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Analysis of Bleeding Complications in Acute Coronary Syndrome: Comparison of Effect of Tirofiban in Diabetic and Non-Diabetic Patients

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Abstract

Background: Coronary artery disease (CAD) is the most prevalent manifestation of cardiovascular diseases and is associated with high mortality and morbidity. The clinical presentations of CAD include silent ischemia, stable angina pectoris, unstable angina, myocardial infarction (MI), heart failure, and sudden death.

Objective: This study was designed to define the frequency of hemorrhagic complications and to identify clinical variables associated with increased risk of bleeding complications in diabetic versus non-diabetic patients presented with acute coronary syndrome whom received aspirin, clopidogrel and heparin only or in combination with GPIIb/IIIa receptors blockade (Tirofiban) and to detect any bleeding complications in all patients during the period of admission in the hospital.

Patients and Methods: 150 patients with ACS were divided into two groups, 82 diabetic patients and 68 non-diabetic patients. 40 patients out of total sample received tirofiban. Assessment of in hospital TIMI bleeding, GRACE and CRUSADE risk scores was estimated for all of them.

Results: We observed that, there is no statistically significant difference in TIMI bleeding in both heparin and tirofiban group in diabetic versus non-diabetic patients. Cardiac catheterization access site was the most frequent location of bleeding most likely secondary to the high rate of coronary angiography performed in the study. Tirofiban added to heparin did not increase the risk of bleeding at the vascular access site.

Conclusion: There was no statistically significant increase in all TIMI bleeding, thrombocytopenia or blood transfusions with the combination of tirofiban with heparin in both diabetic and non-diabetic patients.

Keywords: ACS; CAD; GPIIb/IIIa inhibitors; Tirofiban; Bleeding; Diabetes mellitus

Introduction

Acute coronary syndrome (ACS) is the umbrella term for the clinical signs and symptoms of myocardial ischemia: unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Coronary artery disease can lead to ACS, which describes any condition characterized by signs and symptoms of sudden myocardial ischemia. The term ACS was adopted as it believed to reflect more clearly the disease progression associated with myocardial ischemia. Unstable angina and NSTEMI normally result from a partially or intermittently occluded coronary artery, whereas STEMI results from a fully occluded coronary artery.

Atherosclerotic plaque rupture with luminal thrombosis is the most common mechanism responsible for the majority of acute coronary syndromes and sudden coronary death. Despite continuous advances in medical interventional and surgical therapies for the treatment of atherosclerotic coronary disease the latter remains the principal killer in the Western and the developing world [1]. In addition to being a dominant risk factor for the development of coronary disease, diabetes mellitus is associated with early and late mortality after presentation with an ACS [2]. This risk was approximately equal to other major determinants of mortality following ACS. Additional robust evidence is derived by the TIMI group. An analysis of more than 60,000 ACS patients, 10,613 (17%) of whom had diabetes pooled from 11 trials during 1997 to 2006 demonstrated a nearly two-fold increase in the risk of short-term (30 days) and long-term (1-year) mortality associated with diabetes, independent of all other risk factors [3]. Diabetic patients who present with an ACS have an increased risk of future atherothrombotic adverse events, largely attributable to increased platelet reactivity and higher burden of disease severity at baseline. These patients also derive a greater benefit from established therapies, particularly more intensive platelet-inhibiting therapies, including clopidogrel "pretreatment" and GPIIb/IIIa inhibitor use, particularly during PCI. Since platelet aggregation is an important consequence and initiative factor of the formation of thrombus, antiplatelet therapy has of particular importance. Therefore, we discussed the bleeding complications in diabetic and non-diabetic patients with ACS treated by aspirin, clopidogrel and heparin alone or in combination with glycoprotein IIb/IIIa inhibitors (Tirofiban).

Subjects and Methods

The study included 150 patients with ACS; according to clinical presentation, cardiac enzymes, and Electrocardiography (ECG) admitted to Alexandria university hospital and International cardiac center starting from May 2015 till December 2015 divided into two main groups.

Group I

It included 82 diabetic patients (defined as fasting blood glucose ≥ 126 mg/dl or on treatment).

