

A Prospective Study on Safety of Using Anti-Platelet Therapy in Dengue Hemorrhagic Fever with Thrombocytopenia

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ABSTRACT

Objectives: This study aimed to determine how much extent these anti-platelet drugs are safe for the patient with dengue hemorrhagic fever.

Method: It was a prospective and observational study done for a period of 4 months and the data were obtained from the case sheets of 3 patients admitted in a tertiary care hospital with an acute coronary syndrome and percutaneous coronary intervention with thrombocytopenia. Data were analyzed according to platelet count and which type of anti-platelet drugs are administered to the patients.

Result: whenever patients were suffering from both thrombocytopenia and percutaneous coronary intervention anti-platelet therapy was halted if the platelet count was decreased to below the below 50,000/mcL. Again, this anti-platelet therapy was started to these patients when their platelet count rose up to above 50,000/mcL

Conclusion: The present study shows that it is better to hold anti-platelet therapy when the patient is suffering from severe thrombocytopenia and the therapy will start when there is maximum increase in the platelet count.

Key Words: Dengue hemorrhagic fever, Anti-platelet drugs, Acute coronary syndrome, percutaneous coronary intervention

I. INTRODUCTION

A dengue virus is a single-stranded RNA arbovirus of the Flaviviridae family, and it is closely related to the West Nile virus, the yellow fever virus and the hepatitis C virus [1]. This virus is transmitted by the bite of the female mosquito of the genus *Aedes* (most commonly *Aedes aegypti*). Dengue fever has a broad clinical spectrum ranging from a mild self-limiting febrile illness (classic dengue) to life-threatening dengue hemorrhagic fever and dengue shock syndrome (DHF/DSS). Currently, the disease is endemic in all continents except Europe [2]. Although dengue is essentially an urban malady, it is spreading widely

and steadily in rural India [3]. It is estimated that there are currently 50-100 million dengue cases occurring every year worldwide, including more than 500,000 reported cases of hemorrhagic fever and dengue shock syndrome (DHF/DSS) [4]. In recent times, India has seen a major spurt in dengue, causing widespread panic, and this has stretched the medical services to their fragile limits. One of the most dreaded features of dengue is thrombocytopenia (TCP), which is seen between the 4th and 7th days of the illness when the fever is subsiding. The platelet counts may decline to alarmingly low levels. This is mentioned in the world health organization WHO guidelines of 2009 as a potential indicator of clinical severity [5]. Whenever platelet levels are reduced there might be an increased chance of bleeding manifestations. Coronary artery disease is prevalent in South-east Asia, and there has been an increasing number of percutaneous coronary intervention (PCI) procedures performed with concomitant antithrombotic use [6,7]. Simultaneously in these countries, the prevalence of dengue fever is high due to the endemic nature of the disease [8-10]. Patients undergoing percutaneous coronary intervention (PCI) require a period of dual anti-platelet therapy (DAPT) post-procedure, depending on the stent used as well as the clinical condition of the patient. The omission of anti-platelet agents is associated with the appearance of stent thrombosis. The patient with dengue fever will typically have a drop in platelet count, and the risk of bleeding is the highest toward the end of the febrile period and during the first two days after subsiding of fever. When managing a patient with a recent percutaneous coronary intervention (PCI), who concomitantly develops dengue infection, the physician will have to consider both the risks of bleeding from dengue as well as the risk of thrombosis from the cessation of anti-platelet therapy [11]. In this study, we describe three (3) such cases and discuss a possible algorithm for

