



Correlation of histamine-2 receptor antagonist (H₂RA) and proton pump inhibitor (PPI) to the platelet count in patient with dengue viral infection

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ABSTRACT

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Thrombocytopenia is often associated with clinically worse outcomes in dengue viral infection (DVI) patients. Histamine-2 receptor antagonist (H₂RA) and proton pump inhibitor (PPI) have been reported to induce thrombocytopenia. These drugs are administered to DVI patients due to misinterpretation of abdominal pain. The study aimed to evaluate the correlation between H₂RA and PPI administration with thrombocytopenia event on hospitalized DVI patients. An analytical retrospective cross-sectional study was conducted using medical records of the patient admitted by final diagnosed DVI in seven major hospital in Bandung from January 1st to December 31st, 2015. Patients were separated into two groups i.e. with and without H₂RA and PPI. Pearson point biserial analysis was then applied to evaluate the correlation of each drug administration to platelet count of DVI. A total of 4005 patients with final diagnosed DVI involved in this study. About 11.0% and 25.1% of the patients received H₂RA and PPI, respectively. Mostly the DVI patients receiving H₂RA (55%) and PPI (50.8%) showed the platelet count <50.000/mm³. A very weak positive correlation between the administration of H₂RA (p <0.001; r=0.103) and PPI (p <0.001; r=0.138) with the low platelet count of the patients was observed. In conclusion, the administration of H₂RA and PPI is correlated to the low platelet count in DVI patients. Although the correlation is weak, H₂RA and PPI should be administered with caution due to its thrombocytopenia side effect.

ABSTRAK

Trombositopenia sering dikaitkan dengan luaran klinik yang buruk pada pasien infeksi virus dengue (IVD). *Histamine-2 receptor antagonist* (H₂RA) dan *proton pump inhibitor* (PPI) dilaporkan dapat menyebabkan trombositopenia. Obat ini diberikan pada pasien IVD karena misinterpretasi gejala nyeri abdomen pasien. Penelitian ini bertujuan untuk mengkaji hubungan antara pemberian H₂RA dan PPI dengan kejadian trombositopenia pada pasien rawat inap IVD. Penelitian ini merupakan penelitian potong lintang analitik dengan pendekatan restrospektif menggunakan data rekam medis pasien rawat inap yang terdiagnosis akhir IVD di tuju rumah sakit utama di Bandung periode 1 Januari sampai 31 Desember 2015. Pasien dikelompokkan ke dalam dua kelompok yaitu tanpa dan dengan pemberian H₂RA dan PPI. Analisis poin biserial Pearson dilakukan untuk mengkaji hubungan antara pemberian masing-masing obat terhadap jumlah trombosit pasien IVD. Sebanyak 4005 pasien dengan diagnosis akhir IVD terlibat dalam penelitian. Sebanyak 11.0% dan 25.1% pasien menerima secara berturut-turut H₂RA dan PPI. Sebagian besar pasien yang menerima H₂RA (55.0%) dan PPI (50.8%) menunjukkan jumlah trombosit <50.000/mm³. Terdapat hubungan positif lemah antara pemberian H₂RA (p <0,001; r=0,103) and PPI (p <0,001; r=0,138) dengan jumlah trombosit yang rendah. Simpulan, pemberian H₂PA dan PPI berhubungan dengan jumlah trombosit yang rendah pada IVD. Meskipun hubungannya lemah, pemberian H₂PA dan PPI harus menjadi perhatian karena efek samping trombisitopenianya.

Keywords:

dengue viral infection;
H₂RA;
PPI;
thrombocytopenia;
adverse event;

INTRODUCTION

Dengue viral infection (DVI) is a common arboviral disease in humans that remains to be a global burden in tropic and subtropics countries in the world.¹ Dengue viral infection is characterized by hematologic abnormality presentation, namely, thrombocytopenia. Thrombocytopenia is one indicator of clinical severity which indirectly showed the activity of platelet activation. It is also counted to be a risk predictor for disease progression and prognosis in DVI.²⁻⁴ Furthermore, severe thrombocytopenia ($<50.000/\text{mm}^3$) was independently and significantly associated with the risk of mortality.⁴

According to the World Health Organization (WHO) guideline, DVI patients can be administered some symptomatic therapy such as an antiulcer for gastrointestinal bleeding.¹ Empirically, antiulcer administration in the form histamine-2 receptor antagonist (H_2RA) and proton pump inhibitor (PPI)⁵ become management for abdominal pain in DVI while this symptom was mostly manifested as the result of liver disturbance.⁶ Moreover, these drugs was reported as one of the most drugs prescribed for DVI patients followed analgesic, multivitamin and antipyretic. However, H_2RA and PPI were reported can induce thrombocytopenia event^{7,8} which could worsen the thrombocytopenia condition of DVI patients. In this study, the relationship between the administration of H_2RA and PPI and the lowest platelet counts in DVI patients was reported.

