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Research Article

Cost-effectiveness of esomeprazole and pantoprazole as prophylaxis stress-related mucosal disease therapy in Intensive Care Unit

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ABSTRACT

High risk of bleeding in a patient with a critical condition in an Intensive Care Unit (ICU) resulting requirement use needs prophylaxis for decrease bleeding incident during ICU is entirely accurate. This research is to determine the cost and effectiveness of esomeprazole and pantoprazole as Stress Related Mucosal Disease (SRMD) in the hospital ICU in Surakarta. This research is a retrospective cohort study. The subject is about all inpatients in ICU with the age of 18 to 65 who get esomeprazole and pantoprazole as stress ulcers prophylaxis during December 2016 – December 2018 that meets the criteria inclusion and exclusion criteria. Subjects on this research are 166 patients, where each group esomeprazole therapy (83 patients) and pantoprazole (83 patients). The effectiveness of treatment was observed based on the minor and major bleeding. Furthermore, the cost of therapy is calculated based on the total price paid by the patient for prophylaxis therapy on SRMD and treatment bleeding SRMD that count as Incremental cost-effectiveness ratio (ICER) value. The research result shows that no real difference between patients treated with esomeprazole (88%) and pantoprazole (80,7%) as prophylaxis therapy SRMD (p = 0.286). The use of esomeprazole can save money by IDR 13,456,368.00 (ICER) compared to pantoprazole for each cost reduction in the event of bleeding.

1. INTRODUCTION

Stress-Related Mucosal Disease or SRMD associated with the emergence of acute erosive gastritis can appear only 24 hours after the patient enters the Intensive Care Unit (ICU) (Stollman & Metz, 2005). Gastrointestinal (GI) bleeding can occur in 3-6% of patients admitted to the ICU (Clinical Pharmacy Working Committee, 2013). A study proves that complications from SRMD can cause death in 7 out of 150 (5%) ICU patients (Marik, Vasu, Hirani, & Pachinburavan, 2010)

Provision of stress ulcer prophylaxis in patients can reduce the risk of bleeding by up to 50% (Alshamsi et al., 2016). The most commonly used prophylaxis to prevent SRMD is gastric acid neutralizers (antacids), proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), sucralfate, and misoprostol (Cook et al., 2001). PPIs is the most effective prophylactic agent in preventing stress ulcer bleeding (Schupp, Schrand, & Mutnick, 2003; Ali & Harty, 2009; Barkun, Adam, Martel, & Bardou, 2013; Barletta & Sclar, 2014). The use of esomeprazole at a dose of 40 mg/day intravenously can increase and maintain the intragastric pH faster than

pantoprazole 40 mg intravenously. Maintaining an intragastric pH above six is necessary to keep clotting in patients at risk of rebleeding or ulcer healing (Sesler, 2007).

PPIs can reduce hospitalization costs by USD 2764 (Barkun, Bardou, Pham, & Martel, 2012). Previous research on the use of omeprazole and pantoprazole for SRMD prophylaxis found that the EMV value in the pantoprazole group was IDR 431,490.76 while the omeprazole group was IDR 382,042.57 (Sukengtyas, Andayani, & Budiarti, 2017). The high use of PPIs as stress ulcer therapy and the price difference between esomeprazole of IDR 42,733 and the price of pantoprazole of IDR 39,684.

Against the background of differences in cost, effectiveness, and safety of the two drugs, pantoprazole and esomeprazole, and the importance of using therapy for bleeding in patients with stress ulcers, it is necessary to study effective medicines to prevent complications in the hope of minimizing the cost of patient care in the ICU. Based on the various reasons above, the researchers are interested in researching the effectiveness and cost of therapy of pantoprazole and esomeprazole in the ICU.

2. MATERIALS AND METHODS

The study was conducted using an analytic observational method using a retrospective cohort study. Data is taken from medical record records and financial cost data for December 2016 - December 2018, which meet the inclusion and exclusion criteria. The research subjects were all ICU patients using esomeprazole and pantoprazole therapy as prophylactic therapy for SRMD. The sample in this study amounted to 166 patients, where each group of pantoprazole and esomeprazole therapy was 83 patients.