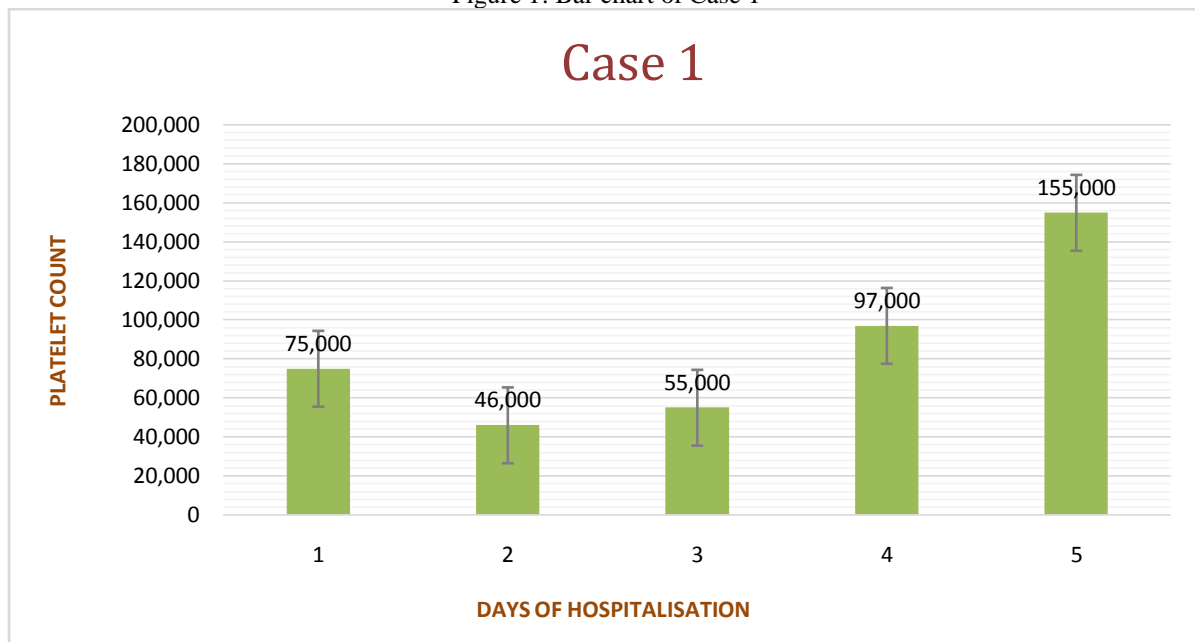
antithrombotic management during acute dengue infections.

Case 1

A 63-year-old male patient was admitted with chills and myalgia. He had a high-grade fever for four days. On admission, he was febrile but hemodynamically stable. Laboratory analysis on admission showed hemoglobin 14.9 g/dl, hematocrit 39%, platelet count 75,000/mcL, and positive with dengue antigen. He was diagnosed with dengue. Two months prior to the admission, he developed stable angina and underwent elective cardiac catheterization, which revealed triple vessel coronary disease. Over two-staged procedures (the last occurring one week prior to the current admission), a total of four drug-eluting stents

(DES) and one bare-metal stent (BMS) were implanted in all three of his coronary arteries. He routinely consumed aspirin 100 mg once daily (OD) and clopidogrel 75 mg once daily (OD). On the second day of hospitalization, the patient's platelet count went down to 46,000/mcL without any sign of active bleeding. Aspirin and clopidogrel were halted. The platelet count rose to 55,000/mcL on the third day, and on the fourth day, increased to 97,000/mcL. Clopidogrel 75 mg once daily was started on the fourth day, and aspirin 100 mg once daily was started on the fifth day, and the count will be increased to 1,55,000/mcL. After discharging from the hospital, doctor advised to use their anti-platelet therapy regularly (see figure 1).