MATERIALS AND METHODS

Patients

This study is part of the Hospital-Based Dengue Case Surveillance in the Municipality of Bandung, West Java, Indonesia in 2015. This analytical

retrospective cross-sectional study was conducted using medical records of the patient admitted by final diagnosed DVI in seven major hospital in Bandung from January 1st to December 31st, 2015. The hospitals involved were Dr. Hasan Sadikin Teaching Hospital, St. Borromeous Hospital, Adventist Hospital, St. Yusuf Hospital, Hermina Mother and Child Hospital Pasteur, Limijati Mother and Child Hospital, and Hermina Arcamanik Hospital.

This study included both children and adults which admitted to those hospitals with a final diagnosis confirmed as DF, DHF, and DSS based on WHO-SEARO 2011 criteria.⁵ Patient with incomplete platelet examination, no information of final diagnosis was excluded. This study used total sampling, then collected data were grouped based on the demographic characteristic of sex, age group,⁶ and final diagnosis.

Protocol of study

The patients were divided into groups that received and did not receive reduced acid secretion drugs (RASDs) during their admission. The output of each group was assessed by the lowest platelet count obtained from platelet examination during the admission period which was classified in an interval manner.⁷ The operational definitions used in this case are drugs that cause a reduction in gastric acid secretion, limited to H_2RA and PPI and platelet counts, which were the lowest platelet counts during the treatment period. The lowest platelet value was selected in consideration that in dengue patients there was a tendency to have thrombocytopenia during the course of the disease.⁸ Therefore, this thrombocytopenia-only condition may be caused by DVI. This study tried to evaluate the correlation whether the lowest platelet values in patients who received RASD compared to those who did

not receive RASD during their treatment period were related to drugs or not. The study had passed the ethical clearance by the Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran, Bandung.

Statistical analysis

Statistics software SPSS version 25 was used for data analysis. Point biserial analysis was used to evaluate the relationship of each H₂RA and PPI administration with the lowest platelet count in DVI patients. The p value <0.05 was considered to be a statistically significant between tested variables. The power of relation interpreted as very

weak (r= 0.00-0.199), weak (r=0.2-0.299), moderate (r=0.4-0.599), strong (r=0.6-0.799) and very strong (r=0.8-1).⁹

RESULTS

A total of 4005 patients who lived in Bandung had admitted to the hospital by final diagnosed DVI were involved in this study. TABLE 1 shows the characteristic of DVI patients demographically and its final diagnosis group. Majority patient was male, accounting for 50.4% of all cases. The patient also dominated respectively by teenagers (12-25) accounting for 31.7%. The most DVI event consecutively was DHF, DF and, DSS.

TABLE 1. Demographic characteristic of DVI patients

Characteristic	n (%)
Gender	
• Male	2018 (50.4)
• Female	1987 (49.6)
Age (years old)	
• 0-5	992 (24.8)
• 6-11	805 (20.1)
• 12-25	1273 (31.7)
• 26-45	683 (17.1)
• >45	252 (6.3)
Final diagnosis	
• Dengue fever	1459 (36.4)
• Dengue hemorrhagic fever	2420 (60.4)
• Dengue shock syndrome	126 (3.1)

The types of drugs given by the hospital to DVI patients in managing the cases were described based on its therapy class in TABLE 2. The most drug prescribed was analgesic-antipyretic, followed by antibiotics then each H₂RA and PPI (FIGURE 1). Some different characteristic of patients received H₂RA

and PPI are showed in TABLE 3. Both patient received H₂RA and PPI were mostly female and patients with final diagnose DHF. The H₂RA was mostly prescribed in Child accounted 51% of all cases, while PPI was more prescribed in adults, in the age group teenager age 12-25 years old (48.0%).

