8-12-2021

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Long To
Henry Ford Health, lto1@hfhs.org

Dana Attar
Henry Ford Health, dattar1@hfhs.org

Brittany Lines
Henry Ford Health, blines2@hfhs.org

Melissa McCarty
Henry Ford Health

Hassan Nemeh
Henry Ford Health, hnemeh1@hfhs.org

See next page for additional authors

Authors

Long To, Dana Attar, Brittany Lines, Melissa McCarty, Hassan Nemeh, Ileana Lopez-Plaza, Zachary R. Smith, Victor Coba, and Jona Lekura

Research Report

Annals of Pharmacotherapy
1–7

DOI: 10.1177/10600280211038705
journals.sagepub.com/home/aop
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Incidence of Heparin-Induced Thrombocytopenia in Patients With Newly Implanted Mechanical Circulatory Support Devices

Long To, PharmD, BCPS[1], Dana Attar, PharmD[1], Brittany Lines, PharmD[1], Melissa McCarty, PharmD[1], Hassan Nemeh, MD[1], Ileana Lopez-Plaza, MD[1], Zachary Smith, PharmD, BCPS, BCCCP[1], Victor Coba, MD[1], and Jona Lekura, PharmD, BCPS[1]

Abstract

Background: Heparin exposure and device-related thrombocytopenia complicate the diagnosis of heparin-induced thrombocytopenia (HIT) in patients receiving mechanical circulatory support (MCS). To improve anticoagulation management for patients with newly implanted MCS devices, incidence of confirmed HIT needs to be further characterized. **Objectives:** The purpose of this study is to describe the incidence of HIT and clinical utility of the 4Ts score in patients with newly implanted MCS devices. **Methods:** This is a retrospective analysis of MCS patients receiving unfractionated heparin from 2014 to 2017. The primary end point was incidence of laboratory-confirmed HIT. Strong positive, likely positive, low probability, and negative HIT categories were established based on heparin-induced platelet antibody (HIPA) and serotonin release assay (SRA). Secondary end points include characterization of platelet trends, argatroban use, incidence of HIT among each of the MCS devices, and utility of 4Ts score. **Results:** A total of 342 patient encounters met inclusion criteria, of which 68 HIPA tests and 25 SRAs were ordered. The incidence of HIT was 0.88% (3/342) and 4.4% (3/68) in patients with suspected HIT. Of the 68 HIPA tests, 3 (4.4%) were considered strong positive and 3 of the 25 SRAs were positive. Median 4Ts score was 4 [2.5-4] and optical density 0.19 [0.11-0.54]. The positive predictive value for the 4Ts score was 0.15 (CI = 0.03-0.46) and negative predictive value, 0.93 (CI = 0.82-0.98). **Conclusion and Relevance:** HIT occurs infrequently with newly implanted MCS devices. The 4Ts score appears to have a high negative predictive value for ruling out HIT.

Keywords

heparin-induced thrombocytopenia, unfractionated heparin, 4T-score, percutaneous mechanical circulatory support, ventricular assist device, extracorporeal membrane oxygenation

Introduction

Mechanical circulatory support (MCS) devices are frequently used for temporary or permanent hemodynamic support in patients with cardiogenic shock or end-stage heart failure.[1,2] Despite their ability to provide life-sustaining hemodynamic support, MCS devices are associated with serious hematologic complications, including hemorrhage, hemolysis, thrombocytopenia, and thrombosis.[2-4] In particular, thrombocytopenia can be directly related to the anticoagulation therapy required to prevent thrombotic complications. Because of its short duration of action and reversibility, unfractionated heparin (UFH) is the most frequently used anticoagulant in the acute setting during MCS implantation.[5] A serious adverse effect associated with UFH is heparin-induced thrombocytopenia (HIT), which can develop in 0.1% to 5% of patients.[6] Anti-PF4/heparin antibodies are detected in 25% to 50% of post–cardiac surgery patients; however, only 1% to 3% are reported to have clinically relevant HIT.[7,8] When HIT is suspected, an alternate nonheparin anticoagulant such as a direct thrombin

