 86	0.268
Subtotal	IDR **241,289.93 ± 246.883.13**	IDR **531,501.36 ± 785,204.79**	

* = Significant Different
SD = Standart Deviation

The average costs in this study consisted of stress ulcer prophylaxis cost and treatment of ulcer/bleeding costs in ICU. The average cost was represented with EMV. The average costs required in the lansoprazole and pantoprazole group are explained in Figure 1.

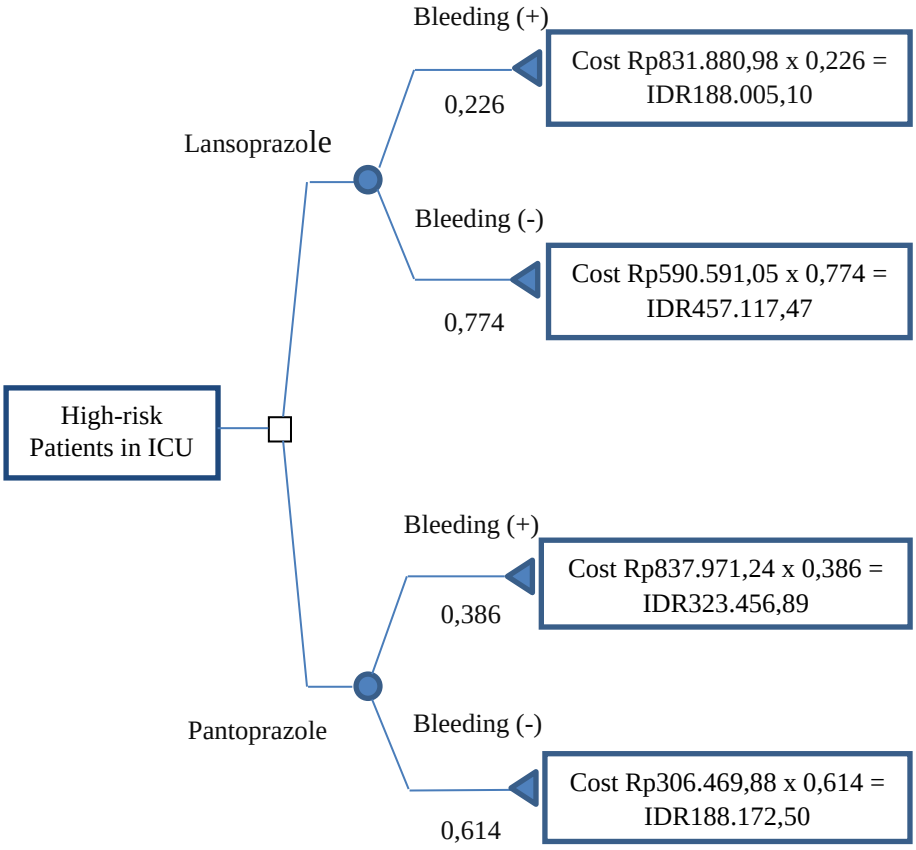

Figure 1: Expected monetary value

This study suggested that the EMV of lansoprazole group was higher than pantoprazole group (IDR 645,122.57 and IDR 511,629.39 respectively). However, the difference was not statistically significant. More detailed observation found that the cost of bleeding outcome in the pantoprazole group was higher than that of lansoprazole. But the opposite result was found in non-bleeding outcome.

Prophylaxis drug cost between lansoprazole and pantoprazole group (IDR573,181.52±224,427.21 and IDR 284,280.93±160,843.74 respectively) was significantly different according to statistical analysis (P value=0.000). Higher prophylaxis drug cost was observed in the lansoprazole group. The difference in the average of prophylaxis drug costs was mainly due to different drug prices. Prosogan® injection, the patent drug of lansoprazole, was used in the lansoprazole group. Whereas, generic drug was used in pantoprazole group. Consequently, administering patent drug of lansoprazole require a greater average prophylaxis drug costs than generic pantoprazole.

The length of stay was possibly might affect the costs required by patients during the treatment period in the ICU as well. The longer the patient treated in ICU, the greater the costs required (Aygencel and Turkoglu, 2011). According to Table 1, the proportion of patients' length of stay between the two groups was not balance and proven statistically (P-value = 0.007). Length of stay more than 7 days certainly greatly affected the average prophylaxis drug costs in the pantoprazole group. Nevertheless, as mentioned before, the average prophylaxis drug cost in the pantoprazole therapy group was much lower than the lansoprazole group. This finding ensured that the influence of drug prices on prophylaxis drug cost were more dominant than the effect of length of stay.

The cost of prophylaxis medical device represented the cost of syringes used for administering prophylaxis drug injections. The 10 cc syringe was used in this study for both lansoprazole and pantoprazole group. Patients in the lansoprazole group required a lower average cost of prophylaxis medical device than those in the pantoprazole group (IDR17.409,52±6.816,62 and IDR22.188.95±12.494.63). This finding was supposedly related to the number of prophylaxis medical device, which was directly proportional to the total number of prophylaxis drugs administered during the treatment period in ICU. One factor affecting the number of prophylaxis drugs needed by the patients was the length of stay (Aygencel and Turkoglu, 2011). The longer the patient treated in ICU, the greater the number of prophylaxis drug required. As mentioned before in Table 1, the proportion of patients who stay in ICU for more than 7 in the pantoprazole group was greater than that of the lansoprazole group (43.9% and 21% respectively) so did the number of medical devices required in pantoprazole group.

Bleeding costs in this study comprised the cost of drugs used to treat gastrointestinal bleeding and the cost of drugs for post-bleeding side effects. The drugs used to treat gastrointestinal bleeding consisted of sucralfate, tranexamic acid, and vitamin K. While the drugs used manage post-bleeding side effects were any drugs/treatment indicated for post-bleeding side effects such as blood pressure fell drastically or impaired food absorption causing the need for parenteral nutrition. The average bleeding cost in pantoprazole group was IDR531.501.36±785.204.79. While lower cost was required in the lansoprazole group (IDR 241.289.93±246.501.36). As mentioned before in Table 1, a higher proportion of those who experienced bleeding was observed in the pantoprazole group. Therefore, this finding could explain why it required higher cost to manage bleeding in the pantoprazole group. Moreover, the severity of bleeding might influence the average cost of bleeding as well. There were more patients experiencing major bleeding in the pantoprazole group than lansoprazole group. Further statistic analysis on drug and non-drug cost of both groups showed that neither the drug cost nor the non-drug cost between 2 groups was different significantly.

Research Limitation

Researchers could not control the factors that could affect the effectiveness of therapy, such as the number of comorbid and ulcerogenic drugs. Length of stay is not only caused by gastrointestinal bleeding but is influenced by the main diagnosis

CONCLUSION

There were 77.4% of patients in the lansoprazole group who did not experience bleeding, whereas 61.4% of patients in the pantoprazole group did not experience bleeding. The effectiveness difference of lansoprazole and pantoprazole as a stress ulcer prophylaxis in ICU was not statistically significant (P-value >0.05). Costs for the prophylaxis of stress ulcers is lower on the use of pantoprazole compared to lansoprazole. Further research is needed using 2 groups that are equally homogeneous so that the research results can be used for decision making.

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