The inclusion criteria were patients who were admitted to the ICU at RSUD Dr. Moewardi for at least one day with an age of ≥ 18 years old with at least one of the significant criteria in the form of coagulopathy (including treatment of induced coagulopathy, platelet count < 50,000 mm^3, INR > 1.5, or PTT > twice average values) or respiratory failure in the form of mechanical ventilation ≥ 48 hours, or two minor criteria, namely spinal cord injury, multiple trauma with trauma to more than one part of the body, liver failure (total bilirubin level > 5 mg/dL, AST > 150 U/L, or ALT > 150 U/L), head trauma (GCS ≤ 10 or inability to obey simple orders), history of gastric ulceration or gastrointestinal bleeding for one year SMRS, sepsis/septic shock (using vasopressors and/or positive cultures of the suspected microorganisms), length of stay in the ICU ward > one week, and high dose corticosteroid therapy (≥ 250 mg/day). Patients admitted to the hospital with a diagnosis of gastrointestinal bleeding and receiving other gastric acid suppressant combination therapy were excluded.

The tools and materials used in this study were formula data retrieval to collect secondary data taken from medical records, and patient medical expenses were retrospectively taken from the financial department. Cost data includes the use of prophylactic drugs, therapy costs, and medical equipment costs.

The study's procedure or course was started by surveying RSUD Dr. Moewardi Surakarta to determine the hospital's prevalence of SRMD. Furthermore, the research permit arrangement was carried out by making an Ethical Clearance which was submitted to the Ethical Committee for Medical and Health Research, Faculty of Medicine, Dr. Moewardi Surakarta. Research population data were collected according to the inclusion criteria made through medical record data. Cost data from the finance department to see the costs incurred by patients for SRMD prophylactic therapy.

Data analysis on the variables studied was carried out using the help of SPSS for Windows version 16.0. Patient characteristics and therapeutic effectiveness were tested using the Chi-square analysis, while to determine the difference in therapy costs, the independent t-test was used. If the data were not normally distributed, the Mann-Whitney test was performed.

3. RESULTS AND DISCUSSIONS

Patient Characteristics

Based on **Table 1**, it can be seen that the comparison of characteristics in the form of sex, age, length of stay, duration of use of SRMD prophylaxis, and the number of ulcerogenic drug use between the esomeprazole and pantoprazole therapy groups were not statistically significant ($p > 0.05$). Research by Maclaren & Campbell (2014), stated that the number of male patients (72%) more than female patients (68%). Smoking is one of the causes of ulcer susceptibility and has a higher risk of ulcer recurrence (Maity, Biswas, Roy, Banerjee, &

Table 1. Patient characteristics between esomeprazole and pantoprazole therapy groups

Characteristics	Esomeprazole (%) (n = 83)	Pantoprazole (%) (n = 83)	p (sig)
Gender			
Male	51 (61,4)	57 (68,7)	0,416
Female	32 (38,6)	26 (31,3)	
Insurance			
BPJS	74 (89,2)	65 (90,4)	1,000
General	9 (10,8)	8 (9.6)	
Age			
18-30	8 (9,6)	11 (13,3)	0,433
31-40	5 (6,0)	3 (3,6)	
41-65	51 (61,4)	43 (51,8)	
>65	19 (22,9)	26 (31,3)	
Medical Diagnosis			
CNS Disease	36 (42,9)	33 (40,2)	0,083
Respiratory Disease	20 (23,8)	16 (18,9)	
CVD Disease	16 (19,0)	13 (16,3)	
Others	11 (14,3)	21 (24,6)	
ICU Stay			
≤ 7 days	66 (79,5)	53 (63,9)	0,068
> 7 days	17 (20,5)	30 (36,1)	
Amount of Risk Factors			
1-2	43 (51,8)	42 (50,6)	0,671
3-4	36 (43,4)	39 (47,0)	
>4	4 (4,8)	2 (2,4)	
Duration of use SRMD Prophylaxis			
1-7	63 (75,9)	52 (62,7)	0,077
8-14	20 (24,1)	26 (31,3)	
>14	0 (0)	5 (6,0)	

Bandyopadhyay, 2003; Li et al., 2014). Previous research stated that there was no significant difference in age demographics with PPIs for the treatment of bleeding in GI (Maclaren, Reynolds, & Allen, 2014). According to Mohebbi & Hesch (2009), patients treated for more than one week have a more significant risk factor for SRMD.

SRMD prophylaxis in ICU patients can be done if one considerable risk factor or two minor risk factors. Several studies have shown that an increase in risk factors corresponds to an increased risk of bleeding caused by stress ulcers. Stated that the two main factors causing bleeding are coagulopathy and the use of a ventilator (Cook et al., 2001).

