CHEST

Use of IV Immunoglobulin G in Heparin-Induced Thrombocytopenia Patients Is Not Associated With Increased Rates of Thrombosis

A Population-Based Study

To the Editor:

Heparin-induced thrombocytopenia (HIT) is a severe prothrombotic syndrome with a mortality rate of 10%.[1] Case reports and case series, including three published in *CHEST*,[2-4] show that IV immunoglobulin G (IVIg) can rapidly and durably counteract HIT antibody-mediated platelet activation in cases of severe protracted HIT. Although limited data from these and other papers[5] support the use of IVIg in severe settings of HIT, it is well documented that "positive-result bias" enhances the likelihood of publication of studies that demonstrate salutary effects of interventions while those with neutral/negative results often remain unpublished.[6] IVIg preparations have a black box warning for thrombosis in a number of potential predisposing states, including advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and having cardiovascular risk factors.[7] Notably, HIT is one of the most hypercoagulable conditions described,[8] with a high thrombosis burden of approximately 30%.[1] Thus, an important concern is that IVIg use in the HIT setting may further fuel the prothrombotic phenotype and predispose to additional thrombosis. Because IVIg-treated HIT patients are infrequently encountered, this concern is unlikely to be adequately investigated by a single- (or even multi-) center evaluation. The goal of the study presented in this report was to evaluate whether rates of arterial and venous thrombosis were higher in IVIg-treated patients compared with those who were not treated with the drug. For this, we analyzed the Nationwide (National) Inpatient Sample (NIS), the largest publicly available all-payer inpatient health care database in the United States, which was developed for the Healthcare Cost and Utilization Project. Unweighted, it contains data from more than 7 million hospital stays each year; weighted, it comprises more than 35 million hospital admissions nationally.[9]

Methods

Hospital discharges with an ICD-9-CM (The International Classification of Diseases, Ninth Revision, Clinical Modification) code for HIT (289.84) in the NIS were used to compare outcomes in adult patients (≥18 years) who did and did not receive IVIg (ICD-9-CM code 99.14) from October 1, 2008 to December 31, 2014. Discharges with diagnoses suggestive of a history of thrombosis (ICD-9-CM codes V12.51, V12.52, V12.55), idiopathic thrombocytopenic purpura (287.31), or secondary thrombocytopenia (287.4) were excluded. Patient characteristics included age, sex, all patient refined diagnosis related groups (APR-DRG) severity index, and APR-DRG mortality index. ICD-9 codes used have been described previously.[1] Primary outcomes included arterial thrombosis and venous thrombosis. Additional outcomes examined included bleeding, amputation, and in-hospital mortality. Variables were compared by IVIg treatment status by using survey weighted χ^2 tests for categorical variables and analysis of variance for continuous variables. Survey weighted multiple logistic regression was used to model each binary outcome by IVIg treatment status while adjusting for age, sex, APR-DRG severity index, and mortality index.

Conditional logistic regression analysis was performed as a sensitivity analysis for the multiple logistic regression results. In the conditional logistic regression model, control subjects were matched with IVIg cases at a 5:1 ratio by nearest age and exact sex, APR-DRG severity index, and mortality index.

Results

HIT patients treated with IVIg and those without were similar in age and sex (Table 1). Consistent with the limited published experience on IVIg use in HIT, those who received IVIg had much higher APR-DRG severity indexes compared with those that were not treated with the drug ($P < .001$, Table 1). For example, 70% of patients in the IVIg group had "extreme loss of function" relative to only 43% in the untreated group (Table 1). Similarly, IVIg-treated HIT patients had higher risks of dying compared with the untreated group ($P = .002$, Table 1). Table 2 details rates of thrombosis, bleeding, amputation, and in-hospital mortality in the patient groups. Multiple logistic regression showed that

TABLE 1] Demographics and APR-DRG Severity and Mortality Indexes of the Study Population

Variable	Demographics	HIT Without IVIg Treatment		HIT With IVIg Treatment		*P*
		Unweighted (No.)	Weighted, n (%)	Unweighted (No.)	Weighted, n (%)	
Study Period	2008-2014	23,863	116,454 (100%)	56	275 (100%)	
Age	18-64, y	10,528	51,326 (44%)	30	147 (53%)	.165
	65+, y	13,335	65,128 (56%)	26	129 (47%)	
Sex	Male	12,068	58,893 (51%)	28	138 (50%)	.926
	Female	11,795	57,561 (49%)	28	138 (50%)	
APR-DRG severity index	Min-mod loss of function	2,906	14,232 (12%)	2	10 (4%)	< .001
	Major loss of function	10,758	52,524 (45%)	15	74 (27%)	
	Extreme loss of function	10,199	49,698 (43%)	39	192 (70%)	
APR-DRG mortality index	Min-mod likelihood of dying	7,567	36,952 (32%)	12	59 (21%)	.002
	Major likelihood of dying	7,920	38,655 (33%)	12	59 (21%)	
	Extreme likelihood of dying	8,376	40,847 (35%)	32	158 (57%)	