TABLE 2. List of prescribed drugs in DVI patients

Drug therapy class	Patients n (%)
Analgesic-antipyretic	3672 (91.8)
Corticosteroid	457 (11.4)
Antibiotic	1541 (38.5)
PPI	1004 (25.1)
H2RA	442 (11.0)
Antacid	140 (3.5)

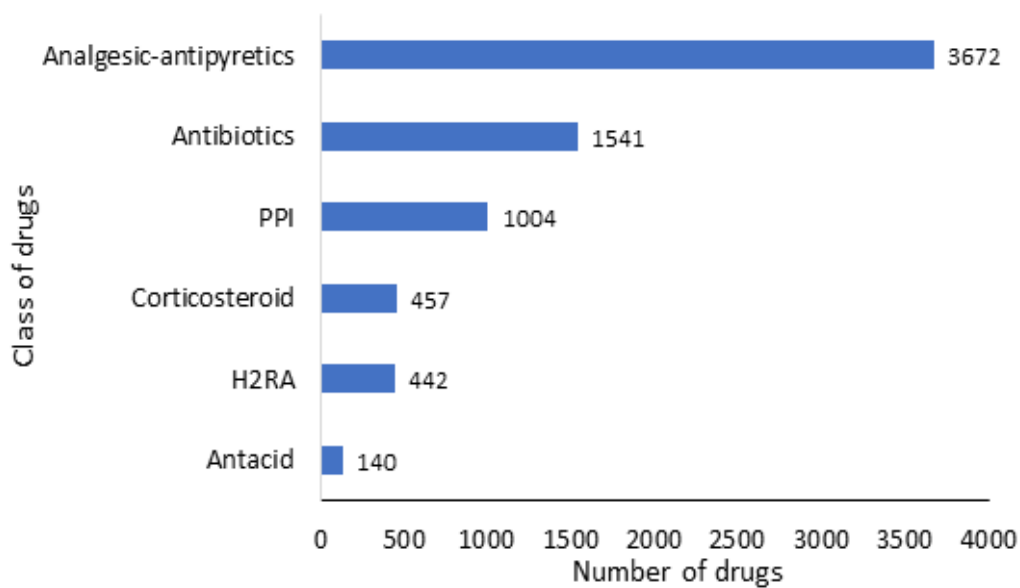


FIGURE 1. List of prescribed drugs in DVI patients

TABLE 3. Characteristic of patients received H₂RA and PPI

Characteristic	PPI	H ₂ RA
	n (%)	n (%)
Gender		
• Male	463 (46.1)	212 (48.0)
• Female	541 (53.9)	230 (52.0)
Age (years old)		
• 0-5	35 (3.0)	104 (24.0)
• 6-11	179 (18.0)	224 (51.0)
• 12-25	476 (48.0)	107 (24.0)
• 26-45	309 (31.0)	42 (9.0)
• >45	120 (12.0)	19 (5.0)
Final diagnosis		
• Dengue fever	251 (25.0)	143 (32.0)
• Dengue hemorrhagic fever	729 (73.0)	255 (58.0)
• Dengue shock syndrome	24 (2.0)	44 (10.0)

TABLE 4. Thrombocyte count of the patient received RASD

RASD Administration	Thrombocyte count				
	<50.000	50.000 - <100.000	100.000 - <150.000	≥150000	
	243	128	52	19	
H ₂ RA	Yes	55.00%	29.00%	11.80%	4.30%
		15.10%	9.40%	7.10%	6.40%
	No	1369	1239	678	277
		38.40%	34.80%	19.00%	7.80%
PPI		84.90%	90.60%	92.90%	93.60%
	Yes	510	316	142	36
		50.80%	31.50%	14.10%	3.60%
		31.60%	23.10%	19.50%	12.20%
	No	1102	1051	588	260
		36.70%	35.00%	19.60%	8.70%
	68.40%	76.90%	80.50%	87.80%	

The low platelet counts during hospital admission based on H₂RA and PPI status showed in TABLE 4. There was 11% of all patients who received H₂RA and 25.1% received PPI during their admission to the hospital showed in TABLE 2. Each of the group received RASD and not received, was dominated by patients with low platelet count <50.000/mm³, even though mostly in a group of patients received RASD dominated by low platelet count <50.000/mm³, accounted in chronological order for H₂RA and PPI, 55% and 50.8%, respectively.

TABLE 5. Correlation of RASD and platelet count

Drug	p	r
H ₂ RA	<0.001	0.103
PPI	<0.001	0.138

The relation of each of RASD group, specifically H₂RA and PPI with patient low platelet count is showed in TABLE 4. Administration of H₂RA significantly was correlated with low platelet count (p<0.05), although it was classified very weak (r=0.103). Furthermore, administration of PPI was also correlated

with low platelet count (p<0.05) with very weak correlation (r=0.138).

