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Original Article

Splenectomy in patients with immune (idiopathic) thrombocytopenic purpura (ITP) appears to be protective against developing aortic valve disease

Fathima Haseefa[1], Mohammad Reza Movahed[1,2], Mehrtash Hashemzadeh[3], Mehrnoosh Hashemzadeh[1,4]

[1]University of Arizona, College of Medicine, Phoenix, AZ, USA; [2]University of Arizona Sarver Heart Center, Tucson, AZ, USA; [3]Long Beach VA Healthcare System, VA, USA; [4]Pima College, Tucson, AZ, USA

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Abstract: Background: Immune thrombocytopenia (ITP) has been shown to be independently associated with aortic valve disease (AVD). However, whether ITP patients who have undergone splenectomy are also at increased risk for AVD has not been researched. The goal of this study was to evaluate any association between AVD and splenectomy in patients with ITP. Method: We used the Nationwide Inpatient Sample from 2005 to 2014 as 10 consecutive years randomly selected. Using ICD-9 codes for AVD, ITP, and splenectomy, a total of 108,434 patients were identified with ITP, 4,282 of which had undergone splenectomy. We performed uni- and multivariate analysis adjusting for baseline characteristics. Results: Univariate analysis revealed a significantly lower rate of AVD in ITP patients with splenectomy compared to no splenectomy in 2007, 2009, and 2010 with a trend of this association during the other years. For example, in 2007, 0.6% of ITP patients with history of splenectomy had AVD versus 2.0% of ITP patients without splenectomy (OR, 0.29; 95% CI, 0.09-0.91; $P = 0.02$). Similarly, in 2010, 0.2% of ITP patients with history of splenectomy had AVD versus 1.9% of ITP patients without splenectomy (OR, 0.13; 95% CI, 0.02-0.92; $P = 0.02$). After adjusting for age, gender, race, diabetes, hypertension, hyperlipidemia, and tobacco use, we confirmed that ITP patients with splenectomy have no association with prevalence of aortic valve disease (2005: OR, 0.48; 95% CI, 0.18-1.30; $P = 0.15$; 2014: OR, 0.88; 95% CI, 0.36-2.16; $P = 0.77$). Conclusion: Based on a large inpatient database, our previous finding of ITP patients' association with AVD is only present in patients without splenectomy, and splenectomy appears to exert a protective effect on developing aortic valve disease in ITP patients, warranting further investigation.

Keywords: Splenectomy, immune thrombocytopenic purpura, idiopathic thrombocytopenic purpura, ITP, thrombocytopenia, platelet disorders, aortic valve disease, aortic stenosis

Introduction

Immune thrombocytopenia, previously known as idiopathic thrombocytopenic purpura (ITP), is an autoimmune disorder that presents with excessive bleeding and easy bruising due to acquired thrombocytopenia after excluding other causes [1]. Studies have identified the primary pathophysiological mechanisms as autoantibody production against platelet glycoproteins and cytotoxic T-cell mediated platelet destruction, along with impaired megakaryocyte maturation, reduced platelet production, and phagocytosis by macrophages [2]. The annual incidence of ITP in the United States is approximately 6.6 per 100,000 adults with peak incidence at 20 to 50 years of age; the prevalence is approximately 23.6 per 100,000 adults [3].

The mainstay of treatment for ITP is immunosuppression using glucocorticoids to decrease the destruction of platelets. Approximately one-third of cases can achieve remission with glucocorticoids [4]. Patients who are not steroid responsive may undergo a partial or total splenectomy since the spleen is the primary site for removal of antibody-coated platelets [5]. Additionally, splenectomy would remove splenic lymphocytes that may be responsible for producing the autoantibodies [6]. Splenectomy has been shown to achieve remission in about 66

percent of ITP cases in adults, albeit with potential risk of surgical complications and increased susceptibility to infections [5]. ITP may persist or recur post splenectomy due to platelet clearance in other tissues such as lymph nodes, bone marrow, and liver [7]. Newer second-line therapy options include rituximab, an anti-CD20 chimeric monoclonal antibody that targets B cells for elimination, and thrombopoietin receptor agonists which stimulate the production of megakaryocytes and platelets. However, these pharmacologic treatments have lower long-term remission rates than splenectomy [8].

