Case Report

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Prediction of risk of major bleeding with using CRUSADE bleeding score in Acute coronary syndrome patients: A case series

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Abstract

Use of intravenous heparin in Acute coronary syndrome possess a major risk of bleeding to patients. However, the estimation of risk using bleeding scores in Indian settings is yet to be established. These case series assess the risk of major bleeding associated with the use of Antithrombotic agents in patients with acute coronary syndrome using CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score. Relevant patient data was collected from hospital records and patients were followed up till discharge. All the four cases reported showed the risk of in-hospital bleeding with antithrombotic agents evident as two cases of hematuria, one case of gum bleeding and one case of hemorrhagic stools. All the patient presented with chest pain to the hospital; following a diagnosis of the acute coronary syndrome, they were prescribed with antiplatelets and anticoagulants. This accompanied a bleeding event which was categorized using CRUSADE bleeding risk score. In-hospital major bleeding imposes a burden on the patient's quality of life. Use of CRUSADE bleeding score helps to predict the severity of risk in a less expensive, non-invasive manner. Further, large scale studies will pave the way for using CRUSADE as an efficient bleeding predictor score.

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INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death in India and accounted for approximately 21% of deaths in the year 2010, with 10% of all deaths occurring due to acute coronary syndrome (ACS) (Prabhakaran *et al.*, 2016). Hemorrhagic manifestations are the most common adverse drug reactions associated with antithrombotic agents employed in the management of ACS. According to a 2014 study, patients on ACS management were at risk of major bleeding of 7.2 events per 100 person-years and the risk of fatal bleeding is 1.31 per 100 person-years (Qiu and Grine, 2017). There are no Antithrombotic or Antiplatelet agents that decrease ischemic risk without simultaneously increasing the risk of bleeding. Therefore, minimizing bleeding complications is an important objective in the management of patients with ACS as it also decreases expenditure attributed to major bleeding.

The decision to administer an anticoagulant or antiplatelet drug must be based on the assessment of the risk of thrombosis and its complications with a greater clinical concern of the risk of bleeding in specific patients. Concordant to this, bleeding risk scoring systems have been developed to

identify the predictors of bleeding. Quantitative assessment by these stratification systems of the risk of major bleeding has been found to be precise and reliable as an early prediction of bleeding events may reduce unintended adverse reactions by appropriate modification of ongoing therapy. Out of all the available bleeding risk scores, we have inferred that the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines)bleeding risk score is the most accurate, robust, and well-calibrated risk-stratification tool for predicting hemorrhagic complications when compared to all other existing bleeding risk scores (Flores-Ríos *et al.*, 2013).

We report four cases of ACS treatment-induced hematuria, gingival bleeding and hemorrhagic stools in patients who presented to the casualty with a chief complaint of chest pain to be evaluated, and whose bleeding risk was predicted using the CRUSADE bleeding score.

MATERIALS AND METHODS

Approval was sought from the institutional review board, Government District Headquarters Hospital, Ooty, Tamilnadu, India before the commencement of the study. All three patients who developed bleeding manifestations were monitored from admission to discharge, and their informed consent was obtained. Data collection included patient demographics, relevant medical history, laboratory investigations and hemorrhagic complications.

RESULTS AND DISCUSSION

Case 1

A 70-year-old female with a past medical history significant for hypertension and Coronary Artery Disease (CAD) for 3 years had presented to the casualty for the evaluation of her complaints of chest pain radiating to her left arm with palpitations that had begun 5 days ago. She denied nausea, vomiting, or any complaints of difficulty in breathing. The patient has been a homemaker, while her family history had no relevance to her presenting condition.