[1]Henry Ford Hospital, Detroit, MI, USA

Corresponding Author:
Long To, Department of Pharmacy, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI 48202, USA.
Email: lto1@hfhs.org

inhibitor (DTI) can be used until the diagnosis of HIT can be ruled out or confirmed.[9]

Differentiation between MCS device–related thrombocytopenia and HIT is challenging, and limited literature exists to assist clinicians in this scenario.[3] Patients who require MCS devices are at risk for the development of HIT because of high doses of heparin administration during implantation and prolonged infusion of UFH to prevent thrombus formation. Therefore, it is critical to identify the true incidence of HIT and when to modify anticoagulation therapies to provide safe and effective care for critically ill patients. Clinical prediction tools such as the 4Ts score exist to predict HIT but were not designed for patients being treated with MCS devices.[10,11] There are limited data on assessing the predictive value of the 4Ts score in patients being treated with MCS.[12,13] This study aims to evaluate the incidence of acute HIT in patients with newly implanted MCS devices receiving UFH and characterize the 4Ts score in predicting HIT in the study population.

Methods

This was a retrospective study conducted at a tertiary care center. Patients were included if they were ≥18 years old and admitted to the cardiovascular intensive care unit from January 1, 2014, to January 1, 2017, and underwent placement of MCS requiring anticoagulation with UFH. The MCS devices utilized included durable left ventricular assist devices (LVADs), such as the HeartMate II and HeartMate 3 (Abbott, Pleasanton, CA), HeartWare (HeartWare, Miami Lakes, FL), percutaneous ventricular assist devices (PVADs) such as CentriMag (Abbott, Pleasanton, CA), TandemHeart (CardiacAssist, Pittsburgh, PA), Impella (Abiomed, Danvers, MA), and venovenous, and venoarterial, extracorporeal membrane oxygenation (ECMO). Included patients were grouped into the suspected HIT group if they had a heparin-induced platelet antibody (HIPA) or serotonin release assay (SRA) result and the HIT not suspected group if the assays were not ordered. The HIPA or SRA were ordered by the treating clinician based on clinical suspicion and trends of platelet reduction from baseline. Patients were excluded if they had a documented history of a heparin allergy or were pregnant. The study was approved by the institutional review board.

The primary outcome was to describe the incidence of laboratory-confirmed HIT in the study population. Laboratory assays used to confirm the diagnosis of HIT included the HIPA (PF4 ELISA, Immucor) and SRA. The PF4 ELISA reports optical density (OD) to predict the likelihood of developing HIT antibodies. An OD of ≥0.4 is considered positive and SRA is positive if ≥20% of serotonin release occurred with low-dose UFH exposure. Because SRA is the gold standard for diagnosis of HIT, a positive SRA regardless of OD was considered positive. In the case where SRA was not available, OD was used to determine the presence of HIT antibodies. Patients were categorized into 4 groups of describing the likelihood of HIT using quantitative interpretation of OD and SRA measurements from a previous study.[14] The following definitions were used to define HIT: strong positive (SRA positive and/or OD ≥2), likely positive (OD = 1.01-1.99), low probability (OD = 0.41-1), and negative (OD ≤0.4 or negative SRA). Patients who met the definition for strong positive were included in the primary analysis for incidence of HIT. Secondary objectives include comparing the overall incidence of thrombocytopenia (platelet $< 100 \times 10^3/\mu L$) and platelet trends between patients who had suspected HIT and those who did not have suspected HIT, evaluating the utility of the 4Ts score, and describing the use of DTI in the study population.

Data collected include baseline demographic information, platelet count (on admission or at baseline defined as last normal value within the past 100 days, and up to 14 days post–device implantation), IV UFH, and DTI orders (dosing and duration). Because of poor documentation of 4Ts scores in the medical record, the investigators retrospectively collected the 4Ts score for each patient who had the HIT panel or SRA ordered. Two investigators collected 4Ts scores for patients and used the same data collection template for consistency. The 4Ts score was calculated on the first date the HIPA panel and SRA were ordered. If the assays were ordered on separate dates, the 4Ts score was calculated on the date the first assay was ordered. The lowest platelet count for each patient was included for each day post–device implantation for 14 days. Any subjective determination of 4Ts score, that is, other causes of thrombocytopenia or thrombosis, only incidents documented in the patient's chart was counted. The study categorized the likelihood of HIT based on the 4Ts score into low probability (score < 4) or moderate to high probability (≥4). Categorical variables are presented as n (%). Continuous variables are presented as means (SDs) or median (interquartile range), as appropriate.