Group II

It included 68 non-diabetic patients.

All patients randomly assigned to one of the treatment groups: 65 diabetic patients received aspirin, clopidogrel and heparin only, 17 diabetic patients received aspirin, clopidogrel, heparin and GPIIb/IIIa (Tirofiban), 45 non diabetic patients received aspirin, clopidogrel and heparin only and 23 non-diabetic patients received aspirin, clopidogrel, heparin and GPIIb/IIIa (Tirofiban).

All patients underwent general, cardiac examination, laboratory tests as (CK-MB, troponin, CBC, Liver function tests, Renal function tests PT, PTT, INR), ECG, Echocardiography, risk stratification using GRACE and CRUSADE risk scores, assessment of in hospital bleeding according to TIMI classification.

Exclusion criteria: Advanced liver diseases, and coagulopathy.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using minimum and maximum, mean, standard deviation and median. Comparison between different groups regarding the categorical variables was tested using Chi-square test. Significance of the obtained results was judged at the 5% level.

Results

This study included 150 patients, 114 males and 36 females. Their mean age was 58.79 ± 11.77 yrs, 57.3% are having hypertension and 54.7% were diabetics.

	Diabetics (n=82)	Non-Diabetics (n=68)	MW	p
GRACE score				
Min.-Max.	65.0-260.0	49.0-162.0	2.483*	0.013*
Mean ± SD.	120.20 ± 31.17	107.54 ± 26.17		
Median	114	104.5		
Death (%)				
Min.-Max.	1.0-90.0	1.0-29.0	2.433*	0.015*
Mean ± SD.	11.60 ± 14.75	7.29 ± 6.86		
Median	6.0	4.5		

Table 1: Comparison between the two studied groups according to GRACE score and death (%).

Table 1 shows comparison between diabetic and non-diabetic patients according to GRACE score and death (%), there is statistically significant difference in both GRACE and in hospital death percentage in both groups.

Table 2 shows comparison between diabetic and non-diabetic patients according to crusade and in hospital major bleeding. There is statistically significant difference in crusade and in hospital major bleeding in both groups.

	Diabetics (n=82)	Non-Diabetics (n=68)	Test of Sig.	p
Crusade				
Min.-Max.	10.0-77.0	2.0-52.0	t =	<0.001*
Mean ± SD.	36.10 ± 13.81	24.35 ± 12.23	5.459*	
Median	36.5	23		
In hospital major bleeding				
Min.-Max.	3.80-26.30	2.70-13.20	MW=	<0.001*
Mean ± SD.	9.04 ± 4.16	5.97 ± 2.46	5.374*	
Median	8.5	5.4		

Table 2: Comparison between the two studied groups according to crusade and in hospital major bleeding.

Table 3 describes the details of TIMI bleeding and blood transfusion in both groups TIMI major bleeding were infrequent in both groups, without statistically significant difference in all TIMI bleeding in both groups.

	Diabetics (n=82)		Non-Diabetics (n=68)		χ^2	p
	No.	%	No.	%		
TIMI bleeding						
No bleeding	68	92.9	54	79.4	1.48	$^{MC}p=0.818$
Major	1	1.2	0	0		
Minor	3	3.7	4	5.9		
Minimal	10	12.2	10	14.7		
Blood transfusion						
No	80	97.6	66	97.1	0.036	$^{FE}p=1$
Yes	2	2.4	2	2.9		

Table 3: Comparison between the two studied groups according to TIMI bleeding and blood transfusion.

Figure 1 shows that there are trends towards more events in minor and minimal TIMI bleeding in both groups.

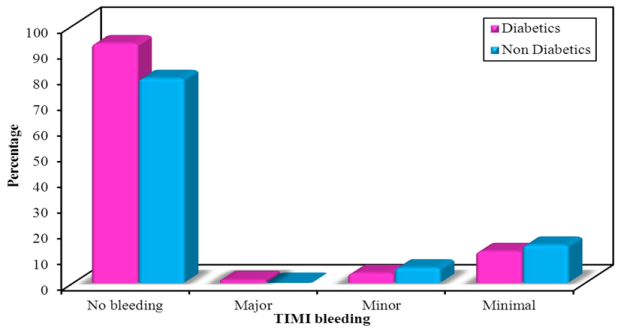

Figure 1: Comparison between the two studied groups according to all TIMI bleeding.