On examination, the patient was afebrile with otherwise normal vital signs but an increased heart rate of 120 beats per minute. The patient's laboratory investigation of a complete blood count was remarkable for a high WBC count of 11.3 x 10^3 cells/mm^3 with 75% of polymorphs, 20% of lymphocytes and 5% of monocytes. Alongside, the patient's ECG revealed sinus tachycardia and henceforth a diagnosis of Coronary artery disease with unstable angina, and suspected Anterior Wall Myocardial Infarction (old AWMI) was made. The patient was administered 5000IU of Inj. Heparin QID, Inj. Ranitidine 2cc (50mg) BD, Tab. Aspirin 150mg OD, Tab. Clopidogrel 75mg OD, Inj. Furosemide 20mg BD, Tab. Spironolactone 25mg OD, Tab. Atorvastatin 10mg 2 HS and Tab. Atenolol 50mg OD on the 1^{st} day of admission.

However, her ECG on the 2^{nd} day indicated a complete left bundle branch block (LBBB) with irregular R-R interval, which modified the previous diagnosis to include Atrial Fibrillation with Coronary Vasodilator Reserve. Thus, Tab. Digoxin 0.25mg OD was added and Tab. Atenolol was replaced with Tab. Metoprolol 50mg OD. The patient's CRUSADE bleeding score was calculated and found to be 49 and In-hospital risk of bleeding was found to be 12.1% which showed a high risk of bleeding The same treatment continued until the 4^{th} day of hospitalization, where the patient's ECHO denoted severe left ventricular (LV) dysfunction with an ejection fraction of 27% while the patient's BP was elevated to 160/90mm Hg and thus Tab Metoprolol was replaced with Tab. Carvedilol 3.125mg OD. On the same evening, the patient complained of hematuria, and severe constipation, and so was prescribed with Tab. Lactulose 5mg 2 HS and Liquid Paraffin 10ml HS with no other changes in therapy. The patient was monitored periodically and discharged two days later on Tab. Aspirin 150mg OD, Tab. Clopidogrel 75mg OD, Tab. Furosemide 40mg OD, Tab. Spironolactone 25mg OD, Tab. Atorvastatin 10mg 2 HS, and Tab. Carvedilol 3.125mg OD.

Case 2

A 57-year-old male with a past medical history significant of hypertension and uncontrolled diabetes mellitus since past 4 years on irregular medication, had presented to the casualty for the evaluation of his complaints of chest pain that had commenced 3 days ago. The patient had noted profuse sweating and pain radiating to the back but denied any vomiting or dyspnea complaints.

On examination, the patient was afebrile and had normal vital signs but appeared uncomfortable. Also, the patient's laboratory investigation indicated a high WBC count of 15.3 x 10^3 cells/mm^3 with 83% of polymorphs, 41% of lymphocytes and 6% of monocytes. Elevation of liver enzymes specified as SGOT – 208 U/L, SGPT- 45 U/L and ALP - 56 U/L was also observed and his serum creatinine was 1.5mg/dL. Further, the patient's urinalysis was remarkable for 3-4 pus cells,3-5 epithelial pus cells and the presence of sugar. The patient's high

Table 1: Categorization of Bleeding risk using CRUSADE score (Continued as Table 2)

Gender (M/F)	Age (Years)	Weight (Kg)	Sr. Cr (mg/dL)	Baseline HCT (%)	HR (Bpm)	SBP (mmHg)	GFR (mL/min)
F	61	58	0.7	37.5	88	140	77
M	55	76	1.5	44	74	130	60
F	70	89	1.2	37.4	112	150	61
F	64	74	1.9	35.9	82	170	36

F-Female, M-Male, Sr. Cr -Serum Creatinine, HCT-Hematocrit, SBP-Systolic Blood Pressure, PVD-Prior Vascular Disease, DM-Diabetes Mellitus, CBS-Crusade Bleeding Score

Table 2: Categorization of Bleeding risk using CRUSADE score

PVD (Yes/No)	DM (Yes/No)	Signs of CHF at the time of admission	CBS	Risk of In-hospital bleeding (%)	Category
Yes	No	Yes	44	10.4	High Risk
Yes	Yes	Yes	49	12.1	High Risk
Yes	Yes	Yes	57	15.3	Very High Risk
Yes	Yes	Yes	54	14	Very High Risk

