Comparison of Bleeding and Major Cardiovascular Event Between Enoxaparin and Fondaparinux in Non ST-Elevation Myocardial Infarction with Diabetes Mellitus

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Abstract : Background : Non ST-segment elevation myocardial infarction (NSTEMI) has been known to have comorbidities, such as diabetes mellitus (DM). Diabetic increases the risk of cardiovascular event by 2 – 4 times compared with non-diabetic (NDM) patients. In diabetic patients, there are haemostasis disturbances, such as platelet hypereactivity, hypercoagulation, and decrease of fibrinolysis. This study aims to assess the effect of anticoagulant in terms of bleeding and MACE in NSTEMI with DM.

Method : This prospective study included 67 consecutive patients with NSTEMI and DM from January – October 2018 admitted to Adam Malik General Hospital. The patients were divided into 2 groups, enoxaparin and fondaparinux. In hospital bleeding and MACE were observed. The chi-square and fisher test analysis was performed to calculate the relative risk (RR).

Result : A total 67 patients in this study, there are 51 (76%) men with mean age 55 years old. There are 7 (10.4%) patients experienced minor bleeding event. This study found that enoxaparin group showed higher bleeding event than fondaparinux group, but not significantly different (RR 2.576, p-value 0.259). There are 26 (38.8%) patients experienced MACE, including heart failure, cardiogenic shock, arrhythmia, and stroke. This study also found there is significantly differences in MACE between two groups, fondaparinux showed smaller MACE than enoxaparin (RR 1.946, p-value 0.035).

Conclusion : There are no differences in the in-hospital bleeding between enoxaparin and fondaparinux in NSTEMI with DM. Fondaparinux also showed less MACE compared to enoxaparin in this patients, but this may be influenced by several factor.

Keyword : Enoxaparin, fondaparinux, NSTEMI, DM.

Introduction

Acute coronary syndrome (ACS) is one of the most important cardiovascular problems because of high rates of hospital care and mortality. Based on WHO data in 2015, ischemic heart disease is the main cause of
death in the worldwide. There are more than 8 million deaths within one year. In Indonesia, the main cause of death was also occupied by this condition in all age groups, which amounted 12.9% based on Sample Registration System (SRS) data in 2014. The prevalence of non-ST elevation myocardial infarction (NSTEMI) when compared with ST elevation myocardial infarction (STEMI) appears to be higher, with characteristics of patients who are usually older and have many comorbidities, one of which is diabetes mellitus.

Diabetes mellitus (DM) is one of the widely known factor that increasing the risk of cardiovascular disease 2 – 4 times greater than non-diabetic patients. Patient with acute myocardial infarction (AMI) with DM have the same mortality risk as someone who has had previous AMI without diabetic. An observations made on unstable angina pectoris (UAP) and NSTEMI patients in OASIS-5 showed an increase in post-infarct complication rates and mortality in patients with DM compared to non-diabetic (OR 1.57) for 2 years follow-up. Previous studies showed a close relationship between ACS and DM, including the number of occurrences of stent thrombosis, revascularization of target lesions, recurrent infarction, and major cardiovascular events.

In diabetes mellitus, insulin resistance causes hyperglycaemia. This hyperglycaemia reduces the synthesis of nitric oxide from the walls of blood vessels, thereby increasing the likelihood of atherosclerosis. Other than that, hyperglycaemia and dyslipidemia also cause haemostasis disturbances. Several studies show that diabetes mellitus causes dysfunction, platelet hyper reactivation, and hypercoagulation status. In DM there is a decrease in anti-thrombin III (AT), protein C and protein S and also an increase in several coagulation factors, such as fibrinogen, factors VII, VIII, XI, and XII. In addition, type 1 plasminogen activation inhibitors (PAI) also increase, reducing fibrinolysis. The combination of these conditions causes hypercoagulation status. This has a role not only in the increased risk of myocardial infarction, but also in the prognosis of patients with diabetic.

There are several choices of anticoagulants that can be given to NSTEMI with different mechanisms and side effects. From OASIS-5 comparing the use of enoxaparin and fondaparinux in NSTEMI patients showed no difference on reduced risk of mortality, infarction or recurrent ischemia in 9 days, but lower bleeding rates on fondaparinux use (HR 0.52, p <0.001).

A recent study assessing the relationship between the use of fondaparinux versus low molecular weight heparin (LMWH) and clinical outcomes in NSTEMI patients, showed that there are differences in major bleeding and mortality during treatment and follow-up up to 180 days between the use of fondaparinux and enoxaparin. However, no studies have attempted to compare the effects of bleeding and major cardiovascular events in the use of enoxaparin and fondaparinux, specifically in patients with NSTEMI with DM. This study aims to assess the effect of anticoagulant in terms of bleeding and major cardiovascular event (MACE) in NSTEMI with DM.