We previously found higher rates of aortic valve disease (AVD) in adults with ITP overall based on a retrospective analysis of the Nationwide Inpatient Sample (NIS) from 2002 to 2011 [9]. Possible explanations include endothelial damage by autoantibodies via antigenic mimicry, downregulation of factors inhibiting calcification due to infiltration of inflammatory cells, and resistance to fibrinolysis [10-13]. However, there is a lack of research on whether splenectomy affects the risk of AVD in ITP patients. A retrospective cohort study by Chandan et al. reported increased risk of developing cardiovascular disease (CVD) including ischemic heart disease, heart failure, and stroke/transient ischemic attack (TIA) in ITP patients who underwent splenectomy compared to those who did not (adjusted IRR, 1.69; 95% CI, 1.22-2.34; $P = 0.001$) [14]. Atherosclerosis and the development of CVD as defined by Chandan et al. share similarities with AVD, specifically aortic stenosis. This study aims to identify any association between AVD and ITP patients who underwent splenectomy versus ITP patients without splenectomy in order to evaluate the role of splenectomy regarding presence of AVD in this population.

Methods

We used the Nationwide Inpatient Sample (NIS), which was developed for the Healthcare Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). This all-payer inpatient database is sampled from U.S. hospitals that comprise 97 percent of discharges nationwide. It is publicly available for researchers to analyze a variety of clinical and nonclinical variables including primary and secondary diagnoses and procedures and is exempt by the Institutional Review Board (IRB).

We utilized the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) codes for AVD (424.1), ITP (287.31 and 287.3), and splenectomy (41.43, 41.5). We used the NIS database and randomly selected 10 consecutive years for our study, 2005 to 2014. Inclusion criteria were as following: Patients ≥ 18 years of age and patients with a diagnosis of ITP based on the ICD-9 coding. Patients were divided into two groups based on their splenectomy status. Excluded were patients less than 18 years of age without an ITP diagnosis.

Using the Statistical Package for Social Sciences (SPSS) software, we performed univariate analysis with the chi-square test to evaluate any association between AVD and ITP patients with splenectomy versus ITP patients without splenectomy. We then performed multivariate logistic regression analysis adjusting for age, gender, race, type 2 diabetes (250.00 and 250.02), hypertension (401.0, 401.1, and 401.9), hyperlipidemia (272.0, 272.1, 272.2, and 272.4), and tobacco use (305.1, 305.10, 305.11, 305.12, 305.13 and V158.2). Odds ratios and 95% confidence intervals (95% CI) were calculated. Two-sided *P*-values less than or equal to 0.05 were considered as statistically significant.

Results

This study included a total of 108,434 adults with ITP from the 2005 to 2014 database, 4,282 of which had undergone splenectomy. In the ITP and no splenectomy group, 2,214 patients (2.13%) had AVD vs. 35 patients (0.82%) in the ITP and splenectomy group. Our previously published data showed that ITP patients have a higher association with AVD (OR, 1.35; 95% CI, 1.16-1.57; $P < 0.001$) [9]. Using univariate analysis separating ITP patients with and without splenectomy showed that AVD was significantly lower in ITP patients who had a splenectomy compared to ITP patients without splenectomy in 2007, 2009, and 2010 with a trend of this association during the remaining years (**Table 1**; **Figure 1**). For example, in 2007, AVD was present in 0.6% of ITP patients with history of splenectomy versus 2.0% of ITP patients without splenectomy (OR,

Table 1. Prevalence of AVD among ITP patients with and without splenectomy, 2005 to 2014