Table 4 and Figure 2 shows that the catheterization site was the commonest site for bleeding in both groups followed by hematuria, GIT bleeding was more frequent in non-diabetic, without statistically significant difference in the site of bleeding in both groups.

	Diabetics (n=82)		Non-Diabetics (n=68)		X^2	p
	No.	%	No.	%		
Catheterization site	7	8.5	7	10.3	0.136	0.713
Hemoptysis	2	2.4	2	2.9	0.036	^{FE}p=1
Hematuria	4	4.9	2	2.9	0.363	^{FE}p=0.69
Gastrointestinal	1	1.2	5	7.4	3.642	^{FE}p=0.092
Unknown	1	1.2	0	0	0.835	^{FE}p=1

Table 4: Locations of all TIMI bleeding in diabetic and non-diabetic patients.

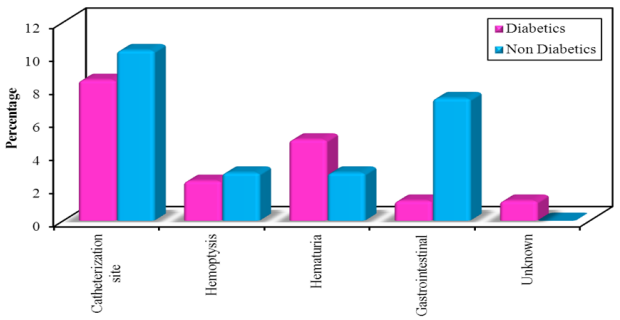

Figure 2: Locations of all TIMI bleeding in diabetic and non-diabetic patients.

Table 5 and Figure 3 describe the details of TIMI bleeding and blood transfusion in heparin alone and Heparin+tirofiban group in total sample. TIMI major bleeding was infrequent in both groups, without statistically significant difference in all TIMI bleeding in both groups.

	Heparin alone (n=110)		Heparin+tirofiban (n=40)		X^2	p
	No.	%	No.	%		
TIMI bleeding						
No bleeding	93	84.5	29	72.5	4.374	^{MC}p=0.19
Major	1	0.9	0	0		
Minor	5	4.5	2	5		
Minimal	11	10	9	22.5		
Blood transfusion						
No	107	97.3	39	97.5	0.006	^{FE}p=1
Yes	3	2.74	1	2.5		

Table 5: Bleeding complication and blood transfusion in heparin alone and Heparin+tirofiban group in total sample.

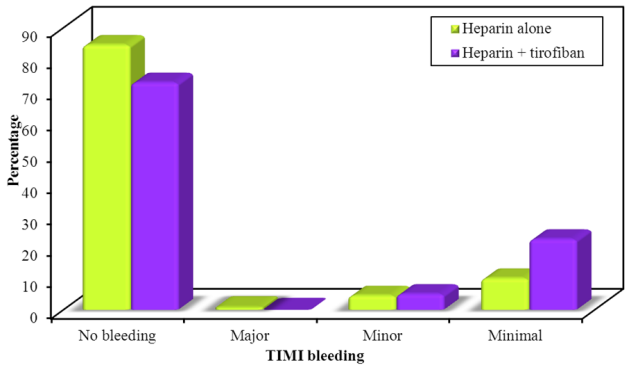

Figure 3: TIMI bleeding in heparin alone and Heparin+tirofiban group in total sample.

Table 6 shows that the catheterization site and GIT bleeding were more frequent in heparin group versus hemoptysis and hematuria in tirofiban group with statistically significant difference in hemoptysis in the tirofiban group (P value 0.005).

	Heparin alone (n=110)		Heparin+tirofiban (n=40)		X^2	FEp
	No.	%	No.	%		
Catheterization site	11	10	3	7.5	0.217	0.761
Hemoptysis	0	0	4	10	11.301*	0.005*
Hematuria	3	2.7	3	7.5	1.74	0.193
Gastrointestinal	4	3.6	2	5	0.142	0.658

Unknown	1	0.9	0	0	0.366	1

Table 6: Locations of all TIMI bleedings in heparin alone and heparin +tirofiban groups.