Method

Population and Design

This prospective study included 67 consecutive patients with NSTEMI admitted to Adam Malik General Hospital in Medan, Indonesia from January 2018 until October 2018. The inclusion criteria are NSTEMI patients, according to the guidelines criteria, who diagnosed with diabetes mellitus and complete medical record. Diabetes mellitus was defined as a history of anti-diabetic insulin usage or one of the following criteria: HbA1c level ≥ 6.5%, fasting blood glucose ≥ 126 mg/dl. The exclusion criteria are patients who admitted with cardiogenic shock, eGFR< 20 ml/i, history of chronic kidney disease (CKD) or haemodialysis, and patients who suffered from cardiac arrest. Patients who met the inclusion and exclusion criteria were then recruited as subjects.

All patients received standard medication therapy according to the guidelines for the management of NSTEMI, including antiplatelet and anticoagulant, statins, angiotensinconvertingenzyme inhibitor or angiotensin receptor antagonists, nitrates, and β-blockers. The use of diuretic and vasoactive drugs including dopamine, dobutamine, adrenaline, noradrenaline, was recorded.

The patients were divided into 2 groups according to the use of anticoagulant, enoxaparin and fondaparinux. In-hospital bleeding event and MACE were observed, including all-cause mortality, acute heart failure, life threatening arrhythmias, cardiogenic shock, and stroke.
Statistical Analysis

All statistical analyses were carried out using the SPSS statistical software, version 19.0. The data were presented with mean ± SD or median and interquartile range for continuous variables. Categorical variables presented as percentage. The normality test for continuous variables in all study subjects using one sample Kolmogorov-Smirnov (n > 50). In continuous variables compared with two free samples T test (Two Samples Independent Student's t-test) on normal distributed data or Mann Whitney U Test if the data is not normally distributed. In categorical variables, an analytical test is performed using chi squared or fisher exact tests. The p value < 0.05 was considered as statistically significant.

Result

A total of 67 patients who met the inclusion and exclusion criteria for this study were divided into two groups based on the use of anticoagulant. There were 33 subjects (49.3%) in enoxaparin group and 34 subjects (50.7%) in fondaparinux group.

In this study, 51 subjects (76%) were male with an average age of 55 years. There were no significant differences between the two groups in terms of age, gender, risk factors, hemodynamic parameters, laboratory results, initial ejection fraction, GRACE score, TIMI risk score, and Crusade score. However, there were significant differences in ECG images during the initial presentation between the two groups. In the enoxaparin group there were more subjects with depressed ECG images at initial presentation when compared with the fondaparinux group [88% vs. 64.7%; p value 0.026]. In this study also did not find a significant difference between therapy during in-hospital treatment in both groups (Table 1).

In this study, there is mild bleeding, such as hematuri, in 7 subjects (10.4%) and most commonly found in the enoxaparin group. However, this did not differ significantly [p-value 0.259, RR 2.576 (95% IK : 0.537 – 12.36)] (Table 2). In this study, 26 subjects (38.8%) experienced MACE during treatment. Mortality was found in 2 subjects (6%), 14 subjects (43%) experienced worsening heart failure, 6 subjects (18%) experienced cardiogenic shock, 8 subjects (24%) experienced arrhythmia malignancy, and 3 subjects (9%) had an ischemic stroke (Figure 1).

There were significant differences in MACE between the two groups in this study [p-value 0.035, RR 1.946 (95% IK: 1.015 - 3.73)]. Major cardiovascular events were found to be greater in the enoxaparin group, which was 17 subjects (51.5%), compared to fondaparinux group which was 9 subjects (26%) (Table 3).