Results

A total of 1102 hospital admissions were screened resulting in 335 unique patients meeting study inclusion criteria and 342 hospital encounters (Figure 1). The median age of the population was 62.6 years [52.8-70], and there were 123 Impella, 91 LVADs, 60 ECMO, 14 PVADs, and 54 patients receiving MCS device support with more than 1 device. Additional demographic characteristics are listed in Table 1.

A HIPA with OD, SRA, or both labs were ordered in 68 encounters suspected to have HIT by the primary team. Three patients met the definition of strong positive HIT. Therefore, the overall incidence of HIT for the entire study population was 0.88% (3/342 encounters). In patients with suspected HIT, the incidence was 4.4% (3/68) with a median

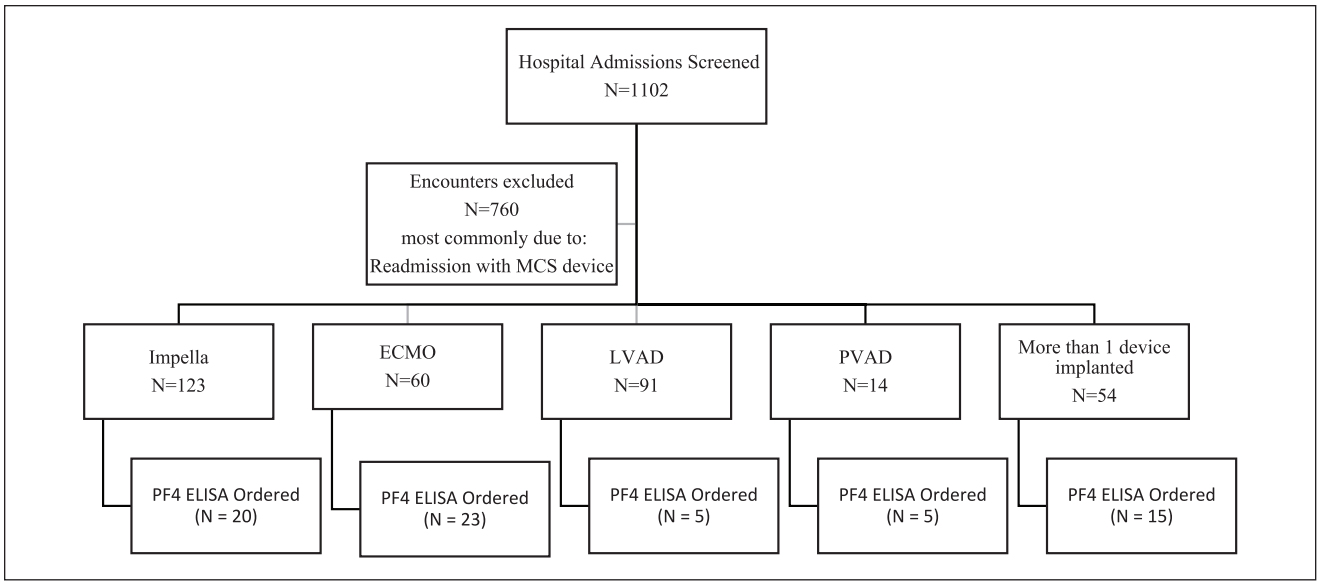

Figure 1. Inclusion and exclusion criteria.
Abbreviations: ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; MCS, mechanical circulatory support; PVAD, percutaneous ventricular assist device.

Table 1. Baseline Characteristics.

Characteristics	n = 342
Age (years), median (IQR)	62.5 (52.6-70.2)
Male, n (%)	222 (66.3)
Length of stay (days), median (IQR)	18.9 (7.0-31.2)
Device type, n (%)	
Impella	123 (36)
ECMO	60 (17)
LVAD	91 (27)
PVAD	14 (4)
>1 Device	54 (16)
Duration of MCS device (days), median (IQR)	
Impella	4 [2, 6]
ECMO	8.79 [4, 11.15]
LVAD	N/A
PVAD	2.88 [1, 23.9]
Baseline platelet ($\times 10^3/\mu L$), median (IQR)	204 (162-260)

Abbreviations: ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; LVAD, left ventricular assist device; MCS, mechanical circulatory support; PVAD, percutaneous ventricular assist device.

