

**Research Article****MONITORING OF ANTITHROMBOTICS'ADVERSE EFFECT ON UNSTABLE ANGINA PECTORIS PATIENTS IN A PUBLIC HOSPITAL OF YOGYAKARTA, INDONESIA****DYAH ARYANI PERWITASARI**

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ABSTRACT

Patients with unstable angina pectoris are at risk of death or recurrent ischemic events, despite receiving aspirin and heparin. The benefit from using aspirin in high-risk vascular disease patients comes at the cost of increased gastrointestinal complications. The complications include gastroduodenum ulcerations, dyspepsia, esophagitis and ulcerations in the stomach and duodenum. This research investigated the monitoring of antithrombotics adverse effect in a public hospital of Yogyakarta during January 2006-December 2007.

This research used patients' medical records as patients' database in adverse drug effect monitoring. The populations were all unstable angina inpatients in a public hospital of Yogyakarta January 2006 to December 2007.

We identified that the adverse effects' monitoring has been done well. The monitoring has been done to the gastrointestinal disturbance (100%), bleeding risk (30%), thrombocytopenia (35%) and renal dysfunction (20%). There were 35% patients experienced antithrombotics' adverse effects, such as bleeding, thrombocytopenia and renal dysfunction. Clinical manifestation of dual antithrombotic therapy was experienced by 10% patients.

Keywords: Monitoring, Adverse effect, Antithrombotic, Unstable angina pectoris, Indonesia

INTRODUCTION

The use of aspirin as dual therapy with another antiplatelet was increasing at the last decade to prevent and treat cardiovascular, cerebrovascular and peripheral arterial disease. According to American Heart Association statistic, 700 000 patients had stroke, 13 million had coronary artery disease, and 8 to 12 million suffered from peripheral arterial disease in 2002. Each year, 1.2 million patients in the United States receive dual antiplatelet therapy with aspirin and clopidogrel after percutaneous coronary intervention with drug-eluting stents ¹.

Gastrointestinal ulcer complications are 2- to 4-fold more common in patients who take 75 to 300 mg/d of aspirin compared with controls ^{2,3}. Daily aspirin doses of 100 mg or greater were associated with no clear benefit in patients taking aspirin only and possibly with harm in patients taking clopidogrel. Daily doses of 75 to 81 mg may optimize efficacy and safety for patients requiring

aspirin for long-term prevention, especially for those receiving dual antiplatelet therapy. ⁴. Combined antithrombotic treatment also confers particular risk and is associated with high incidence of gastrointestinal bleeding ³.

During a 4-year period in the United Kingdom Transient Ischemic Attack study, gastrointestinal complications in patients taking aspirin ranged from mild dyspepsia (31%) to life-threatening bleeding and perforation (3%)⁵.

METHODS

We used unstable angina pectoris inpatients in a public hospital of Yogyakarta as the subjects during January 2006 to December 2007. We observed adverse effect of antithrombotics by seeing the patients' medical records as database.

RESULTS

We recruited 21 patients with unstable angina pectoris during the research period. Patients' demographic were listed in table 1.

Tabel 1 : Patients' demographic data

	%
Sex (N=21)	
Male	52,4
Female	47,6
Age (N = 21)	
< 40	0
≥ 40	100
Total drug number	
≤ 4	19,1
> 4	80,9
Underlying disease (n=14)	
Hyperlipidemia	14,3
Hypertension	21,4
Diabetes mellitus	7,14
Hyperlipidemia and Hypertension	28,6
Diabetes mellitus and Hypertension	28,6

There were two kinds of the occurrence of the coronary heart disease as the risk factor, that is could not be prevented and prevented. The risk factor that could not be prevented are the age and gender. Whereas, the risk factor that could be prevented are hyperlipidemia, hypertension and diabetes mellitus. The occurrence of coronary heart disease are increasing with the increase of age (> 40

years old) and more often happened to the man compared with the woman. The number of drugs that were received by the patients is regarding the possibility of the occurrence of drug interaction. More of drug number that were received by the patients can increase the occurrence of drug interaction. Table 2 showed the distribution of antithrombotics in unstable angina pectoris patients.