| Table 1. Baseline clinical characteristic of subject study |
|-----------------------------------------------------------|
| **Variable**      | **Total Sample n = 67** | **Enoxaparin n = 33** | **Fondaparinux n = 34** | **p-value** |
| Male (%)          | 51 (76)                   | 25 (75.8)              | 26 (76.5)              | 0.945       |
| Age               | 55 ± 9                    | 55 ± 7                 | 54.5 ± 11              | 0.793       |
| Onset (jam)       | 24 (1 – 120)              | 24 (3 – 120)           | 24 (1 – 96)            | 0.664       |
| Hypertension      | 44 (65.7)                 | 22 (66.7)              | 22 (64.7)              | 0.866       |
| Smoker            | 42 (62.7)                 | 20 (60.6)              | 22 (64.7)              | 0.729       |
| Dyslipidaemia     | 19 (28.4)                 | 10 (30)                | 9 (26.5)               | 0.728       |
| Heart rate        | 86 (55 – 150)             | 85 (60 – 150)          | 86 (55 – 140)          | 0.975       |
| Blood pressure    |                           |                       |                       |             |
| Systolic          | 132 ± 23                  | 129 ± 22               | 136 ± 24               | 0.239       |
| Diastolic         | 80 (60 – 110)             | 80 (60 – 110)          | 80 (60 – 110)          | 0.659       |
| ST-segment depression | 51 (76)               | 29 (88)                | 22 (64.7)              | 0.026       |
| TIMI risk         |                           |                       |                       |             |
| Low risk          | 18 (26.9)                 | 9 (27)                 | 9 (26.5)               | 0.941       |
| Moderate – high risk | 49 (73.1)              | 24 (73)                | 25 (73.5)              |             |
| GRACE score       | 101 ± 26                  | 102 ± 27               | 100 ± 25               | 0.876       |
| Crusade score          | Low          | Moderate – high risk |     |  |     |     | 0.462 |
|-----------------------|--------------|---------------------|-----|---|-----|-----|-------|
|                       | 19 (28.4)    | 8 (24)              | 11 (32) | 23 (67) |     |     |       |
| Ejection fraction     | 42 (24 – 68) | 42 (25 – 61)        | 42 (24 – 68) |     |     |     | 0.725 |
| Laboratory results    |              |                     |     |     |     |     |       |
| Haemoglobin (gr/dl)   | 13.5 ± 2.1   | 13.2 ± 1.9          | 13.7 ± 2.2 |     |     |     | 0.289 |
| Leucocyte (10³/mm³)   | 10.2 (1.6 – 30.4) | 9.8 (1.6 – 19.3) | 10.4 (5.7 – 30.4) |     |     |     | 0.059 |
| Thrombocyte (10³/mm³) | 276.2 ± 89.7 | 280 ± 87.7          | 272.5 ± 9.3 |     |     |     | 0.739 |
| eGFR (ml/i)           | 66.6 (20.2 – 110) | 64 (20.4 – 128.8) | 67.1 (20.2 – 163.6) |     |     |     | 0.598 |
| Blood glucose (mg/dl) | 250.6 ± 126  | 231.8 ± 119.5       | 269 ± 131.2 |     |     |     | 0.230 |
| Fasting blood glucose (mg/dl) | 145 (63 – 459) | 142 (63 – 442) | 146 (73 – 459) |     |     |     | 0.229 |
| HbA1C                 | 9 ± 2.2      | 9 ± 2.3             | 9 ± 2.1 |     |     |     | 0.974 |
| Troponin I (µg/dl)    | 0.98 (0 – 32) | 0.88 (0 – 32)       | 1.0 (0 – 17.8) |     |     |     | 1.000 |
| CKMB (U/L)            | 36 (16 – 181) | 35 (16 – 181)       | 37 (17 – 152) |     |     |     | 0.783 |
| Cholesterol total (mg/dl) | 166 (85 – 338) | 166 (98 – 311) | 166 (85 – 338) |     |     |     | 0.960 |
| Triglyceride (mg/dl)  | 132 (44 – 1057) | 130 (44 – 1057) | 142 (50 – 276) |     |     |     | 0.970 |
| HDL (mg/dl)           | 32.5 ± 8.5   | 31.5 ± 8.7          | 33.5 ± 8.4 |     |     |     | 0.346 |
| LDL (mg/dl)           | 110 (53 – 473) | 108 (54 – 473) | 122 (53 – 283) |     |     |     | 0.684 |
| Therapy               |              |                     |     |     |     |     |       |
| Antiplatelet          | 67 (100)     | 33 (100)            | 34 (100) |     |     |     | -     |
| Nitrate               | 64 (95.5)    | 30 (91)             | 34(100) |     |     |     | 0.114 |
| ACE-I/ARB             | 60 (89.6)    | 29 (88)             | 31 (91.2) |     |     |     | 0.709 |
| Betablocker           | 57 (85)      | 30 (90.1)           | 27 (79.4) |     |     |     | 0.187 |
| Statin                | 67 (100)     | 33 (100)            | 34 (100) |     |     |     | -     |
| Diuretic              | 38 (56.7)    | 18 (54.5)           | 20 (58.8) |     |     |     | 0.724 |

Note: *significant if p-value < 0.05. (eGFR, estimated glomerulus filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein).

Table 2. Bleeding event during hospitalisation based on anticoagulant.

| Anticoagulant | Bleeding (+) | Bleeding (-) | Total | RR (95% IK) | p-value |
|--------------|--------------|--------------|-------|-------------|---------|
| Enoxaparin   | 5 (15.2)     | 28 (84.8)    | 33 (100) | 2.576 (0.537 – 12.36) | 0.259* |
| Fondaparinux | 2 (5.9)      | 32 (94.1)    | 34 (100) |             |         |
| Total        | 7 (10.4)     | 60 (89.6)    | 67 (100) |             |         |

*Fisher Exact test
In this study, showed the same mortality rate between enoxaparin and fondaparinux [3% vs. 2.9%, RR 1.030 (95% CI: 0.067 - 15.799), p-value 1,000,]. While the comparison of the incidence of heart failure was more common in enoxaparin group (11 subjects, 33.3%) than fondaparinux group (4 subjects, 66.7%) [RR 2.833 (95% CI: 1.002 - 8.011), p-value 0.034]. Cardiogenic shock and arrhythmias were found to be higher in the enoxaparin group than fondaparinux group, but there were no significant differences (p-value 0.427 and p-value 0.476). While the incidence of stroke during treatment was found to be more in fondaparinux group than enoxaparin group, but is also did not differ significantly (p-value 1,000).

