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A Comparison of the Clinical Impact of Enoxaparin-induced Bleeding Measured by two Different Classifications among Patient with Acute Coronary Syndrome

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Abstract:

The risk of bleeding events that occur during the course of randomized clinical trials on various anti thrombotic medication is still an important issue. The existing guidelines for classifying bleeding events often presents variable results in the reported incidence of bleeding events within the same clinical trial. We analyzed data from 128 ACS patients treated with Enoxaparin in a randomized clinical trial to compare the association between the different degrees of in-hospital TIMI and GUSTO bleeding. In TIMI bleeding group, no TIMI bleeding, TIMI minimal bleed, TIMI minor bleed and TIMI major bleed were 92.9%, 4.7%, 1.6% and 0.8%, respectively. Patients with a TIMI minor bleed were younger (60.8±1.6 yrs; p 0.001) and those with TIMI major bleed had higher mean weight (61.08±1.25 kg; p 0.001), diabetes mellitus (100%; p 0.001) and hyperlipidemia (100%; p 0.001). In GUSTO bleeding group no bleeding, mild, moderate and severe bleeding was 89.84%, 4.68%, 3.91% and 1.56% respectively. Worsening GUSTO bleeding severity was associated with a gradient of increasing age (p 0.001), mean weight (p 0.002), with hypertension (p 0.001), diabetes mellitus (p 0.001), and hyperlipidemia (p 0.001).

Key words: Acute coronary syndromes (ACS), Thrombolysis In Myocardial Infarction (TIMI), Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)

Introduction:

Coronary heart disease (CHD) is a worldwide health epidemic. In the United States, for example, it is estimated that 13.7 million Americans have CHD, including more than 7.2 million individuals who already have had a myocardial infarction. In the group of persons older than 30 years of age, 213 per 100,000 individuals have CHD[1]. *Acute coronary syndrome* (ACS) is a unifying term representing a common end result, acute myocardial ischemia. Acute ischemia is usually, but not always, caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis, and is associated with an increased risk of cardiac death and myonecrosis. Therapy for the treatment of acute ischemic heart disease includes anti thrombotic medications and the use of early invasive risk stratification[2]. This combination of treatments has improved the outcomes of patients with acute coronary syndromes (ACS); but the risk of bleeding still an important issue[3,4]. Clinical investigators systematically identify bleeding events that occur during the course of randomized clinical trials on various anti thrombotic medications. Among the existing guidelines for classifying bleeding events[5], many clinical trials utilize one of two bleeding classifications: the Thrombolysis In Myocardial Infarction (TIMI) classification, and/or the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) classification. However, there are limited data on the relative merits of either scale at predicting clinical outcomes. Also the existence of these two systems often presents variable results in the reported incidence of bleeding events within the same clinical trial. For example, in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, the rate of TIMI major bleeding among patients treated with the platelet inhibitor, eptifibatide was 3.0%, and that of GUSTO severe bleeding in this same group was 1.1%, and the proportion of patients to have no TIMI bleeding (84.2%) also differs from that of patients to have no GUSTO bleeding

(68.8%)[6]. We analyzed data from two in-hospital randomized clinical trials to compare the association between the different degrees of in-hospital TIMI and GUSTO bleeding and short clinical outcomes.

Methods:

- Place of study: UCC, BSMMU
- Period of study: October 2011 to March 2012
- Study design: Prospective observational study
- Study population: 128
- Inclusion criteria:
- Patients were included in the study after obtaining informed consent. The selection of patients having Acute Coronary Syndrome.
- Exclusion criterias
  Old MI
  Acute LVF
- Sampling technique:

  Purposive type of non-probability sampling
- Sample size: 128
- Data collection & procedure:

Concomitant treatment with aspirin (dose ranges between 80 and 325 mg daily) and enoxaparin, a low molecular weight heparin (LMWH) were recommended by protocol in the trial. The use of other medications and procedures were at the discretion of the treating physicians.

Definition: The TIMI bleeding classification is a laboratory-based scale[7] while the GUSTO bleeding classification is a clinically based scale[8] (Table 1). The TIMI definition of bleeding uses four categories: major, minor, minimal, and none. The GUSTO bleeding definition also uses four categories: severe or life-threatening, moderate, mild, and none.

Data on the date, time, severity, and location (including "unidentifiable") of each in-hospital bleeding event was collected prospectively. Detailed clinical data, including treatments (such as blood transfusion), baseline, and nadir hemoglobin or hematocrit values after each bleeding event, and hemodynamic status during each bleeding event, was collected on all patients in both trials. For patients who will be experienced more than one bleeding episode, only the most severe bleeding episode was considered.

Table-I

Key Elements of the TIMI and GUSTO Bleeding Classifications

TIMI Bleeding Classification

- Major: Intracranial hemorrhage or 5 g/dl decrease in the hemoglobin concentration or 15% absolute decrease in the hematocrit
- Minor: Observed blood loss: 3 g/dl decrease in the hemoglobin concentration or 10% decrease in the hematocrit

  No observed blood loss: 4 g/dl decrease in the hemoglobin concentration or 12% decrease in the hematocrit
- Minimal: Any clinically overt sign of hemorrhage (including imaging) that is associated with a 3 g/dl decrease in the hemoglobin concentration or 9% decrease in the hematocrit

GUSTO Bleeding Classification

- Severe or life-threatening: Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
- Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise
- Mild: Bleeding that does not meet criteria for either severe or moderate bleeding

Statistical analysis. Patients were grouped according to the presence or absence of a bleeding event. Patients who experienced a bleeding event were further classified based on bleeding severity according to the TIMI and GUSTO scales. Categorical variables are expressed as percentages, and continuous variables are expressed as medians and interquartile ranges. Baseline characteristics were compared using chi-square tests for categorical variables and the non-parametric Kruskal-Wallis test for continuous variables.

