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Eptifibatide Induced Thrombocytopenia in Acute Coronary Syndrome: A Real-World Data

Zubair Shahid[1], Ahmed Mahfouz[2], Ashraf Ahmed[3], Alaa Rahhal[4], Dina Soliman[5], Mariam Imran[6], Elmustafa Abdalla[7], Unus Bedardeen[8], Mohammed Elmurtada[9], Firyal Ibrahim[10], Mohamed Yassin[11], Shehab Fareed Mohamed[12]

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Corresponding Author(s):

Ashraf Ahmed
Department of Internal Medicine, Yale University, Bridgeport Hospital, CT, USA Email: Ashrafo2017@homtial.com

Abstract: Background: Eptifibatide is a known antiplatelet that is used in patients undergoing percutaneous coronary intervention for ACS, and it is proven to have a positive outcome. Despite thrombocytopenia not being reported in the pivotal trials, the emerging literature associated this link. We aim to further investigate this association and provide real-world data from a single centre. Methods: A retrospective study was conducted in Heart Hospital at Hamad Medical Corporation from 2016 to 2022. All patients admitted with ACS and received Eptifibatide were included in the study. Patients with confirmed secondary causes of thrombocytopenia were excluded. The data is reported in the form of mean, median, standard deviation, interquartile range, and percentage. Results: Twenty-six patients met the inclusion criteria, with an average age of 54 ± 11 years, and all patients were males. The baseline platelets count was 157 ± 80, and haemoglobin was 14 ± 2. Fourteen patients had platelets drop by more than 50% of their baseline. Thrombocytopenia developed after eptifibatide infusion by 36 ± 29. The average haemoglobin post-eptifibatide infusion was 13.5 ± 1.7 g/dL. Three patients required platelet transfusion, 23 patients were managed conservatively, and one patient died. Conclusion: Eptifibatide can cause life-threatening thrombocytopenia, which can be simply reversed by ceasing the infusion. However, platelet transfusion might be necessary in some patients. Neither the mechanism nor the risk factors are clear, and further studies are recommended to understand this association better.

Keywords: Eptifibatide, glycoprotein IIb/IIIa receptor inhibitor, Acute coronary syndrome, Thrombocytopenia

1. Introduction

Eptifibatide (Integrilin) is a glycoprotein IIb/IIIa (GP IIb/IIIa) receptor inhibitor that prevents platelet activation. It is approved by the Food and Drug Administration (FDA) for the treatment of acute coronary syndrome (ACS) and for patients undergoing percutaneous coronary intervention (PCI), as it has been shown to be safe and to improve composite outcomes of death and myocardial infarction while maintaining a favourable safety profile. Like other antiplatelet agents, eptifibatide increases the risk of bleeding through its mechanism of action; however, secondary thrombocytopenia was not initially reported during the early introduction of the drug or in pivotal clinical trials. A few reports in the emerging literature have since investigated the association between eptifibatide and the development of thrombocytopenia, including profound and life-threatening thrombocytopenia. Nevertheless, the true incidence of this adverse event remains unknown.

There is limited data exploring the association between eptifibatide use and thrombocytopenia, and the literature is scarce regarding the management of such patients, which poses challenges in clinical practice. In this retrospective study, we aim to describe the general characteristics, demographics, management, and outcomes of eptifibatide-induced thrombocytopenia from nationwide data experience.

2. Methodology

After obtaining approval from the institutional review board (MRC-01-22-778), we retrospectively analysed the database from the Heart Hospital at Hamad Medical Corporation (HMC) in Qatar over five years, from 2016 to 2022. We screened all patients admitted with acute coronary syndrome (ACS) to the institution during this period. Our study included patients who received eptifibatide infusion and subsequently developed thrombocytopenia. Thrombocytopenia was defined as a platelet count of ≤ 100 ×10⁹/L. For classification purposes, mild thrombocytopenia was defined as a

[1,8] Department of Cardiology, Heart Hospital, Hamad Medical Corporation, Doha, Qatar.
[2, 4] Pharmacy Department, Hamad Medical Corporation, Doha, Qatar
[3] Department of Internal Medicine, Yale University, Bridgeport Hospital, CT, USA
[5,7] Laboratory Department Hematopathology, Hamad Medical Corporation, Doha, Qatar
[6] Department of Internal Medicine, Hamad Medical Corporation, Doha, Qatar
[9, 10,11,12] Department of Haematology, NCCCR, Hamad Medical Corporation, Doha, Qatar

platelet count of ≤ 100-50 ×10⁹/L, severe thrombocytopenia as 50-20 ×10⁹/L, and profound thrombocytopenia as < 20 ×10⁹/L. Eptifibatide-induced thrombocytopenia was diagnosed by exclusion after all other possible aetiologies were ruled out.