APR-DRG = all patient refined diagnosis-related groups; HIT = heparin-induced thrombocytopenia; IVIg = IV immunoglobulin G.

the adjusted odds of thrombosis were not statistically different between the groups (Table 3). Similar results were obtained in conditional logistic regression of matched data (Table 4). Bleeding, amputation, and in-hospital mortality were also similar between the two groups (data not shown). The length of follow-up for the outcomes noted was higher in IVIg-treated HIT patients (19.48 [11.41-30.21], median [interquartile range]) compared with HIT patients not treated with IVIg (9.31 [4.70-17.50]). This was not surprising, because IVIg is used in the setting of days to weeks of protracted thrombocytopenia resulting in prolonged hospital stay.

Discussion

An increasing number of reports have used IVIg in the context of treating severe HIT.[10] These studies have reported IVIg efficacy by demonstrating durable platelet recovery. The most frequent dose used was 2 g/kg body weight, but in some cases even higher amounts have been used,[5] causing concern for IVIg-induced thrombosis in this already prothrombotic state. Most published reports on this topic have included single or only a few cases, making quantifying the IVIg-induced thrombosis risk challenging because of small numbers and a possible positive-result publication bias.

TABLE 2] Outcomes in HIT Patients: Thrombosis, Bleeding, Amputation, and In-Hospital Mortality in HIT

Outcome	HIT Without IVIg Treatment			HIT With IVIg Treatment		
	Unweighted, No.	Weighted, No.	Percent of Discharges (± SE)	Unweighted, No.	Weighted, No.	Percent of Discharges (± SE)
Arterial thrombosis	2,987	14,574	12.51 ± 0.23	7	35	12.70 ± 4.55
Venous thrombosis	4,899	23,926	20.55 ± 0.32	13	65	23.69 ± 5.58
Bleeding	1,432	6,992	6.00 ± 0.17	5	23	8.51 ± 3.48
Amputation	206	1,004	0.86 ± 0.06	0	N/A	N/A
In-hospital mortality	2,355	11,507	9.89 ± 0.22	6	30	10.88 ± 4.25

See Table 1 legend for expansion of abbreviations.

TABLE 3] Multiple Logistic Regression: Thrombosis in HIT Patients Treated With IVIg Compared With Those Not Treated With IVIg

Outcome	aOR [95% CI]	*P*
Arterial Thrombosis	0.766 [0.342-1.714]	.5169
Venous Thrombosis	0.922 [0.492-1.729]	.8009

See Table 1 legend for expansion of abbreviations.

A large meta-analysis of 31 randomized controlled trials of IVIg treatment found no evidence of increased thrombosis risk among IVIg-treated patients but cautioned that care should be taken in extrapolating their results to patients with higher baseline risks of thromboembolism[11] (such as the HIT patient population we examined). In this study, analysis of HIT discharge data from the NIS over a more than 6-year period did not suggest an increase in incidence of venous or arterial thrombosis in patients who received IVIg compared with those who did not receive the drug. The number of IVIg-treated HIT discharges in our study (weighted) was more than 10-fold higher than the number of confirmed/possible HIT patients treated with IVIg that have been published (n = 27).[5] This "big data" approach eliminates potential positive-result bias that can confound interpretation of case report publications. However, this study has important limitations. The diagnosis of HIT can be challenging to verify; however, in a recent study,[1] the diagnostic sensitivity and specificity of the heparin- induced thrombocytopenia ICD-9-CM code were determined to be 90.9% (57.1-99.5, 95% CI) and was 94.4% (91.1-96.6), respectively. Because of limitations of the NIS dataset, the extent to which non-heparin anticoagulants contributed to outcomes such as bleeding, the timing of outcomes (eg, thrombosis) in relation to treatment (IVIg) and whether IVIg increased thrombotic risk in some patient subsets while decreasing it in others cannot be defined. Also, despite the use of data from a multi-year period, only a handful of HIT patients treated with IVIg were noted. Hence, results should be interpreted with caution.

TABLE 4] Conditional Logistic Regression of Matched Data: Thrombosis in HIT Patients Treated With IVIg Compared With Those Not Treated With IVIg

Outcome	OR [95% CI]	*P*
Arterial thrombosis	0.875 [0.392-1.953]	.744
Venous thrombosis	0.867 [0.481-1.562]	.634

See Table 1 legend for expansion of abbreviations.

In summary, this population-based study supports the safety of IVIg use in HIT, but a prospective randomized treatment study may be necessary to provide conclusive information on thrombotic and other risks associated with administration of this off-label therapy in HIT patients.

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