Baseline differences with p values <0.05 were considered significant.

Results:

A total of 128 ACS patients treated with Enoxaparin in the clinical trial had complete data. Patients were grouped according to the presence or absence of a bleeding event. Patients who experienced a bleeding event were further classified based on bleeding severity according to the TIMI and GUSTO scales.

In TIMI bleeding group, 92.9% patients had no TIMI bleeding, 4.7% of patients experienced a TIMI minimal bleed, 1.6% of patients experienced a TIMI minor bleed, and 0.8% experienced a TIMI major bleed. Baseline characteristics of the patients in TIMI bleeding group are shown in table 1. There were significant differences in baseline characteristics across the TIMI bleeding categories. Patients with a TIMI minor bleed were younger (60.8±1.6 yrs) compared with those having either a TIMI minimal (61.56±3.1yrs) or major bleed (66.24±1.87 yrs) (p 0.001). In contrast, a higher proportion of patients who experienced a TIMI major bleed had higher mean weight (61.08±1.25 kg; p 0.001), diabetes mellitus (100%; p 0.001) and hyperlipidemia (100%; p 0.001).

In GUSTO bleeding group no bleeding, mild, moderate and severe bleeding was 89.84%, 4.68%, 3.91% and 1.56% respectively. Baseline characteristics of patients by GUSTO bleed severity are shown in table 2. Worsening GUSTO bleeding severity was associated with a gradient of increasing age (p 0.001) and mean weight (p 0.002). GUSTO severe bleeding was found in an increasing proportion of patients with hypertension (100%; p 0.001), diabetes mellitus (100%; p 0.001), and hyperlipidemia (100%; p 0.001).

Table-II

Baseline Characteristics of Patients by TIMI Bleeding Severity (Numbers Shown Are Percentages)

Characteristics	No Bleeding (n =119)	TIMI Minimal Bleeding (n=6)	TIMI Minor Bleeding (n=2)	TIMI Major Bleeding (n=1)	p Value
Demographic					
Mean age, yrs ±(SD)	58.18±7.74	61.56±3.12	60.8±1.64	66.24±1.87	0.001
Female patients	31	-	-		
Mean weight, kg	55.83±5.73	56.14±2.73	57±2.94	-61.08±1.25	0.001
Medical history					
Diabetes mellitus	42 (35.59)	4 (66.66)	2 (100)	1 (100)	0.003
Hypertension	68 (57.62)	1 (83.33)	2 (100)	1 (100)	0.45
Hyperlipidemia	117 (99.15)	1 (83.33)	(0)	(0)	0.001
Chronic renal insufficiency	13 (11.01)				
Prior MI	17 (14.4)				
Prior stroke	3 (2.57)				
Prior PCI	5 (4.23)				
Prior CABG	2 (1.69)				
Prior CHF	3 (2.54)				
In-hospital procedures					
Cardiac catheterization	6 (5.04)	-	-	-	
PCI	2 (1.69)				

CHF = congestive heart failure; GUSTO = Global Strategies for Opening Occluded Coronary Arteries; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Table-III

Baseline Characteristics of Patients by GUSTO Bleeding Severity (Numbers Shown Are Percentages)

Characteristics	No Bleeding (n =115)	GUSTO Mild Bleeding (n=6)	GUSTO Moderate Bleeding (n=5)	GUSTO Severe Bleeding (n=2)	p Value
Demographic					
Mean age, yrs	57.88±7.34	60.46±2.52	62.8±1.94	63.54±2.87	0.001
Female patients	31	-	-	-	
Mean weight, kg	55.27±5.24	58.17±2.83	59±3.94	60.08±2.25	0.0002
Medical history					
Diabetes mellitus	41 (35.65)	1 (16.66)	3 (50)	2 (100)	0.001
Hypertension		2 (33.33)	2 (40)	2 (100)	0.001
Hyperlipidemia	65 (56.52)	2 (33.33)	3 (50)	2 (100)	0.001
Chronic renal insufficiency	112 (97.39)				
Prior MI	13 (11.30)				
Prior stroke	17 (14.78)				
Prior PCI	3 (2.60)				
Prior CABG	5 (4.34)				
Prior CHF	2 (1.74)				
	3 (2.60)				
In-hospital procedures					
Cardiac catheterization	6 (5.04)				
PCI	2 (1.69)				

CHF = congestive heart failure; GUSTO = Global Strategies for Opening Occluded Coronary Arteries; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Discussion:

This study showed that increasing mean age, higher mean weight, hypertension, diabetes mellitus, and hyperlipidemia were associated with increasing bleeding risk in GUSTO score. In case of TIMI score young age is associated with minor bleeding risk, but higher mean weight, diabetes mellitus and hyperlipidemia were associated with increasing bleeding risk. Sunil et al[9] in a large study (n= 15454) found similar association baseline characteristics with increasing bleeding risk in GUSTO score. However, older age in TIMI minor bleeding, and significant association of hypertension but no association of hyperlipidemia with major TIMI bleeding in their study differ with our study.

Thus, our study has shown that both the GUSTO and TIMI bleeding scales identify patients at increased risk for adverse clinical events and has important implications for both clinical care and clinical research. Our results add to other previous studies by demonstrating that that bleeding complications, regardless of severity, are associated with worse clinical outcomes among patients with acute ischemic heart disease in whom thrombolytic therapy is not used.

Finally, including both bleeding deûnitions in the same mode, GUSTO bleeding was associated with a worse prognosis and that TIMI bleeding did not affect the risk among patients who also met criteria for GUSTO bleeding. In terms of adverse outcomes, assessment of bleeding using clinical criteria is more important than using laboratory criteria[9].

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