Table 7 describes the details of TIMI bleeding and blood transfusion in all studied groups. TIMI major bleeding was infrequent in all groups, without statistically significant difference in all TIMI bleeding in all groups. There is only one patients had TIMI major bleeding (in the Heparin arm of the diabetic group).

	Diabetics				**Non-Diabetics**				**χ^2**	**MCp**
	Heparin alone (n=65)		**Heparin+tirofiban (n=17)**		**Heparin alone (n=45)**		**Heparin+tirofiban (n=23)**			
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**		
TIMI bleeding										
No bleeding	57	87.7	11	64.7	36	80	18	78.3	5.055	0.164
Major	1	1.5	0	0	0	0	0	0	2.272	1
Minor	1	1.5	2	11.8	4	8.9	0	0	5.702	0.063
Minimal	6	9.2	4	23.5	5	11.1	5	21.7	4.237	0.219
Blood transfusion										
No	64	98.5	16	94.1	43	95.6	23	100	2.339	0.486
Yes	1	1.5	1	5.9	2	4.4	0	0		

Table 7: Comparison between the all studied groups according to TIMI bleeding and blood transfusion.

Table 8 shows that there are 28 patients (18.66%) out of the total sample had TIMI bleeding and no statistically significant difference in Baseline characteristics of patients with TIMI bleeding

Clinical variables	**TIMI bleeding**				**Test of Sig.**	**p**
	No (n=122)		**Yes (n=28)**			
	No	**%**	**No**	**%**		
Age	58.84 ± 11.32		58.57 ± 13.81		t=0.107	0.915
Weight	85.70 ± 10.09		86.68 ± 8.50		t=0.477	0.634
Gender						
Male	93	76.2	21	75	χ^2=0.019	0.891
Female	29	23.8	7	25		
Smoker						
Non-smoker	72	59	11	39.3	χ^2=3.859	MCp=0.127
Current smoker	46	37.7	16	57.1		
Ex-smoker	4	3.3	1	3.6		
Hypertension						
Normotensive	54	44.3	10	35.7	χ^2=0.680	0.41
Hypertensive	68	55.7	18	64.3		
DM						
No	54	44.3	14	50	χ^2=0.303	0.582
Yes	68	55.7	14	50		
Cr clearance						
<30	2	1.6	1	3.6	χ^2=1.844	MCp=0.402
30-60	22	18	7	25		
>60	98	80.3	20	74.4		
Clinical presentations						
STEMI	56	45.9	14	50	χ^2=0.154	0.695
NSTEMI	54	44.3	14	50	χ^2=0.303	0.582
Unstable A	12	9.8	0	0	χ^2=2.994	FEp=0.124
Prior PCI						
No	105	86.1	23	82.1	χ^2=0.280	FEp=0.564
Yes	17	13.9	5	17.9		
Prior CABG						
No	119	97.5	28	10	χ^2=0.703	FEp=1.000
Yes	3	2.5	0	0		
Prior aspirin						
No	102	83.6	23	82.1	χ^2=0.035	FEp=0.785
Yes	20	16.4	5	17.9		

PCI duration >100min						
No	117	95.9	28	100	1.187	^{FE}p=0.584
Yes	5	4.1	0	0		
PCI						
No	31	25.4	5	17.9	0.712	0.3911
Yes	91	74.6	23	82.1		

Table 8: Baseline characteristics of patients with and without TIMI bleeding in total sample.

Discussion

Thrombus formation caused by unstable coronary plaque rupture, platelet activation, aggregation and adhesion was the pathological basis of acute myocardial infarction (AMI) [4]. After restoration of blood flow of infarct-related artery by PCI, slow blood flow or no-reflow was one of the major complications of emergency PCI. Acute or sub-acute thrombosis was the most serious complications and cardiovascular events (major adverse cardiac events, MACE) in emergency PCI for AMI [5]. The incidence of slow flow or no-reflow and thrombotic event for diabetic patients after emergency PCI was significantly higher than that of general population [6], dual anti-platelet therapy of thromboxane (TXA2) inhibitor (aspirin) and P2Y12 receptor inhibitors was the main therapeutic measures to prevent thrombosis.