Figure 1: Bar chart of Case 1



Case 2

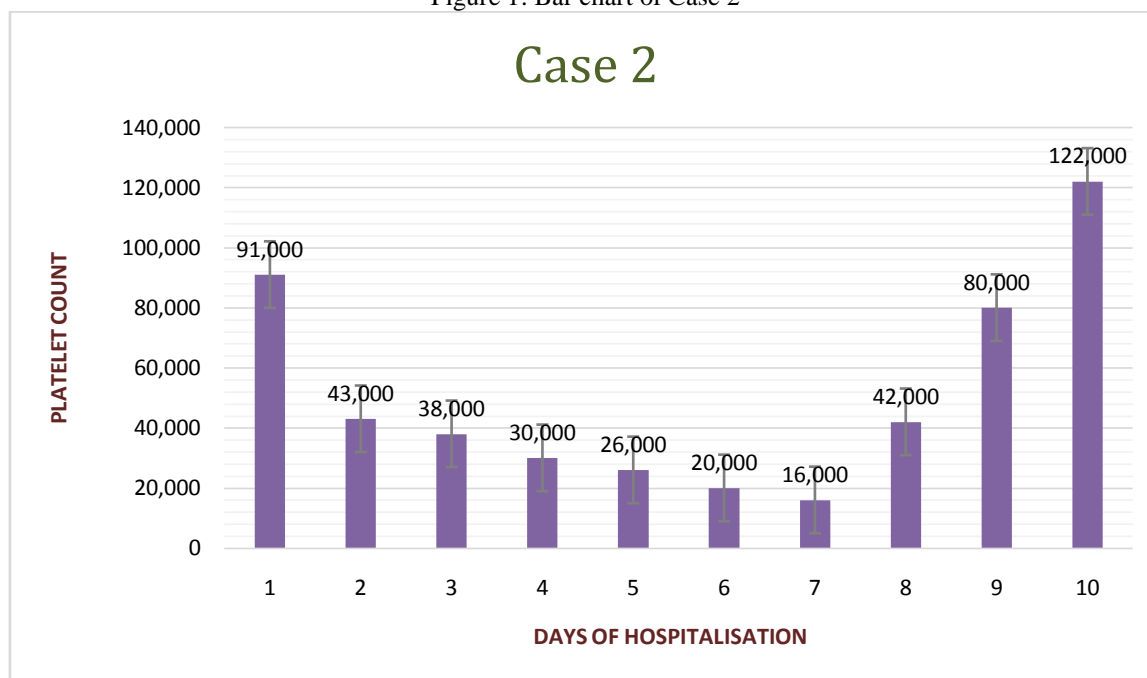
A 77-year-old male patient was admitted with cold and cough, and fever for three days. On admission, he was febrile but hemodynamically stable. His initial hematocrit was 40%, and platelet count was 91,000/mcL. He was suspected of having dengue infection, which was subsequently confirmed by a positive dengue antigen. Seven months previous, he underwent percutaneous coronary intervention with one drug-eluting stent (DES) to the right posterior descending artery and right posterior-lateral artery, respectively. He was planned for one year of Dual anti-platelet therapy (DAPT) with aspirin and clopidogrel. Four years prior, he also

had drug-eluting stent (DES) implantation at the bifurcation of his left anterior descending (LAD) for angina. On the fourth day of hospitalization, his platelet count dropped to 43,000/mcL. There were no signs of active bleeding. Aspirin and clopidogrel were stopped. His platelet counts were gradually decreased day by day to 16,000/mcL on the seventh day. The platelet count rose to 42,000/mcL on the eight-day. Both anti-platelet Drugs were started on the ninth day, during which platelet count was 80,000/mcL, followed by 1,22,000 on the tenth day (see figure 2).

NOTE: On day seven, doctor had a plan to make platelet infusion (SDP-single donor platelet) if the

platelet count were further dropped.