Table 2. Distribution of antithrombotics in unstable angina pectoris patients (N=20)

Antithrombotic	Number of patients	%
Aspirin	11	55
Aspirin + heparin/LMWH	5	25
Clopidogrel	1	5
Aspirin + Ticlopidine	1	5
Aspirin + Clopidogrel + LMWH	2	10

The use of antithrombotics, both antiplatelet and anticoagulant has become main medical treatment for coronary arterial diseases, based on their roles that was important to prevent the pathogenesis of thrombosis and atherosclerosis complication, antithrombotic

in the pathogenesis and the process complication atherosclerosis⁶.

Intravenously used of heparin was indicated to the patients who had the risk of unstable angina pectoris with intermediate to high level. The experts

recommended that heparin was better to be given to the patients as immediately as possible when the diagnosis was upheld⁷. The American Heart Association (AHA) recommended to give anticoagulant as immediately as possible to the unstable angina pectoris patients⁸.

Six randomized placebo-controlled trial with heparin showed 54% decrease of mortality and myocardium infarction for the first week.

One meta-analysis with three randomized controlled trial showed 56% decrease of mortality and myocardium infarction with aspirin and heparin combination. However, another meta-analysis showed 33% decrease of mortality and myocardium infarction with aspirin and heparin combination⁸.

Several researches proved that the use of Low Molecular Weight Heparin (LMWH) in unstable angina pectoris was more effective and safe than heparin. LMWH reduced the number of heart attack incidents and reduce the number of complication. A review suggested that heparin and LMWH had the same effectiveness in preventing the death, but LMWH could reduce the risk of the myocardium infarction, revascularization and thrombocytopenia⁹.

The randomized open-label pilot research with 219 unstable angina pectoris patients accepted aspirin (200 mg/day), aspirin-heparin and aspirin- LMWH (nadroparin). The combination of aspirin and LMWH significantly reduced the level of ischemic incident. Based on the study, the use of LMWH was more recommended than the

use of heparin because of the effectiveness and the LMWH ' safety⁸.

The collaboration of 195 meta-analysis with more than 143,000 patients showed a reduction of 22% occurrence of blood vessels necrosis, myocardium infarction and stroke with aspirin to the unstable angina pectoris. The ISIS-2 (Second International Study of Infarct Survival) explored the aspirin's ability in reducing patients' mortality due to unstable angina pectoris and recommended to give aspirin as early as possible⁸.

RISC research (Research ounce Instability in Coronary artery disease) found that low dose aspirin was also effective in the unstable coroner's syndrome , 3 months after giving of aspirin 75 mg/the day for a long time. Giving aspirin for 5 days significantly could reduce the infarction incident and mortality of 64%¹⁰.

The widely used of clopidogrel was proven in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). The total of 19,185 patients was randomised to accept aspirin 325 mg/day or clopidogrel 75 mg/day. Results of the research showed the decline in the risk in ischemic stroke, the myocardium infarction, or the blood vessels necrosis of 8.7% in giving clopidogrel. The side-effect caused by clopidodrel were rash and diarrhoea with the small incident. Moreover, there were no incident of neutropenia. Clopidogrel had the same effectiveness with aspirin⁸.

Table 3 showed the adverse drug effects' monitoring based on the patients' medical records.

Table 3: Monitoring of antithrombotics'adverse effect

Drug	Adverse effect	Number of patients with monitoring of Adverse Effect (%)	Number of patients with Adverse drug effect (%)
Aspirin	Gastrointestinal disturbance	20 (100)	-
Aspirin	Bleeding	5 (25)	1 (5)
Aspirin- <i>thienopyridine</i> <i>agents</i>	Gastrointestinal disturbance	1 (5)	-
Aspirin- Heparin/Enoxaparin	Bleeding	3 (15)	2 (10)
Aspirin	Thrombocytopenia	4 (20)	2 (10)
Aspirin + Enoxaparin	Thrombocytopenia	3 (15)	1 (5)
Enoxaparin	Renal dysfunction	4 (20)	1 (5)

Currently available clinical data do not support the routine, longterm use of aspirin dosages greater than 75 to 81 mg/d in the setting of cardiovascular disease prevention. Higher dosages, which may be commonly prescribed, do not better prevent events but are associated with increased risks of gastrointestinal bleeding¹¹.