OD of 0.19 [0.11-0.54]. The HIPA was ordered on median day 3 [1-5] from device implantation.

Of the 68 HIT tests, 62 were negative, 3 were low probability of HIT with ODs of 0.41 to 1, and 3 were strong positive based on SRA (Table 2). A single patient with strong positive HIT was in each of the ECMO, Impella, and PVAD subgroups. There were 15 patients with ODs of 0.41 to 1, of whom 12 had negative SRA. Three patients did not have SRA sent and were included in the low-probability HIT group because we were unable to rule out HIT with SRA. Even though 4 patients had ODs between 1.01 and 1.99, all 4 had negative SRA results and were, therefore, categorized as negative HIT. A total of 25 SRAs were ordered, of which 3 were positive.

The overall median 4Ts score for the suspected HIT group was 2 [1-3]. For patients with strong positive HIT, the median 4Ts score was 4 [2.5-4]. The median 4Ts score for the low-probability HIT group was 3 [2-3], and it was 2 [1-3] for the negative HIT group. No patients were categorized as likely positive HIT because of confirmed negative SRA. The sensitivity and specificity analysis of the 4Ts score were 0.33 (CI = 0.06-0.76) and 0.82 (CI = 0.70-0.90), respectively. The positive predictive for the 4Ts score was 0.15 (CI = 0.03-0.46), and negative predictive value was 0.93 (CI = 0.82-0.98).

The percentage of patients who developed thrombocytopenia are presented in Figure 2. Significant thrombocytopenia seems to be present from day 1 to day 7 post–device implantation, after which the prevalence decreased to less than 20%. When platelet trend was analyzed between suspected HIT and no suspected HIT groups, thrombocytopenia developed on postimplantation day 4 and recovered (defined as platelet count $> 100 \times 10^3/\mu L$) by day 9 in the suspected HIT group (Figure 3). Of the patients with suspected HIT, 11 had had heparin exposure in the past 100 days.

Of the 68 encounters with suspected HIT, argatroban was administered to 25 (36.8%) and was continued for a median of 4 [2-13.25] days. Three of these patients were found to have strong positive HIT, 0 had possible HIT, and 22 were later identified as negative HIT (88%). The median

Table 2. Optical Density and Serotonin Release Assay Distribution.

Patients with suspected HIT	Total (n = 68)	Impella (n = 20)	ECMO (n = 23)	LVAD (n = 5)	PVAD (n = 5)	>1 Device (n = 15)
Overall OD of 68 patients, median (IQR)	0.19 (0.11-0.54)					
Negative HIT, n (%)	62 (91.2)	17	22	5	4	14
OD, median (IQR)	0.17 (0.11-0.38)	0.13 (0.1-0.54)	0.17 (0.11-0.35)	0.19 (0.18-0.67)	0.25 (0.12-0.47)	0.17 (0.12-0.28)
SRA ordered	22	6	8	3	1	4
Negative, n	22	6	8	3	1	0
Indeterminate, n	0	0	0	0	0	0
Positive, n	0	0	0	0	0	0
Low probability, n (%)	3 (4.4)	2	0 (0)	0 (0)	0 (0)	1
OD, median (IQR)	0.67 (0.64-0.71)	0.67 (0.64-0.71)				0.67[a]
SRA ordered, n	0	0				0
Likely positive, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
OD, median (IQR)	N/A					
SRA ordered	N/A					
Strong positive, n (%)	3 (4.4)	1	1	0 (0)	1	0 (0)
OD, median (IQR)	2.91 (1.7-3.06)	2.91[a]	0.50[a]		3.21[a]	
SRA ordered, n	3	1	1		1	
Negative, n	0	0	0		0	
Indeterminate, n	0	0	0		0	
Positive, n	3	1	1		1	

Abbreviations: ECMO, extracorporeal membrane oxygenation; HIT, heparin-induced thrombocytopenia; IQR, interquartile range; LVAD, left ventricular assist device; OD, optical density; PVAD, percutaneous ventricular assist device; SRA, serotonin release assay.
[a]IQR not calculated because only 1 patient met criteria.