Figure 1: Bar chart of Case 2

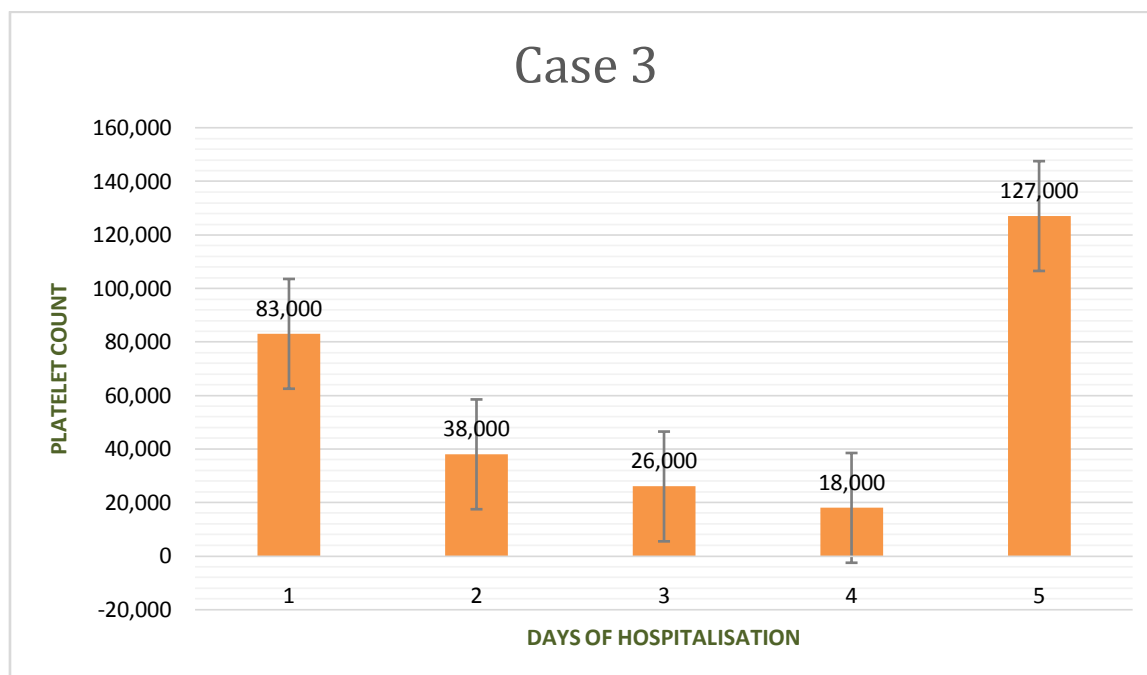


Case 3

A 55-year-old male patient was admitted with fever, rigors and muscle aches for three days. On admission, he was febrile, hemodynamically stable, with spontaneous bruising noted on his arms. Laboratory analysis showed hemoglobin 15.4 g/dl, platelet count 83,000/mcL, white blood cell count 5,900/mcL, and positive dengue IgM antibody. He was diagnosed with dengue with warning signs. He was previously diagnosed with unstable angina two months prior to this admission, underwent cardiac catheterization, and was found to have one-vessel coronary disease. At that time, he was implanted two drug-eluting stents (DES) in ostial to proximal

left anterior descending (LAD). He routinely consumed aspirin 100 mg once daily and clopidogrel 75 mg once daily. Aspirin and clopidogrel were immediately stopped after the patient was diagnosed with dengue with warning signs. Further hydration was given with normal saline. The next day, his platelet count was dropped to a minimum of 38,000/mcL, and he developed even more ecchymosis on his forearms. His platelet was gradually increasing, and on day 5 of hospitalization, the platelet count was 1,27,000/mcL. Aspirin 100 mg Once daily and clopidogrel 75mg was restarted on this day (see figure 3)

Figure 1: Bar chart of Case 3



II. MATERIALS AND METHODS

METHODOLOGY:

The major objective of the study is to know how much extent these anti-platelet drugs are safe for the patient with dengue hemorrhagic fever.

STUDY DESIGN

It was a prospective and observational study carried out in various tertiary care hospitals located in Hyderabad premises. It was conducted over a period of four months, i.e, from November 2019 to February 2020. Institutional ethical committees of various hospitals were grant permission to carry out these studies in their hospitals.