F-Female, M-Male, Sr. Cr -Serum Creatinine, HCT-Hematocrit, SBP-Systolic Blood Pressure, PVD-Prior Vascular Disease, DM-Diabetes Mellitus, CBS-Crusade Bleeding Score

blood sugar levels indicated by an RBS level of 332 mg/dL was also recorded. The patient's CRUSADE bleeding score was found to be 54, and In-hospital risk of bleeding was found to be 14% which signified a high risk of bleeding. As also, the patient's abnormal ECG suggested an Anteroseptal Myocardial Infarction (ASMI). A diagnosis of ACS with ASMI with underlying hypertension and diabetes mellitus was made, and so, the patient was immediately thrombolysed with Inj. Streptokinase at a dose of 1, 50,000 IU over 60 mins. The patient was also administered with 5000IU of Inj. Heparin QID, Tab. Aspirin 150mg OD, Tab. Clopidogrel 75mg OD, Inj. Ranitidine 2cc (50mg), Tab. Atorvastatin 80mg OD, and Tab. ISDN 10mg OD on the 1^{st} day of admission. Alongside, the patient was administered subcutaneous insulin and maintained on a diabetic diet.

Although the patient's chest pain decreased on the second day, he complained of mild hematuria. However, no changes in therapy were made with regard to this. On the 3^{rd} day, Tab. Enalapril 2.5 mg BD and Tab. Metoprolol 25mg OD were added. The patient also complained of inability to sleep and thus, Tab. Diazepam 5mg 2 HS was prescribed. There were no fresh complaints or changes in treatment from days 4-7. On the 7^{th} day, the patient was discharged on the resolution of all complaints with Tab. Amlodipine 2.5mg BD, Tab. Metformin 500mg BD, Tab. Glibenclamide 5mg BD, Tab. Aspirin 150mg OD, Tab. Clopidogrel 75mg OD, Tab. Vitamin B complex, 30.5 mg OD.

Case 3

A 61-year-old female with a past medical history of systemic hypertension and old Anterior Wall MI since the past 4 years on regular medication, had presented to the casualty for the evaluation of her complaints of chest pain that had started 3 days ago. The patient had pain radiating to the back but denied any vomiting or dyspnea complaints.

On examination, the patient was afebrile and had normal vital signs but appeared uncomfortable. Patient's urinalysis revealed 5-6 pus cells and 2-3 epithelial pus cells. The patient's CRUSADE bleeding score was found to be 44, and In-hospital risk of bleeding was found to be 10.4% which showed a high risk of bleeding. ECG suggested an old Anteroseptal Myocardial Infarction (ASMI). A diagnosis of coronary artery disease with hypertension was made, and so, the patient was administered with 5000IU of Inj. Heparin QID, Tab. Aspirin 75mg OD, Tab. Clopidogrel 75mg OD, Tab. Ranitidine 150mg BD, Tab. Atorvastatin 20mg OD, and Tab. ISDN 5 mg TDS, Tab. Enalapril 2.5mg BD, Tab. Metoprolol 25mg OD, T. Diazepam 10mg OD on the 1^{st} day of admission. Alongside, the patient complained of constipation for which Tab. Bisacodyl 10mg OD was added.

Although the patient's complaint of chest pain decreased on the second day, he complained of gum

bleeding. However, no changes in therapy were made with regard to this. On the 3^{rd} day Inj. Heparin was stopped due to gum bleeding on the 5^{th}-day inj. Heparin was reintroduced which resumed the gum bleeding in the patient. On the same day, the patient was discharged at request.

Case 4

A 57-year-old male with a past medical history significant for hypertension for 18 years had presented to the casualty for the evaluation of his complaints of chest pain radiating to the left side that had begun one week ago. He denied vomiting or any complaints of difficulty in breathing.

On examination, the patient had normal vital signs. The patient's laboratory investigation of a complete blood count, renal and liver function tests and urinalysis was only profound for a high WBC count of 12.6 x 10^3 cells/mm^3 with 70% of polymorphs, 22% of lymphocytes, 8% of monocytes and his serum creatinine was 1.5mg/dL. The patient's CRUSADE bleeding score was found to be 41, and In-hospital risk of bleeding was found to be 9.5% which showed a high risk of bleeding. Alongside, the patient's ECG was normal, and henceforth a diagnosis of CAD with unstable angina was made, and the patient was administered T. Ranitidine 150mg BD, Tab. Aspirin 150mg OD, Tab. Clopidogrel 75mg OD, T. Atorvastatin 10mg 2 HS, and Tab. Atenolol 50mg OD and Inj. Labetalol 20mg iv bolus over 8min on the 1^{st} day of admission.