However, there were still serious complications due to thrombosis in some patients, IIb/IIIa receptor inhibitors plus dual anti-platelet therapy can effectively reduce the incidence of slow flow or no-reflow, reduce acute and sub-acute thrombosis, reduce AMI complications and the occurrence of MACE [7], but the occurrence probability of the bleeding in the triple combination treatment of anti-platelet drugs significantly increased. How to weigh the risks of thrombotic events and bleeding complications was a serious problem that we must face [8].

In hospital bleeding

All bleeding events and blood transfusion: There was an elevated incidence of bleeding and only 2 patients required blood transfusion on both groups. Neither incidence of bleeding nor blood transfusion was statistically significant. The power to detect a statistically significant difference in these endpoints was limited by the small number of events. Our results are in agreement with Vaduganathan [9], Huynh et al. [10] and Liu et al. [11] as they did not find significant difference in major bleeding events when tirofiban and other glycoprotein IIb/IIIa inhibitors were added to heparin. Cardiac catheterization access site was the most frequent location of bleeding most likely secondary to the high rate of coronary angiography performed in the study. Tirofiban added to heparin did not increase the risk of bleeding at the vascular access site.

Bleeding and gender: In our study, male patients representing (75%) of TIMI bleeding group compared to females (25%). This risk increase was independent of age and body weight, this is matching with Tsung-Hsien et al. [12] as there were 38 males in the TIMI bleeding group (71.7%) out of 53 patients

While in Alexander et al. [13], women experience more bleeding than men in the course of routine care for NSTE ACS. This higher relative risk in women is apparent with or without treatment with GPIIb/IIIa inhibitors. In addition, treatment with appropriately dosed GPIIb/IIIa inhibitors is associated with a greater bleeding risk than no treatment, and excess dosing is associated with further elevation in this risk among women and men alike. This difference may be due to small number of females in our study and more men were hypertensive with more risk of bleeding in Huynh et al. [10] and our study.

Hypertension and bleeding: In our study, 72% and 39.7% had hypertension in both diabetic and non-diabetic group respectively, 18 patients (64.3%) out of 28 patients included in all TIMI bleeding group were hypertensive (put the P value was 0.41), which is similar with Pierre et al. [14]. In the study of Lin and Tsung-Hsien et al. [12], 35 patients had hypertension in TIMI bleeding group (66.04%) with P value <0.01. In Huynh et al. [10], Tsung-Hsien et al. [12] and our study, elevated blood pressure was associated with increased risk of bleeding. The small number of major bleeding events also limits our power to detect statistically significant differences in this measure. The explanation for elevated blood pressure as a risk factor for increased risk of bleeding is not clear, and may be due to fragility of the small vessel beds in patients with prolonged uncontrolled hypertension.

Diabetes and bleeding: In our study, 28 patients (18.66%) have TIMI bleeding out of 150 patients (50%) in both diabetic and non-diabetic group, 14 patients out of 82 diabetic patients (17.07%) and 14 patients out of 68 non-diabetic patients (20.58%) which is in agreement with Tsung-Hsien et al. [12]. In the study of Pierre et al. [14] 12 patients (21.8%) out of 55 patients had DM in TIMI major bleeding.

In our study of diabetic patients, 1.5% had TIMI major bleeding in heparin group, and all TIMI bleeding represented 12.3% and 35.2% in heparin and tirofiban group respectively, while in non-diabetic patients no one had TIMI major bleeding, 20% and 21.7% had all TIMI bleeding in heparin and tirofiban group respectively, this is similar with Kleiman et al. [15] and Pierre et al. [14]. There was a modest though not statistically significant incremental risk of non-major TIMI bleeding with the combination of tirofiban plus heparin.

Conclusion

Finally it may be concluded that there is no statistically significant increase in all TIMI bleeding, thrombocytopenia or blood transfusions with the combination of tirofiban plus heparin in both diabetic and non-diabetic patients. The power to detect a statistically significant difference in these endpoints was limited by the small number of events.

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