STUDY CRITERIA

Patients who are admitted in the emergency department with thrombocytopenia, and they were already using anti-platelet therapy for acute coronary syndrome, or percutaneous coronary intervention were included in the study. Pediatric patients, pregnant women, lactating mothers were excluded from the study. Patients who are not suffering from thrombocytopenia but are using anti-platelet drugs are excluded from the study, similarly, patients who are suffering from thrombocytopenia but not using anti-platelet drugs are excluded from the study.

DATA COLLECTION:

The demographic details of the patient, drugs prescribed, and information regarding past

how many Months they are using anti-platelet drugs, these data were collected in a prepared prescribed format. All the relevant and necessary data were collected from a) patient case profile, b) treatment chart, c) interviewing with healthcare professionals, d) interacting with the patients or their caretakers at the bedside (family, friends) any other relevant sources.

STUDY PROCEDURE

All the patients admitted during the study period (4 mo) from in-patient were reviewed prospectively on a daily basis by the clinical pharmacist. The patient who met the study criteria were included in the study. Data of those patients were collected and documented. All the enrolled patients were monitored intensively from day to day till the day of discharge and change to drug therapy, if any, was noted on a daily basis were documented. The final obtained data was analyzed, and results were formulated.

DATA ANALYSIS

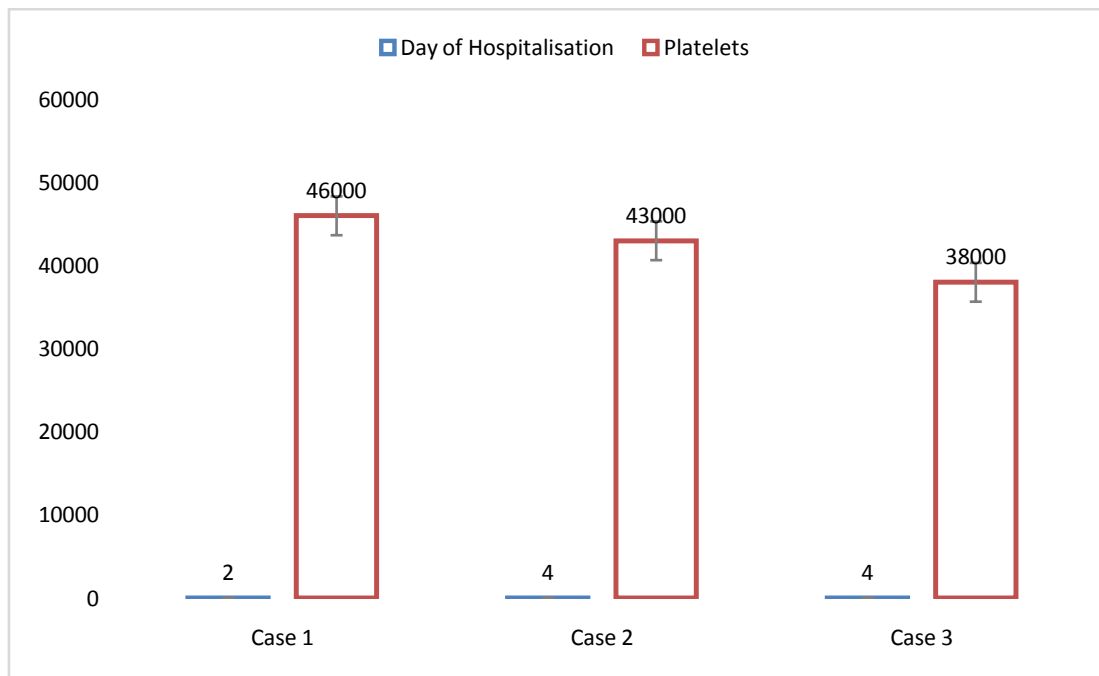
The collected data were evaluated using descriptive statistics, and the results were represented as percentages.