On the 2^{nd} day, patients' vitals were normal, but the heart rate was decreased. Thus, beta-blockers were stopped and Tab. Losartan 50mg OD and Inj. Heparin 5000IU iv QID was added to the therapy. The same treatment continued until the 5^{th} day of hospitalization. On the 6^{th} day, the patient was started with T. ISDN 5mg OD as he had complaints of chest discomfort, the same day patient complained of hemorrhagic stool, but no changes in therapy was made. The patient was monitored and discharged the next day with Tab. Aspirin 150mg OD, Tab. Clopidogrel 75mg OD, Tab. Atorvastatin 10mg 2 HS, and Tab. Losartan 50mg OD, T. Ranitidine 150mg BD, T. ISDN 5mg OD and was asked to come for review after 15days.

The above-reviewed cases presented with complaints of chest pain for further evaluation and were all administered with Inj. Heparin and a long-term course of aspirin and clopidogrel. Currently, dual antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitors (e.g. clopidogrel) along with anticoagulants is recommended in international and local guidelines as first-line therapy for up to 1 year following ACS (Ibanez *et al.*, 2018; Li *et al.*, 2012).

With the greater use of antithrombotic medications and early revascularization, bleeding has become an increasingly important problem. Not only does bleeding result in an immediate threat, but it is also associated with increased coronary artery disease mortality and reinfarction, both in the short and long term (Li *et al.*, 2018).

The reported incidence of bleeding in studies of patients with ACS varies widely. It is largely determined by the study design (randomized trial or community registry), the definition of bleeding severity, patient factors that include demographics (age and sex), comorbidities (diabetes, hypertension, renal and hepatic impairment, and hemostatic disorders), as well as treatment factors that include concomitant therapy (antiplatelet, anticoagulant and fibrinolytic medication), invasive procedures (percutaneous coronary intervention [PCI] and coronary artery bypass graft), and the timing of the drug administration related to procedures and surgery. Older patients and women, as well as patients with anemia, renal dysfunction, high-risk ACS, diabetes, hypertension and those undergoing invasive procedures, are at especially high risk for bleeding. Major bleeding is associated with a 60% increased risk of in-hospital death, and a fivefold increase in one-year mortality and re-infarction (Li *et al.*, 2018).

The most common adverse drug reactions associated with these agents is bleeding, which commonly occurs in the GI tract, nose, urinary tract, subcutaneous/dermal tissue or at puncture or surgical sites. Compared to placebo, aspirin as monotherapy itself is associated with a higher risk of bleeding, which commonly occurs in the GI tract (Fitchett, 2007).

To our knowledge, we are the first to employ the CRUSADE bleeding score and assess its validity in the Indian population. According to the CRUSADE score criteria, patients falling in the Very High-Risk Category have scores $\geq$50, the average score in our patients was also found to be 51 as evident from Table 1, thus validating the accuracy and precision of the prediction of bleeding risk in patients on ACS treatment. Risk stratification systems are the easiest to use, cost-effective and non-invasive method for successful prediction of bleeding events in patients. Optimization of treatment inclusive of antiplatelet agents and anticoagulants based on scores thus obtained ensure safe and efficacious therapy, especially in chronic cases and are therefore encouraged.

CONCLUSION

Although the CRUSADE bleeding risk score was developed in an American hospital setting, we found

good validity of the CRUSADE bleeding score within the four patients in a secondary care hospital in India thus conclude that it is a reliable and accurate predictor of bleeding events. There is a need for stronger evidence to support the use of risk stratification systems. Thus, we further recommend the frequent use of the CRUSADE bleeding risk score in clinical settings and stress the need for studies in a larger population for a longer duration, especially within India.

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