In patients admitted to the ICU, the presence of risk factors can worsen the patient's condition. During their stay in the ICU, each patient has different risk factors. According to Sesler (2007), SRMD prophylactic therapy in patients admitted to the ICU is highly recommended. The recommendation works in patients with major categories, namely patients with coagulopathy or respiratory failure, followed by mechanical ventilators for more than 48 hours, and several minor categories. Patients admitted to the hospital or ICU alone are not the right reason to start prophylaxis. Only patients with respiratory failure requiring mechanical ventilation for more than 48 hours and patients with coagulopathy, head injury, and burns > 35% who have a risk of bleeding are recommended to use prophylaxis (Kerama et al., 2014).

Therapeutic Effectiveness

The effectiveness of therapy was assessed by the patient's clinical outcome, which saw whether or not there was bleeding, major or minor bleeding occurred in patients receiving esomeprazole and pantoprazole prophylactic therapy in the ICU. Minor bleeding can be seen in the patient's medical record in the form of hematemesis, melena, or aspiration of blood in the stomach/nasogastric tube residue that is red, brown, or black. At the same time, major bleeding is a minor bleeding event followed by either a drop in systolic blood pressure or a spontaneous drop in diastolic blood pressure of 20 mmHg or more within 24 hours of bleeding, starting to use a vasopressor or an increase in the vasopressor dose by 20%, a decrease. Minimum hemoglobin 2 g/dL needs two units of packed red cell transfusion (Krag, Perner, & Møller, 2016).

Several factors could have influenced the difference in effectiveness between the esomeprazole and

Table 2. Comparison of bleeding incidence between esomeprazole and pantoprazole therapy groups

Therapy Group	Bleeding	No Bleeding	p
Esomeprazole	10 (12,0%)	73 (88,0%)	0,286
Pantoprazole	16 (19,3%)	67 (80,7%)	

Table 3. Comparison of average costs of prophylaxis SRMD

Type Cost	Average Cost (IDR)		*p*
	Esomeprazole	Pantoprazole	
Prophylaxis Cost			
Medicine	720.514 ± 174.431,46	624.784 ± 226.774,62	0,062
Medical Device	30.051 ± 7.275,04	35.664 ± 12.558,46	0,479
Doctor's visit	580.663 ± 329.309,86	593.735 ±405.960,06	0,405
Lab examination	796.441 ± 267.450,34	822.513 ± 369.748,85	0,633
ICU Care	2.445.181 ± 1.122.676,86	3.231.325 ± 2.228.100,90	0,064
Sub Total	4.249.442± 1.663.321,90	5.048.915± 3.083.317,13	0,434
SRMD Cost			
Medicine	370.321 ± 109.160,81	416.726 ± 266.263,33	0,244
Medical Device	21.653 ± 13.584.71	27.311 ± 23.243,29	0,428
Doctor's visit	657.000 ± 199.474,31	625.938 ± 466.951,88	0,450
Lab examination	869.890 ± 167.155,98	938.663 ± 360.275,35	0,751
ICU Care	2.565.000 ± 601.872,08	3.487.500 ± 2.652.074,66	0,079
Sub Total	4.721.897 ± 1.002.034,76	5.618.936 ± 3.586.780,14	0,489

Table 4. ICER Calculation

	Esomeprazole	Pantoprazole	Difference	ICER
Cost Average	Rp. 1.076.561	Rp. 2.058.895	Rp. 982.335	Rp. 13.456.368
Effectiveness	0,880	0,807	0,073	

pantoprazole groups in preventing bleeding. When viewed from the patient characteristics listed in **Table 1**, there is a difference in the proportion of the risk of the length of stay in the ICU between the two groups. The number of patients with ICU length of stay > seven days was higher in the pantoprazole group than patients in the esomeprazole group. Likewise, the proportion of patients who experienced sepsis who was one of the risks of bleeding was not the same between the two groups, where the number of patients who experienced sepsis was more in the pantoprazole group.