OD for patients who received DTIs was 0.18 [0.113-0.519], and 4Ts score was 2 [1-3]. All 3 patients who had a positive SRA received argatroban.

Discussion

This retrospective analysis found that HIT was suspected in 19.9% (68/342) of patients receiving newly implanted MCS devices, and the diagnosis was confirmed in 0.88% (3/342) of patients. Among patients who had suspected HIT and received testing, 4.4% (3/68) tested positive with SRA. A previous study identified an incidence of HIT of 10.6%, as defined by platelet activation in patients receiving MCS; however, this investigation had a different study design and collected a blood sample on all included patients on postoperative day 7.[8] The difference in methods between studies may explain the variation in HIT incidence because OD and SRA testing were not completed in our study if clinical suspicion for HIT by the treatment team was low, as recommended by evidence-based guidleines.[10]

At our institution, if OD results are <0.4, it is recommended to discontinue DTI therapy and resume the patient on UFH. However, if OD is ≥ 0.4, an SRA should be checked for a more definitive diagnosis of HIT. A total of 25 patients in the present study with suspected HIT were initiated on DTI, and of those, 22 were later determined to be negative for HIT. In all, 12 patients (48%) had an OD <0.4 and were continued on a DTI for a median of 2 days [1-4.5]. Of these 12 patients, 11 had a low-probability 4Ts score and 1 had an intermediate-probability 4Ts score. This study suggests that a greater emphasis may need to be placed on clinical suspicion of HIT in conjunction with the 4Ts score because of potential concerns about the validity of the 4Ts score in the studied population, as recommended by experts.[3] DTIs are prescribed when HIT is suspected despite a low 4Ts score. This can be problematic because clinical suspicion can vary between clinicians. Given the overall low sensitivity and specificity seen with the 4Ts score, a modified 4Ts score may be necessary to account for inevitable drops in platelets witnessed in those with MCS devices, as previously described.[12,13]

The utility of the 4Ts score for HIT showed varying levels of sensitivity (33%) and specificity (82%) in the present study. The results of the sensitivity and specificity analyses are slightly different from those of a recent observational study in patients with MCS devices, which concluded that the areas under the receiver-operating characteristics curve for the 4Ts score was 0.88 (CI 0.759-1.000).[12] The optimal cutoff score for the 4Ts score in this model was a value of 3. However, most of the included patients had intra-aortic balloon pumps, whereas our patients received more complex MCS devices. A second report noted that when using a modified 4Ts score in the MCS population, the score had a sensitivity and specificity of 77.6% and 57%, respectively.[13] The current study reveals a high negative predictive value of 93% in the MCS population, similar to a previous report