DISCUSSION

Dengue viral infection is a common mosquito vector-borne disease in humans. This study presented the drug utilization in managing DVI. Group of antiulcer (RASD) ranked the third most drug prescribed of the hospital, PPI (25.1%) and H₂RA (11%) respectively, following analgesic-antipyretic and antibiotic. A retrospective study conducted in Yogyakarta also obtained similar results.¹⁰ The provision of this administration based on complaints of abdominal pain of DVI patients, other than to prevent the occurrence of gastrointestinal bleeding.¹

This study found that about 11% of DVI patients were given H₂RA during their admission. Most of the DVI patients had low platelet counts <50.000 /mm³. However, only 15% of all low platelet group patients <50.000/mm³, which considered severe thrombocytopenia, received H₂RA. This large number of patients with severe thrombocytopenia despite not prescribed H₂RA could

occur as a result of thrombocytopenia caused by the dengue virus itself. Thrombocytopenia is a manifestation that often occurs in patients with DVI. Dengue virus could cause thrombocytopenia by increasing platelet destruction via immune reactions and releasing inflammatory mediators that could interfere with the process of platelet production.^{11,12}

Previous studies reported that thrombocytopenia could be induced by RASDs, although this event is still considered a relatively rare phenomenon. The evidence of H₂RA induced thrombocytopenia events was confirmed by finding the presence of drug-dependent-antibodies (DDA) in the serum of patients who had severe acute thrombocytopenia after receiving H₂RA.¹³ These antibodies formed due to H₂RA, which even in pharmacological concentrations, were able to recognize the receptor side of GPIIb/IIIa platelet so that they can destroy platelets and cause thrombocytopenia. Reese *et al.*¹⁴ also analyzed the drugs that cause acute hospital-acquired thrombocytopenia in hospitalized patients using 3 different methods to reassert the truth of this incident. The results showed that the H₂RA can cause thrombocytopenia based on clinical data extraction in various case reports, data mining and proven by the presence of antibodies on laboratory examination. Arnold *et al.*¹⁵ also reinforced the occurrence of H₂RA induced thrombocytopenia. The study identified drugs that clinically caused the incidence of drug-induced thrombocytopenia (DITP) included H₂RA. Although those studies had proved the incidence of thrombocytopenia induced by H₂RA. However, all those study were involved non-DVI patients. Until now, the studies reporting the thrombocytopenia induced by H₂RA administration in DVI patients are limited. This study reported the positive significant correlation between H₂RA and low platelet counts

in DVI patients, although the correlation was considered very weak.

This study found about 25.1% of patients with DVI received PPIs during their admission and most (55%) had platelet counts <50.000/mm³ or severe thrombocytopenia. Thrombocytopenia is known not to be a common side effect of PPI drugs. Nevertheless, this study showed a positive significant correlation with very weak strength. Surprisingly, that PPI had a stronger relationship with thrombocytopenia than H₂RA. This could occur since H₂RA has been more known to be able to cause thrombocytopenia so that its use was less than PPI.

Previous studies also reported the decreasing platelet following PPI administration. Aster *et al.*¹⁶ showed that the PPI group can induce thrombocytopenia occurrence. Various PPI classes were also reported in some case reports and reviews of literature.^{17,18} Retrospective analytic studies conducted at Duke University Hospital also found an significantly association between thrombocytopenia events in hospitalized patients who received PPIs during their treatment period.¹⁹ However, these studies were conducted in patients with acute thrombocytopenia during their admission period not DVI patients. Although many studies support the relationship between PPI administration and thrombocytopenia, this phenomenon was still based on the analysis of various case reports and retrospective studies. Therefore, a prospective study is required to confirm this relationship, even less, in DVI patients.

This study has several limitations. First, this study also did not regard the coinfection of patients which might be another cause of thrombocytopenia. Second, in the obtained data, there was no information regarding the timing of starting the drug and the daily platelet value of each patient. Subsequently, this study also did not adjust the confounding variables thus that it can

not be known which factors influence RASD administration and platelet count in DVI patients. Third, as this study used a retrospective approach with a cross-sectional method, the incidence of thrombocytopenia by the patients receiving RASD cannot be distinguished from the incidence of thrombocytopenia that occurs as a result of DVI itself. The limitation of available data regarding the time of RASDs administration, that it is inconvenient to decide the causal precede the effect. Further, prospective studies are needed to better understand the cause-effect of RASD administration on the platelet count.

CONCLUSION

In conclusion, the administration of H₂RA and PPI is correlated to the low platelet count in DVI patients. Although the correlation is weak, H₂RA and PPI should be administered with caution due to its thrombocytopenia side effect.

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