Based on **Table 2**, it can be seen that in the esomeprazole group, patients who experienced gastrointestinal bleeding were less than in the pantoprazole group, namely ten patients (12%) and 16 patients (19.3%). Statistical analysis obtained p value > 0.05 (p = 0.286), which means there was no difference in therapeutic effectiveness between the esomeprazole and pantoprazole groups as SRMD prophylaxis. However, the number of bleeding incidents was higher in the pantoprazole group. According to research, there is no significant difference between omeprazole, pantoprazole, lansoprazole, and esomeprazole in treating reflux esophagitis for eight weeks (Zheng, 2009)

Cost

The cost of dealing with SRMD is the cost that must be incurred to treat bleeding in patients due to the ineffectiveness of SRMD prophylaxis. In **Table 3**, it can be seen that the cost of drugs in handling SRMD in the esomeprazole group is IDR 308,634.73 (USD 21.70) + IDR 570,574.41 (USD 40.11) while the pantoprazole group was IDR 353,362.88 (USD 24.84) + IDR 986,716.42 (USD 69.37). This result is because the average length of stay in the ICU in the pantoprazole group was longer, namely seven days, while for esomeprazole patients, the average was five days. So that risk factors and disease severity can also affect the cost of patient care. The longer the bleeding is handled, the more the cost will be. However, in this study, the bleeding experienced by many patients was minor, so that patients did not need blood transfusions. So that the average patient only needs drugs and medical devices to support bleeding control in SRMD patients.

From the statistical test using Mann-Whitney, the results were obtained p > 0.05 on drugs and medical equipment handling SRMD. That is, respectively, the p-value is obtained = 0.344 and 0.489. So statistically, it was stated that there was no significant difference in the cost of SRMD therapy between the esomeprazole therapy group and the pantoprazole therapy group.

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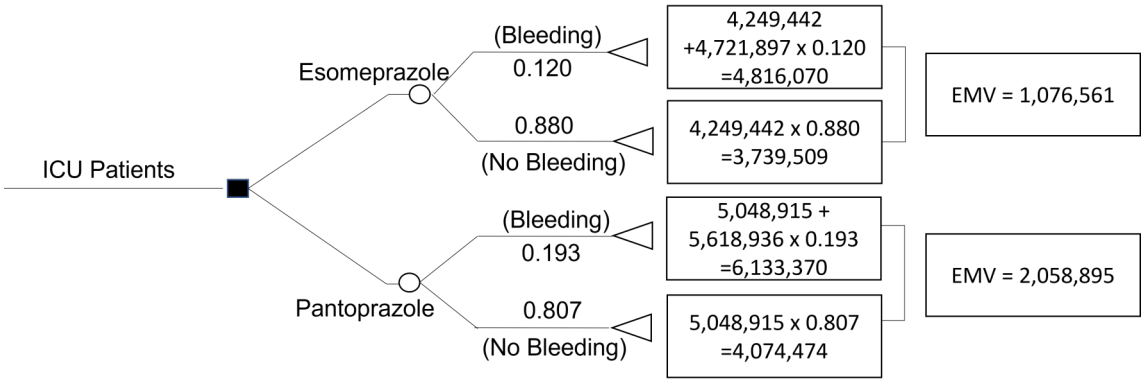

Figure 1. Calculation of EMV between esomeprazole and pantoprazole groups using a decision tree method

Decision analysis evaluates the costs and outcomes expected from a decision on one or more alternative drug use. In this study, the analysis of the cost of SRMD prophylaxis in ICU patients can be seen in **Figure 1**. From the decision tree, the EMV value for esomeprazole was IDR 1,076,561 (USD 75.69), and the EMV value for pantoprazole is IDR 2,058,895 (USD 144.75). The difference between EMV of esomeprazole and pantoprazole is IDR 982,335 (USD 69.06), which means that patients who receive esomeprazole prophylaxis can save the cost of SRMD therapy in the ICU by IDR 982,335 (USD 69.06)/ day.

The cost analysis in this study used the ICER parameter, which compares the cost difference with the effectiveness of the two groups, namely the esomeprazole group and the pantoprazole group. The results of ICER calculations can be seen in the **Table 4**.

The average cost is obtained from the average cost of using prophylaxis with the average cost of prophylactic therapy. So that the ICER value of IDR 13,456,368 (USD 946.02). This result means that the cost that the hospital can save for each increase of one outcome unit in the form of effectiveness on esomeprazole is IDR 13,456,368 (USD 946.02) compared to pantoprazole.

4. CONCLUSIONS

There was no significant difference in the effectiveness of using esomeprazole and pantoprazole as SRMD prophylaxis in the Intensive Care Unit (ICU), where the p-value was > 0.05 (p = 0.286). Using esomeprazole as a prophylactic for SRMD in the Intensive Care Unit (ICU) can reduce hospital costs by IDR 13,456,368 (USD 946.02) per one unit of outcome effectiveness compared with using pantoprazole.

