

Incidence and Outcomes of Heparin-Induced Thrombocytopenia in Patients Undergoing Cardiac Surgery in North America: An Analysis of the Nationwide Inpatient Sample

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Objectives: The objective of this study was to quantify the impact of heparin-induced thrombocytopenia (HIT) on outcomes after cardiac surgery.

Design: Retrospective analysis of national database.

Setting: United States hospitals.

Participants: Patients identified from 186,771 discharge records undergoing cardiac surgery from the Nationwide Inpatient Sample between 2009 and 2010.

Interventions: None.

Measurements and Main Results: Heparin-induced thrombocytopenia was diagnosed in 506 (0.3%), and secondary thrombocytopenia was diagnosed in 16,809 (8.7%). Operative mortality was 11.1% in patients with HIT compared to 4.5% for patients without thrombocytopenia ($p < 0.001$) and 4.0% for patients with a diagnosis of secondary thrombocytopenia ($p < 0.001$). After adjusting for baseline patient comorbidity, the strongest independent predictors of HIT in patients undergoing cardiac surgery were female gender (OR 1.4, 95% confidence interval [CI]

1.28-1.48), congestive heart failure (OR 1.8, 95% CI 1.71-1.98), cardiac insufficiency (OR 2.2, 95% CI 1.97-2.39), atrial fibrillation (OR 1.4, 95% CI 1.30-1.51), liver disease (OR 2.2, 95% CI 1.96-2.50), and chronic renal failure (OR 1.4, 95% CI 1.30-1.51). HIT was associated with significantly increased risk of major adverse postoperative outcomes including death (OR 1.5, 95% CI 1.3-1.7), stroke (OR 2.4, 95% CI 1.9-3.1), amputation (OR 7.46, 95% CI 4.0-14.0), and acute renal failure (OR 2.3, 95% CI 2.1-2.5), respiratory failure (OR 1.9, 95% CI 1.8-2.1), and need for tracheostomy (OR 2.7, 95% CI 2.3-3.1).

Conclusions: Heparin-induced thrombocytopenia is associated with a 50% increase in early mortality, and most patients with this diagnosis experience major postoperative morbidity or functional deficits.

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KEY WORDS: thrombocytopenia, cardiac surgery, HIT, heparin, complications, platelets

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) is a life-threatening disorder caused by antibodies against complexes formed by heparin and platelet factor 4.¹ It usually is characterized by a fall in platelet count to $< 150,000/\mu\text{L}$ or a decrease of more than 50% from baseline and an increase in thrombotic risk to more than 30 times that of control populations.² Patients may present with myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism, and limb or mesenteric ischemia; the associated mortality in postoperative cardiac surgery patients is more than 20%.³ Diagnosis can be challenging, particularly as the available antibody assays vary widely in sensitivity and specificity.⁴ The incidence of HIT after cardiac surgery has been estimated to range from 0.1% to 4%,⁴⁻¹² but evidence is limited to single-center analyses with small patient cohorts. While these studies provide useful data on diagnostic and management strategies, their patient populations are insufficient to accurately quantify the incremental morbidity and mortality associated with this condition in cardiac surgical patients. This study, therefore, utilized the Nationwide Inpatient Sample to determine the incidence, risk factors, and outcomes of HIT in patients undergoing cardiac surgery.

MATERIALS AND METHODS

Patients who underwent cardiac surgery from January 1, 2009 to December 31, 2010 were identified using the Nationwide Inpatient Sample (NIS). The NIS is the largest publicly available database of inpatient hospital care in the United States and is sponsored by the Agency for Healthcare Research and Quality. The database contains information from more than 8 million inpatient stays per year from more than 1,000 hospitals across the country representing more than 40 states. Each record in the database represents an inpatient stay and includes both clinical and nonclinical information such as patient demographics, principal and secondary diagnoses, procedures, discharge status, and charges. The dataset was obtained directly from the NIS and contains diagnoses and procedures coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The study protocol was reviewed by the Institutional Review Board, which waived the need for informed consent since the source consisted of de-identified, publically available data.

Patients were identified from the NIS using the ICD-9-CM procedure codes for coronary bypass surgery (36.10, 36.11, 36.12, 36.13, 36.14, and 36.15), valve surgery (35.20-28, 35.11-14), or aortic replacement (38.45). Patients who underwent on-pump coronary artery bypass were identified using the procedure codes 39.61 (extracorporeal circulation auxiliary to open heart surgery) or 39.66 (percutaneous cardiopulmonary bypass). The baseline patient characteristics that the authors assessed are listed in Table 1. The ICD-9 diagnosis codes used to define these comorbidities are based on Agency for Healthcare Research and Quality comorbid disease categories.¹³

Patients were stratified into 3 groups based on the presence of (1) thrombocytopenia, (2) HIT, and (3) neither (control group), diagnosed by individual clinicians. Baseline characteristics and postoperative outcomes were compared between each group. The primary outcome was in-hospital mortality defined as death at any time during the index hospitalization; secondary outcomes included postoperative stroke, ischemic complications, amputation, venous thromboembolic events, acute renal failure (with or without need for subsequent hemodialysis), mediastinitis, and respiratory failure.