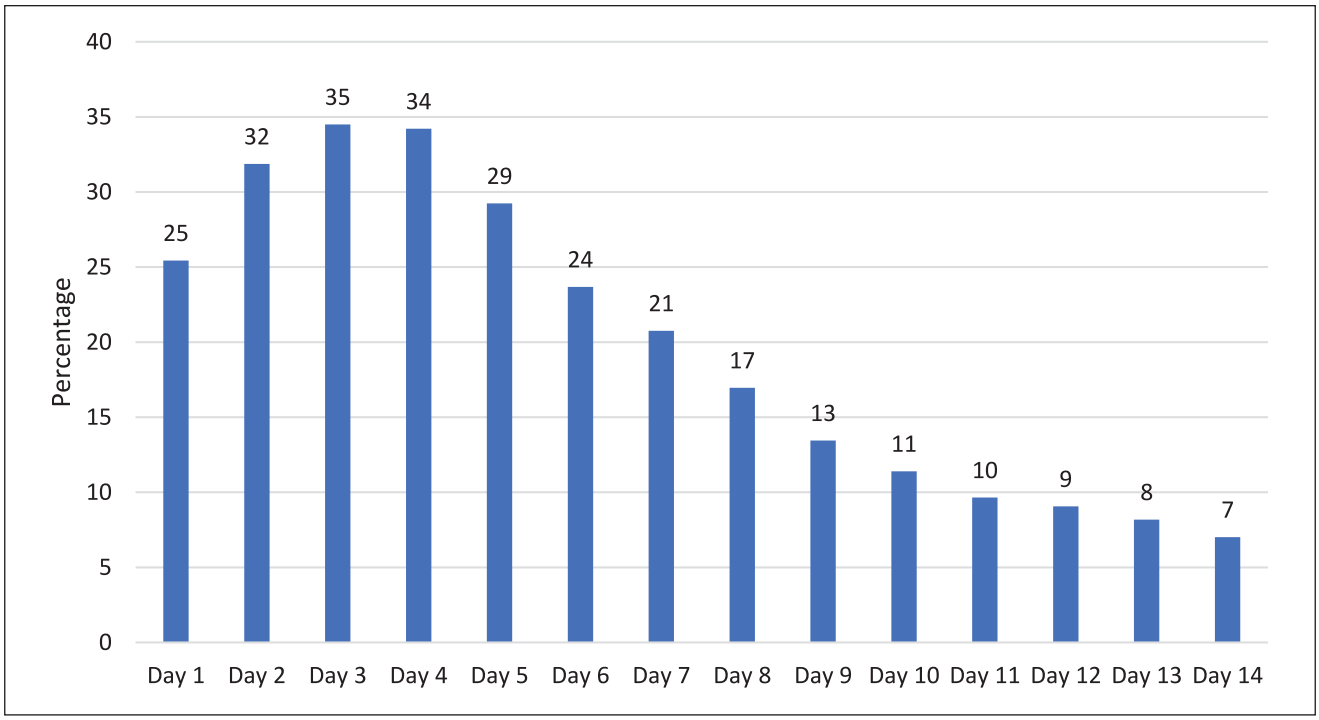

Figure 2. Percentage of patients with thrombocytopenia post–device implantation.

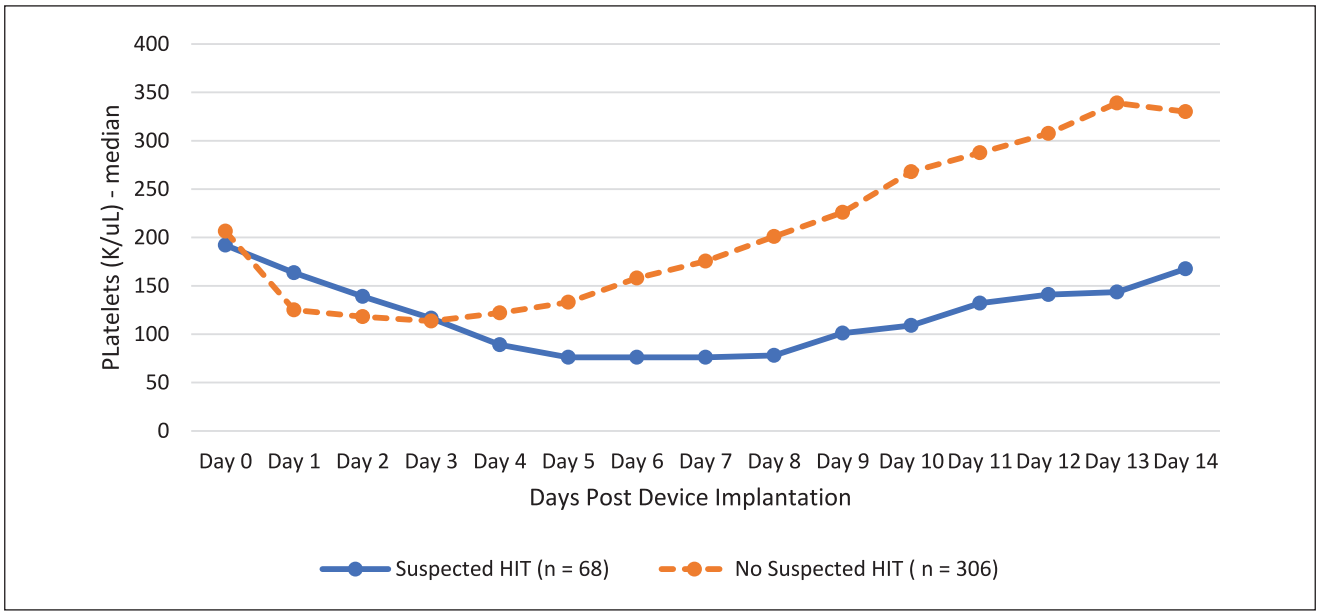

Figure 3. Platelet trend between suspected heparin-induced thrombocytopenia (HIT) and no suspected HIT.