2.1. Inclusion and exclusion criteria

We included all patients admitted with ACS who were managed with eptifibatide and subsequently developed thrombocytopenia as described above. All patients received a loading dose of Aspirin (100%) and either Clopidogrel (96.2%) or Ticagrelor (3.8%) at the door. The decision to start eptifibatide was made by the interventionalist in the catheterization laboratory. Patients with an identified secondary cause of thrombocytopenia were excluded after a thorough investigation. Secondary causes such as heparin-induced thrombocytopenia, immune thrombocytopenia, sepsis, disseminated intravascular coagulopathy, chronic liver disease, or end-stage renal disease were excluded. The exclusion of the secondary causes was confirmed by the unremarkable investigations, and eptifibatide-induced thrombocytopenia was the diagnosis of exclusion.

3. Results

3.2. Baseline characteristics

Twenty-six patients met the inclusion criteria (Table 1), and all the patients in the included cohort are of non-high bleeding risk based on the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria at baseline. None of the patients were over 75 years old, and there was no history of bleeding, haemorrhagic stroke, chronic kidney disease, long long-term anticoagulation use.

All patients were males and predominantly of East Asian origin, with an average age of 54 ± 11 years. Comorbidities included hypertension (42.3%), diabetes (34.6%), and dyslipidaemia (11.5%). The baseline platelet count was 157 ± 80 ×10^9/L and the hemoglobin level was 14 ± 2 g/dl. The admitting diagnoses were ST-elevation myocardial infarction (STEMI) 76.9% non-ST-elevation myocardial infarction (NSTEMI) 15.4%, and unstable angina (UA) 7.7% (Table I).

Table 1: Baseline characteristics (N=26)

Characteristic	N (%)
Male gender	26 (100)
Age	54 ± 11
Region of origin	
Asia	16 (61.5)
Middle East	9 (34.6)
Europe	1 (3.8)
Smoking history	
Smoker	8 (30.8)
Ex-smoker	5 (19.2)
Medical history	
Coronary artery disease	6 (23.1)
Hypertension	11 (42.3)
Type II diabetes	9 (34.6)
Dyslipidemia	3 (11.5)
Cerebral vascular accident / ischemic stroke	0
Peripheral vascular disease	0
Chronic kidney disease	0
Left ventricular thrombus	2 (7.7)
Admitting diagnosis	
STEMI	20 (76.9)
NSTEMI	4 (15.4)
UA	2 (7.7)
Coronary angiography findings	
Single vessel disease	11 (42.3)
Two vessel disease	8 (30.8)
Three vessel disease	7 (26.9)
Thrombotic lesion	9 (34.6)
Plaque	16 (61.5)
Stent thrombosis	2 (7.7)
Number of stents	
0	5 (19.2)
1	17 (65.4)
2	4 (15.4)
Complex PCI	
Yes	6 (23.1)

CTO lesion	1 (3.8)
Angiography access	
Radial	25 (96.2)
Femoral	1 (3.8)
Antiplatelet therapy	
Aspirin	26 (100)
Clopidogrel	25 (96.2)
Ticagrelor	1 (3.8)
Baseline platelet count	157 ± 80 $\times 10^9$/L
Baseline Hb	14 ± 2 g/dL
Length of hospital stay (days)*	6 [5]
Eptifibatide infusion duration (hours)	22 ± 13

*Reported as median [interquartile range] as the parameter is not normally distributed; **STEMI:** ST-elevation myocardial infarction; **NSTEMI:** non-ST elevation myocardial infarction; **UA:** unstable angina

3.2. Outcomes

Following the administration of eptifibatide, platelet counts dropped by more than 50% in over half of the subjects (53.8%). The nadir platelets count was 59 ± 27 $\times 10^9$/L at an average time of 36 ± 29 hours. The average haemoglobin level post-eptifibatide infusion was 13.5 ± 1.7 g/dL. Most patients (90%) were managed conservatively by ceasing the infusion alone. However, three patients received platelets transfusion despite the absence of bleeding. No cardiac adverse events were reported except for one case of ventricular fibrillation, and cardiac arrest resulted in death due to cardiac causes (Table 2).