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1053-0770/2601-0001\$36.00/0

<http://dx.doi.org/10.1053/j.jvca.2013.07.021>

Table 1. Baseline Patient Characteristics

Variable	No Thrombocytopenia n = 169,962 (91%)	2 ^o Thrombocytopenia n = 16,249 (8.7%)	HIT n = 560 (0.3%)	p Value
Age (years)	61.6 ± 17.7	66.9 ± 14.0	66.7 ± 13.4	< 0.001
Female (%)	34.4	34.5	43.2	< 0.001
Elective admission (%)	48.8	53.3	37.1	< 0.001
Transfer from another hospital (%)	15.5	14.2	21.9	< 0.001
Diabetes (%)	32.6	36.2	34.8	< 0.001
Liver disease (%)	3.2	5.5	10.0	< 0.001
Chronic renal failure (%)	10.7	15.0	18.9	< 0.001
Chronic obstructive pulmonary disease (%)	13.3	14.1	16.8	< 0.001
Congestive heart failure (%)	26.2	32.4	48.8	< 0.001
Cardiac insufficiency (%)	6.5	9.5	18.7	< 0.001
Endocarditis (%)	1.1	1.3	1.7	< 0.001
Aortic atherosclerosis (%)	1.4	1.9	1.4	< 0.001
Peripheral vascular disease (%)	7.8	8.9	7.3	< 0.001
Stenosis of precerebral arteries (%)	3.3	4.3	3.7	< 0.001
Atrial fibrillation (%)	30.7	37.2	41.0	< 0.001
Late effects of cerebrovascular disease (%)	1.3	1.3	1.6	0.23
Previous myocardial infarction (%)	8.9	8.1	7.8	< 0.001
Previous cardiac surgery (%)	4.0	3.1	3.8	< 0.001
Previous percutaneous intervention (%)	8.1	6.5	4.4	< 0.001

NOTE. The p value is provided for univariate comparison of patients without thrombocytopenia, to those with heparin-induced thrombocytopenia.

Abbreviation: HIT, heparin-induced thrombocytopenia.

Univariate analysis of outcomes between each patient group was performed using Pearson's chi-squared test for categorical variables and Student's t-test for continuous variables. Multivariate analysis was performed using binary logistic regression using the same aforementioned patient demographics and comorbidities as covariates (excluding co-morbidities when they were used to define the subgroup). Results are demonstrated as odds ratios (OR) and 95% confidence intervals. A p value of <0.05 was considered to be statistically significant. All analyses were performed with SPSS Statistics for Windows, Version 21 (IBM Corporation, Armonk, NY).

RESULTS

Between 2009 and 2010, cardiac surgical procedures were reported in 186,771 hospital admissions in which HIT was diagnosed in 560 (0.3%), and secondary thrombocytopenia was diagnosed in 16,249 (8.7%). Frequencies of all patient characteristics, according to the presence or absence of these diagnostic categories, are listed in [Table 1](#). The group of patients with HIT contained a greater proportion of female patients (43.2% v 34.4%, p < 0.001) than either group of patients without this diagnosis and was characterized by higher rates of chronic renal failure (18.9% v 11.1%, p < 0.001), atrial fibrillation (41.0% v 31.2%, p < 0.001), congestive heart failure (48.8% v 26.7%, p < 0.001), and cardiac insufficiency (18.7% v 6.8%, p < 0.001). Patients who developed HIT were also much more likely to be urgent or emergency admissions and/or transferred into the hospital from another facility.

In the group of patients who developed HIT, 44.2% underwent coronary artery bypass grafting, compared to 45.2% in patients without this diagnosis (p = 0.265), and the proportion of coronary bypass operations that were performed off-pump was 29.5% and 40.8% (p < 0.001), respectively. [Table 2](#) shows the postoperative outcomes of patients with and without thrombocytopenia. Patients with HIT had an operative

mortality of 11.1% compared to 4.5% for patients without thrombocytopenia (p < 0.001), and 4.0% for patients with a diagnosis of secondary thrombocytopenia (p < 0.001). Thromboembolic complications and their sequelae were observed much more frequently in patients with HIT compared to those without it, including venous thromboembolic complications (6.4% v 1.4%, p < 0.001), arterial embolism (2.8% v 0.6%, p < 0.001), renal, hepatic or mesenteric ischemia or infarction, (1.3% v 0.6%, p < 0.001), and amputation (0.6% v 0.1%, p < 0.001). These patients remained in the hospital almost twice as long and were almost twice as likely to be discharged to a skilled care facility.

After adjusting for baseline patient comorbidity, the strongest independent predictors of HIT in patients undergoing cardiac surgery were female gender (OR 1.4, 95% CI 1.28-1.48), congestive heart failure (OR 1.8, 95% CI 1.71-1.98), cardiac insufficiency (OR 2.2, 95% CI 1.97-2.39), atrial fibrillation (OR 1.4, 95% CI 1.30-1.51), liver disease (OR 2.2, 95% CI 1.96-2.50), and chronic renal failure (OR 1.4, 95% CI 1.30-1.51) ([Table 3](#)). Inter-hospital transfer (as opposed to admission from home) was associated with a 20% increase in risk of heparin-induced thrombocytopenia (OR 1.2, 95% CI 1.10-1.32).

Heparin-induced thrombocytopenia was associated with significantly increased risk of major adverse postoperative outcomes including death (OR 1.5, 95% CI 1.30-1.67), stroke (OR 2.4, 95% CI 1.94-3.06), major amputation (OR 7.5, 95% CI 3.97-13.96), and acute renal failure (OR 2.3, 95% CI 2.09-2.47), respiratory failure (OR 1.9, 95% CI 1.77-2.08), and need for tracheostomy (OR 2.7, 95% CI 2.27-3.08) ([Table 4](#)). Secondary thrombocytopenia, in contrast, was associated with reduced mortality (OR 0.7, 95% CI 0.68-0.73), pulmonary embolism (OR 0.87, 95% CI 0.86-0.91), and arterial embolism (OR 0.86, 95% CI 0.78-0.95).

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