III. RESULTS

A prospective, observational study was conducted to know how much extent these anti-

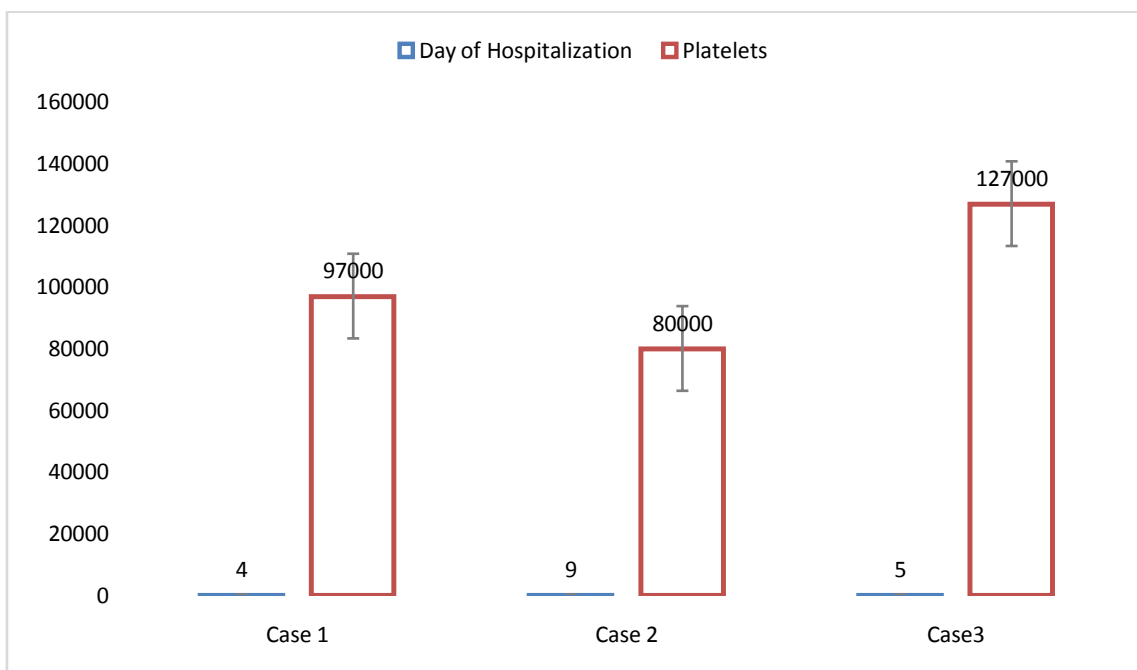
platelet drugs are safe for the patient with dengue hemorrhagic fever. Results were analyzed from the data obtained during the study. In our study for

almost all patients, i.e, 3 [100%], anti-platelets drugs were halted when their platelet counts were decreased after subsiding, the fever.



At which value (platelet count) anti- platelet therapy was halted.

Again, these anti-platelets drugs were restarted whenever their platelet count will be increased to the maximum level (50,000mcL).



At which value (platelet count), anti-platelet count was restarted.

IV. DISCUSSION

In this study, we describe the management of the anti-thrombotic therapy in different scenarios of concomitant dengue and recent percutaneous coronary intervention (PCI). There is currently little evidence regarding the management for the patient who has recent PCI and develops dengue fever. Patients with the, recent percutaneous coronary intervention (PCI) are at high risk of stent thrombosis without using Dual anti-platelet therapy (DAPT) [12,13]. On the other hand, patients with dengue viral infection are at high risk of bleeding [14-16]. Pesaro et al. published several recommendations on the topic, but these were based primarily on expert opinion [17]. In summary, Pesaro's recommendations were as follows: (a) stop all anti-platelets in dengue hemorrhagic fever, (b) continue both anti-platelets in patients with less severe dengue and high risk of thrombosis unless platelet <50,000/mcL and (c) hold at least one anti-platelet if dengue and low thrombotic risk. Managing patients with the recent, percutaneous coronary intervention (PCI) and dengue involves the delicate balancing of the risk of thrombosis and bleeding. Their management should consider the timing of coronary intervention and the severity of the dengue infection [18,19]. Table 1 summarizes the clinical characteristics of