5. REFERENCES

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6. REFERENCE

Ali, T., & Harty, R. F. (2009). Stress-induced ulcer bleeding in critically ill patients. *Gastroenterology Clinics, 38*(2), 245-265.

Alshamsi, F., Belley-Cote, E., Cook, D., Almenawer, S. A., Alqahtani, Z., Perri, D., ... & Alhazzani, W. (2016). Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials. *Critical Care, 20,* 120.

Barkun, A. N., Bardou, M., Pham, C. Q. D., & Martel, M. (2012). Proton pump inhibitors vs. histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: A meta-analysis. *The American Journal of Gastroenterology, 107*(4), 507-520.

Barkun, A. N., Adam, V., Martel, M., & Bardou, M. (2013). Cost-Effectiveness Analysis : Stress Ulcer Bleeding Prophylaxis with Proton Pump Inhibitors , H2 Receptor Antagonists. *Value in Health, 16*(1), 14-22.

Barletta, J. F., & Sclar, D. A. (2014). Use of proton pump inhibitors for the provision of stress ulcer prophylaxis: clinical and economic consequences. *Pharmacoeconomics, 32*(1), 5-13.

Clinical Pharmacy Working Committee. (2013). *Critical Care Pharmacy Handbook*. Selangor, Malaysia: Ministry of Health.

Cook, D. J., Griffith, L. E., Walter, S. D., Guyatt, G. H., Meade, M. O., Heyland, D. K., … Tryba, M. (2001). The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Critical Care, 5*(6), 368.

Kerama, S. K., Okalebo, F. A., Nyamu, D. G., Guantai, E. M., Ndwigah, S. N., & Maru, S. M. (2014). Risk factors and management of stress ulcers in the critical care unit in a Kenyan referral hospital. *African Journal of Pharmacology and Therapeutics, 3*(2), 51-61.

Krag, M., Perner, A., & Møller, M. H. (2016). Stress ulcer prophylaxis in the intensive care unit. *Current Opinion in Critical Care, 22*(2), 186-190.

Li, L. F., Chan, R. L. Y., Lu, L., Shen, J., Zhang, L., Wu, W. K. K., ... & Cho, C. H. (2014). Cigarette smoking and gastrointestinal diseases: the causal relationship and underlying molecular mechanisms. *International journal of molecular medicine, 34*(2), 372-380.

Maclaren, R., & Campbell, J. (2014). Cost-effectiveness of histamine receptor-2 antagonist versus proton pump inhibitor for stress ulcer prophylaxis in critically ill patients. *Critical Care Medicine, 42*(4), 809-815.

MacLaren, R., Reynolds, P. M., & Allen, R. R. (2014). Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. *JAMA internal medicine, 174*(4), 564-574.

Maity, P., Biswas, K., Roy, S., Banerjee, R. K., & Bandyopadhyay, U. (2003). Smoking and the pathogenesis of gastroduodenal ulcer–recent mechanistic update. *Molecular and cellular biochemistry, 253*(1), 329-338.

Marik, P. E., Vasu, T., Hirani, A., & Pachinburavan, M. (2010). Stress ulcer prophylaxis in the new millennium: A systematic review and meta-analysis. *Critical Care Medicine, 38*(11), 2222-2228.

Mohebbi, L., & Hesch, K. (2009, October). Stress ulcer prophylaxis in the intensive care unit. In *Baylor University Medical Center Proceedings* (Vol. 22, No. 4, pp. 373-376). Taylor & Francis.

Schupp, K. N., Schrand, L. M., & Mutnick, A. H. (2003). A cost-effectiveness analysis of stress ulcer prophylaxis. *Annals of Pharmacotherapy, 37*(5), 631-635.

Sesler, J. M. (2007). Stress-related mucosal disease in the intensive care unit: an update on prophylaxis. *AACN Advanced Critical Care, 18(*2), 119-128.

Stollman, N., & Metz, D. C. (2005). Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *Journal of Critical Care, 20*(1), 35-45.

Sukengtyas, D. A. T., Andayanti, T. M., & Budiarti L. E. (2017). Effectivity and Cost Analysis of Omeprazole and Pantoprazole For Stress Related Mucosal Disease Prophylaxis in ICU. *Journal of Management and Pharmacy Practice, 7*(2), 57-64.

Zheng, R. N. (2009). Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for symptom relief in patients with reflux esophagitis. *World Journal of Gastroenterology, 15*(8), 990-995.