of a 90% negative predictive value in an MCS population.[13] These findings support that a 4Ts score ≤3 may serve as a useful tool for clinicians to rule out HIT. The thrombocytopenia and thrombosis that develop when utilizing MCS devices are common device-related adverse effects that may lower the 4Ts score's positive predictive value.[13] Using other clinical criteria such as persistent thrombocytopenia, a secondary fall in platelets after an initial recovery, or thrombus development on therapeutic doses of UFH may help guide clinical decision-making in the absence of an accurate bedside tool to predict the presence of HIT.[3]

Thrombocytopenia is a common complication of MCS devices, but little literature exists to describe the incidence. Our study revealed that up to one-third of patients exhibited thrombocytopenia in the first 5 days of device implantation (Figure 2). The prevalence decreased to less than 20% by day 8. In reviewing the platelet trend for study groups who were categorized as suspected HIT and HIT not suspected, we found that the median platelets for the HIT not suspected group remained $>100 \times 10^3/\mu L$ and drifted upward for 14 days post–device implantation. These findings lend support to the idea that the HIT not suspected group did not exhibit platelet trends suggestive for HIT. For this reason, a HIT panel was not sent. For the group with suspected HIT, the platelets decreased to $<100 \times 10^3/\mu L$ near day 3 and remained low until day 9. This coincided with the HIT panel sent on day 3 [1-5] of device implantation. Because of the low incidence of definite HIT, we hypothesize that the thrombocytopenia is likely a consumptive process related to the MCS devices rather than HIT.

In our study, 3 patients were diagnosed with definite HIT confirmed by SRA. In the first case, the patient received ECMO for 7 days and OD was ordered 2 days after beginning ECMO, which resulted in a value of 0.497. The patient was diagnosed with acute left middle cerebral artery thrombus with cerebrovascular accident. The 4Ts score was 4. The second patient had an Impella implanted for 11 days, and OD was ordered 5 days after Impella placement, which resulted in a value of 2.905. The calculated 4Ts score was 1, and there was no evidence of thrombosis. The third case had a TandemHeart implanted for about 14 hours. OD was ordered the following day after device placement, and this resulted in a value of 3.212. The patient was also found to have a left ventricular apical thrombus. The calculated 4Ts score was 4. In all 3 cases, argatroban was ordered at the time of HIT suspicion and was continued for a total of 4 to 16 days. These cases highlight the clinical utility of early HIPA testing if HIT is suspected based on high-risk characteristics because the SRA confirmatory testing may take 5 to 7 days.[3] Assessment of the 4Ts score in the MCS population as a tool to predict the true presence of HIT may not be adequately sensitive or specific.

There are limitations to this study. First, the retrospective study design can affect the quality of the data through documentation errors within the electronic medical record. There is a potential for calculating the 4Ts score differently among the investigators even with prospective, randomized trials.[14] The 4Ts score calculation is subject to different interpretations depending on the provider who is assessing the patient.[15] To mitigate this, standard data collection templates were used to calculate 4Ts scores to minimize variations among investigators. Investigators reviewed patients and 4Ts score calculation together as a group prior to data collection. In addition, the 4Ts score calculation was limited to only 2 investigators following the same criteria outlined in the study protocol.

Conclusion and Relevance

The incidence of HIT in patients with newly implanted MCS devices is low; yet a large proportion of patients with thrombocytopenia received alternative anticoagulation. The 4Ts score seems to have a good negative predictive value that may allow for its use to rule out HIT. Future research is warranted to identify and validate an accurate bedside HIT predicting tool in patients with MCS devices.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Long To https://orcid.org/0000-0002-9387-449X
Jona Lekura https://orcid.org/0000-0002-4029-0749

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