the three cases. The three cases describe different situations of post percutaneous coronary intervention (PCI) patients who develop dengue fever. The timing of coronary intervention and the number of coronary stents implanted make a difference in thrombotic risk stratification. Current guidelines recommend stable PCI patients to take Dual anti-platelet therapy (DAPT) for at least six months after Drug-eluting stent (DES) implantation; this reduces the risk of adverse events from 0.5% to 3.6% [17-20]. The risk of thrombosis is highest in the initial phase after stent implantation and interruption of anti-platelet therapy during this time puts a patient at high risk of stent thrombosis (even temporary discontinuation within this time period might be associated with higher thrombosis rate). Coronary intervention with multiple stents also increases the risk of stent thrombosis. The severity of dengue infection also impacts management. The patient in case 3 was diagnosed with dengue with warning signs, and all anti-platelet therapy was halted after the diagnosis was made in view of the high bleeding risk. In cases 1 and 2, bleeding manifestations were not observed, and the anti-platelet regime was halted once the platelet count fell below the cut-off's values.

Table-1 Clinical characteristic of three cases

No of cases	Case 1	Case 2	Case 3
Dengue infection	Dengue +ve	Dengue +ve	Dengue +ve
CAD status	Stable CAD post PCI	Stable CAD post PCI	Stable CAD post PCI
Type of Anti-platelets given	Aspirin + Clopidogrel	Aspirin + Clopidogrel	Aspirin + Clopidogrel
Timing of PCI	One week before dengue	Seven months before dengue	Two months before dengue
Risk of thrombosis	High	Low	Moderate-High
Platelet count on admission	75,000.	91,000.	83,000.
Platelet count when anti-platelets halted	46,000.	43,000.	83,000.
Lowest platelet count	46,000.	16,000.	38,000.
Platelet count of the patient when anti-platelet drugs are restarted.	97,000 (4 th day) clopidogrel without aspirin. 1,55,000 (5 th day) clopidogrel + aspirin.	80,000 (9 th day) loaded Clopidogrel 300mg + Aspirin 300mg on same day.	1,27,000 (5 th day) Clopidogrel + Aspirin.
Type of anti-platelets restarted after dengue	Clopidogrel 75mg (4 th day) Aspirin 100mg (5 th day)	Clopidogrel 75mg (9 th day) Aspirin 100mg (9 th day)	Clopidogrel 75mg + Aspirin 100mg on 5 th day

V. CONCLUSION

In conclusion, we describe the management of antithrombotic therapy in three different patients with dengue infection and recent percutaneous coronary intervention (PCI) or Acute coronary syndrome (ACI). Our study suggests that it is better to hold using anti-platelet therapy when their platelet count was less than 50,000/mcL, and again, this therapy will be initiated when their platelet count will be increased to more than 50,000/mcL.

LIMITATIONS

The limitations of our study include the small number of cases. Our findings may not be applicable to other populations and will need to be further validated. Nonetheless, these findings provide reasonable clinical recommendations for the physician to consider when faced with such a difficult scenario.

AUTHORS CONTRIBUTION

Conception or design of work: Pothula Harishwarreddy.

Data collection : Pothula Harishwarreddy.

Data analysis and interpretation : Pothula Harishwarreddy.

Drafting the article : Pothula Harishwarreddy.

Critical revision of the article : Pothula Harishwarreddy, Kotta Balaji, Burriveeranna.

Final approval of the version to be published : Pothula Harishwarreddy, Kotta Balaji, BurriVeeranna.

CONFLICTS OF INTEREST

The authors of this review article declare that we have no conflict of interest.

AUTHORS FUNDING

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