Table 2: Outcomes of eptifibatide use among patients who developed thrombocytopenia (N=26)

Outcome	N (%)
Nadir platelet count ($\times 10^9$/L) *	59 ± 27
Time to nadir count after eptifibatide initiation (hours)*	36 ± 29
Drop in platelet count by 50% from baseline	14 (53.8)
Hb within 24 hours of eptifibatide initiation (g/dL) *	13.5 ± 1.7
Eptifibatide discontinuation	6 (23.1)
platelets transfusion	3 (11.5)
IVIG or corticosteroids use	0
In-Hospital mortality**	1 (3.8)

*Reported as mean ± standard deviation; **Death due to pulseless activity arrest followed by brain death

4. Discussion

Eptifibatide was approved by the FDA based on three large randomized trials: ESPIRIT, IMPACT-II, and PURSUIT. The PURSUIT trial showed benefits in patients with ACS, while both IMPACT-II and ESPIRIT demonstrated benefits in patients undergoing percutaneous coronary intervention (PCI) (3) (4) (6). Collectively, these trials included a total population of 17,022 patients, showed that eptifibatide improved cardiovascular outcomes (12) (13) (14) (15). However, none of these major trials found a significant association between eptifibatide and the development of thrombocytopenia.

The emerging literature has linked and associated eptifibatide to cause thrombocytopenia with a risk of 0.1 - 1% (16) (17) (18) (19) (20). Case reports described eptifibatide-associated thrombocytopenia in both ACS and coronary artery bypass grafting (21) (22) (23). On the other hand, different Glycoprotein IIb/IIIa inhibitors such as Abciximab have been reported to cause thrombocytopenia with an initial event rate of less than 0.7%, increasing to 4.6% upon re-exposure (24). Among this class of drugs, Abciximab is the most prevalent medication to be associated with thrombocytopenia compared to eptifibatide and tirofiban (25) (26) (27).

The mechanism of eptifibatide-induced thrombocytopenia is poorly understood. One hypothesis involves antibody-dependent pathways, where thrombocytopenia occurs upon re-exposure to eptifibatide (28) (29) (30). Therefore, it is recognized as a drug-induced immune thrombocytopenia or more specifically eptifibatide-induced thrombocytopenia (EITA). Although the true incidence and the pathophysiology of these associations remain unclear, the development of these events can be life-threatening (28) (30).

Our analysis of the 26 patients included in the study revealed a male gender predominance of 100%. We noted the male gender predominance in the literature as well, as nine out of ten cases reported in the literature were male (31) (32) (33) (34) (35) (36) (37) (38) (39) (11). Moreover, all the subjects had normal haemoglobin levels and maintained normal levels despite the significant thrombocytopenia induced by eptifibatide. The average platelets dropped from 157 ± 80 to 59 ± 27 $\times 10^9$/L with an average of 36 ± 29 hours after the infusion initiation. Three patients required platelet transfusion, however, no patient received IVIG or steroid. In-hospital mortality accounted for 3.8% as one patient passed away due to cardiac reasons. Notably, no significant bleeding events were reported.

From a practical standpoint, our study provides valuable insights for interventionalists emphasizing the need to be cautious when considering starting eptifibatide in patients with high bleeding risk patients. We recommend

close blood count monitoring in the first 48 to 72 hours, particularly in cases where femoral access was sought given its known bleeding diathesis in comparison to radial access.

5. Limitation

Although the retrospective design is appropriate to answer the study question, the small size poses a significant limitation for this study. Moreover, the male gender predominance impacts the generalizability of the findings. Furthermore, the cohort included in this study consisted of non-high bleeding risk based on the ACR-HBR criteria. Thus, the findings should be interpreted with caution, particularly when applied to patients with high bleeding risk.

6. Conclusion

Eptifibatide-induced thrombocytopenia is uncommon, however, it can lead to life-threatening consequences. In patients with low bleeding risk, the course of the thrombocytopenia is generally benign and can often be reversed simply by discontinuing the infusion, however, platelet transfusion may be required in some patients. The risk factors for eptifibatide-induced thrombocytopenia remain unclear, underscoring the need for close monitoring, particularly in patients with high bleeding risk.

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CRediT Author contribution statements: ZS and AM contributed to the conceptualization of the study. AA, ME, EA, and UB were involved in the initial draft writing. AR carried out the formal analysis. MI and FI were responsible for data collection. HC and MY contributed to data validation. SM supervised the project.

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About the Corresponding Author

Ashraf Ahmed, an IM resident at Yale University/Bridgeport Hospital with a strong passion for cardiology and structural cardiology. He is also a teaching assistant for the Principle and Practice of Clinical Research Course at Harvard T.H. Chan school of Public Health. Committed to medical education, Dr. Ahmed enjoy teaching and life-long learning.