Table 3. MACE during hospitalisation based on anticoagulant.

| Anticoagulant | MACE (+) | MACE (-) | Total | RR (95% CI) | p-value |
|---------------|----------|----------|-------|-------------|---------|
| Enoxaparin    | 17 (51.5)| 16 (48.5)| 33 (100)| 1.946 (1.015 – 3.73)| 0.035* |
| Fondaparinux  | 9 (26)   | 25 (73.5)| 34 (100)|             |         |
| Total         | 26 (38.8)| 41 (61.2)| 67 (100)|             |         |

*Chi-square test

Discussion

In this study, there are 26 subjects (38.8%) experienced MACE during hospitalisation. This was found to be higher when compared with MACE in the NSTEMI population without being distinguished of DM. Previous studies have shown that DM was proven to be a predictor of independent mortality and higher rate of mortality, heart failure, and stroke during treatment inNSTEMI with DM. This shows that in sub-populations with DM showed higher rate of MACE.

Minor bleeding (haematuria) was found in 10.4% of all study samples. There were no significant differences in the incidence of bleeding between the two groups. This is different from previous studies which showed higher enoxaparin bleeding rates compared to fondaparinux during in-hospital care and showed significant differences.

According to Anderson et al. (2010), who assessed the anticoagulant intensity of enoxaparin and fondaparinux in the OASIS-5 study, stated that the anti-Xa peak concentration was lower on fondaparinux. Large variations in the effects of anticoagulants and higher peak concentrations of enoxaparin can also contribute to increasing the risk of bleeding in enoxaparin. In addition, fondaparinux does not have the effect of inhibiting Factor IIa (thrombin) because the molecules that are too short to bind between AT and thrombin are different from enoxaparin which has a long enough structure to bind AT by thrombin and produce anti-FIIa effects.
In this study, the MACE rate was higher in the enoxaparin than fondaparinux group. This is also different from OASIS-5 which showed that fondaparinux has the same effectiveness as enoxaparin in reducing ischemic risk in 9 days (4.5% vs 4.3%, HR 0.97, p-value 0.67). However, in line with the research conducted by Szummer et al. (2015), the incidence of re-infarction, stroke, and mortality was lower in the fondaparinux than enoxaparin (13% vs. 15.2%, OR 0.83). However, both of these studies were conducted in the NSTEMI population with the proportion of sample DM only 25% and 26.4%, so that differences in results could have occurred.

Another study conducted in Brazil with a relatively large proportion of DM samples (46.9%) showed that fondaparinux was better than enoxaparin in reducing mortality, reinfarction, cardiogenic shock, and stroke during treatment (OR 2.93, p value 0.007). Based on previous research, enoxaparin binds non-specifically to plasma proteins, resulting in varying anticoagulant effects. Unlike fondaparinux, which binds specifically to AT to work to inhibit FXa, it provides a more predictable bioavailability, so the effect is also more predictable.

In this study, MACE in enoxaparin group were found to be higher than fondaparinux, which was thought to be influenced by the differences between these two groups. There were more features of ST depression in the enoxaparin group, this certainly affected the GRACE score, so that GRACE scores in the enoxaparin group tended to be higher than fondaparinux, although this did not reach statistical significance. In addition, not all samples in this study were performed with coronary angiography and percutaneous coronary intervention, so that it could affect MACE during treatment.

Previous studies showed that the ECG image with ST depression found at the initial presentation of NSTEMI patients was associated with a higher incidence of 3-vessel disease (three vessel diseases / 3VD) (53.5%) and short-term and long-term outcomes worse. Other studies also showed a much higher 3VD incidence in NSTEMI patients accompanied by DM and had ECG features with ST segment depression than without ST segment depression (80.6% vs 19.4%), and ST depression could also be an independent predictor against 3VD at OR 25.8 (p = <0.001).

Limitation of Study

The limitations of this study include the number of samples of this study is smaller than previous studies and only carried out in one center so that further research needs to be done with a larger number of samples and multicenter. In this study MACE observation was carried out only during hospital treatment.

Conclusion

There are no differences in the in-hospital bleeding between enoxaparin and fondaparinux in NSTEMI with DM. Fondaparinux also showed less MACE compared to enoxaparin in this patients, but this may be influenced by several factor.

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