In this study, patients had no complain of gastrointestinal disturbance such as dyspepsia, the feeling burnt or hot, nausea, vomiting, anorexia, and stomach pain by seeing the patient's medical records. Whereas, gastrointestinal perforation resulting from the use of aspirin could not be known because there were no data related with endoscopy inspection to know the bleeding.

Proton Pump Inhibitors (PPI) should be given to the patients with gastrointestinal bleeding history when they used aspirin and *thienopyridine agents*⁸. There were no patients got PPI in this study, even they got aspirin and *thienopyridine agents*.

Bleeding could be happen in the use of aspirin, heparin and LMWH. The study in United Kingdom about Transient Ischemic

Attack (TIA) during 4 years suggested that the gastrointestinal complications of the patient who used aspirin were including dyspepsia (31%) and dyspepsia with the perforation of 3%¹.

Several researches that compared the occurrence of the major's bleeding (was defined as the occurrence of one or more the incident like the death, accepted 2 package of transfusion units of blood cells, the decline in haemoglobin ≥ 3 g/dL and the bleeding retroperitonium, intracranial or intraocular) to LMWH and heparin showed the bleeding figure that almost same to LMWH and heparin. The research of Efficacy and Safety of Subcutaneous Enoxaparin in Non- Q-Wave Coronary Event/ESSENCE (the sample = 3,171 patients) concluded the major's bleeding of LWMH of 6,5% and heparin of 7%. Based on this explanation the parameter that could be used to know the occurrence of major's bleeding risk was haemoglobin as big as ≥ 3 g/dL from baseline.⁸

Thrombocytopenia was the other side-effect caused by both heparin and LMWH. Percentage of severe thrombocytopenia (platelets < from 50.000/mm³) in enoxaparin was smaller than heparin (2,7% vs 3,4%).

Meanwhile the percentage of thrombocytopenia was almost the same in both heparin and enoxaparin⁸

Patients with the renal dysfunction could increase the risk of the bleeding in the therapeutic dose of LMWH. The ESSENCE study (Efficacy Safety Subcutaneous Enoxaparin in Non- Q-wave Coronary Event) with the post hoc data analysis and

the study of Thrombolysis and Thrombin Inhibition in Myocardial Infarction IIB concluded that CrCl ≤ 30 mL/minute can increase the major's bleeding risk to the patient with LMWH¹².

Table 4 showed monitoring of adverse drug reaction caused by dual therapy of antithrombotics.

Table 4: Monitoring of adverse effects caused by dual therapy of antithrombotics

Antithrombotic	Antithrombotic	Adverse effects' monitoring	Clinical Manifestation	Number of patients (%)
Aspirin	Enoxaparin	Prolonged APTT	Manifested	1(5)
Aspirin	Heparin	Prolonged APTT and PT	Manifested	1(5)
Aspirin	Ticlopidin	Bleeding	Not Manifested	1(5)
Clopidogrel	Enoxaparin	Bleeding	Not Manifested	1(5)

The dual therapy of aspirin and oral anticoagulant (warfarin), heparin, LMWH, ticlopidine, clopidogrel and dipyridamol could increase the risk of the bleeding. The use enoxaparin together with antiplatelet (aspirin, dipiridamol, ticlopidine, clopidogrel and antagonist IIB/IIIa) could increase the risk of the bleeding. The extension the PT value and APTT from normal was also the sign of the risk of bleeding resulting from the use anticoagulant especially heparin. There were 2 patients experienced prolonged of APTT which was caused by aspirin-heparin/enoxaparin¹³.

CONCLUSION

Adverse effect reactions which were resulted from antithrombotic utilization in unstable angina pectoris patients have been monitored well. The monitoring has been done to the gastrointestinal disturbance, bleeding risk, thrombocytopenia and renal dysfunction. There were 35% patients experienced antithrombotics'adverse effects, such as bleeding, thrombocytopenia and renal

dysfunction. Clinical manifestation of dual antithrombotic therapy was experienced by 10% patients. This study need to be confirmed with larger sample size before be applied on clinical practice.

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