Year	ITP & Splenectomy	ITP & No Splenectomy	*p*-value	Odds Ratio (95% CI)
2005	1.0%	2.2%	0.06	0.47 (0.21-1.06)
2006	1.0%	1.7%	0.28	0.58 (0.23-1.40)
2007	0.6%	2.0%	0.02	0.29 (0.09-0.91)
2008	0.7%	1.8%	0.09	0.38 (0.12-1.19)
2009	0.5%	2.1%	0.01	0.22 (0.05-0.88)
2010	0.2%	1.9%	0.02	0.13 (0.02-0.92)
2011	0.7%	2.0%	0.05	0.34 (0.11-1.06)
2012	1.1%	2.5%	0.12	0.43 (0.16-1.16)
2013	0.9%	2.4%	0.09	0.38 (0.12-1.17)
2014	1.7%	2.6%	0.57	0.67 (0.28-1.63)

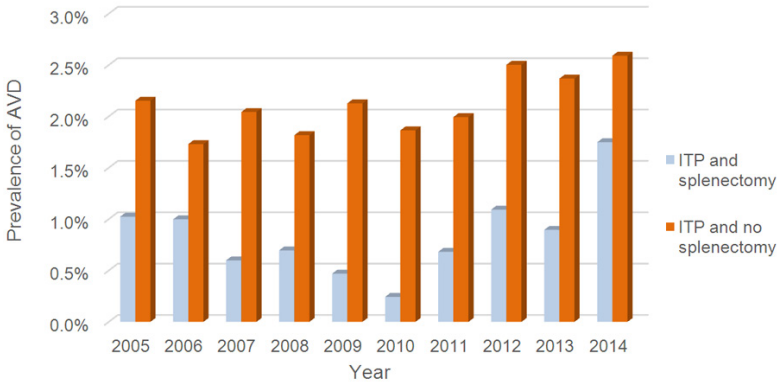

Figure 1. Prevalence of AVD among ITP patients with and without splenectomy over a 10-year period.

Table 2. Multivariate adjusted odds ratios evaluating any association between presence of AVD with ITP patients with splenectomy

Year	Odds Ratio	95% CI	*p*-value
2005	0.478	0.176-1.304	0.149
2006	0.499	0.157-1.586	0.239
2007	0.327	0.080-1.333	0.119
2008	0.408	0.129-1.287	0.126
2009	0.255	0.063-1.035	0.056
2010	0.159	0.022-1.140	0.067
2011	0.440	0.140-1.386	0.161
2012	0.547	0.201-1.487	0.237
2013	0.492	0.156-1.554	0.227
2014	0.876	0.355-2.160	0.774

0.29; 95% CI, 0.09-0.91; *P* = 0.02). Similarly, in 2010, AVD was present in 0.2% of ITP patients who had a splenectomy versus 1.9% of ITP patients without splenectomy (OR, 0.13; 95% CI, 0.02-0.92; *P* = 0.02). Based on univariate analysis mentioned above, we suspected that ITP patients with splenectomy should have no association with AVD. In order to study this hypothesis, we performed a multivariate analysis of only ITP patients with splenectomy and AVD throughout the 10-year period after adjusting for gender, age, race, tobacco use, hyperlipidemia, diabetes, and hypertension. The multivariate analysis confirmed that there is no association between ITP patient with splenectomy with aortic valve disease (**Table 2**). For example, in 2005, the adjusted odds ratio for AVD in ITP patients with splenectomy was 0.48 (95% CI, 0.18-1.30; *P* = 0.15). Similarly, in 2014, the adjusted odds ratio was 0.88 (95% CI, 0.36-2.16; *P* = 0.77).

Discussion

We previously published a study showing that ITP patients have a higher prevalence of AVD [9]. However, we included patients with ITP in that study regardless of their treatment status. The role of splenectomy in these patients was not known. In order to evaluate if splenectomy has any effect on the presence of aortic valve disease, we repeated our analysis of ITP patients with and without splenectomy. Interestingly, we found that only ITP patients without splenectomy had a higher association with aortic valve disease and not ITP patients with splenectomy. In multivariate analysis, ITP patients had no association with AVD in all 10 years studied. The analysis of this study of a

total of more than 100,000 patients (108,434) obtained from the 2005 to 2014 NIS database suggests that the presence of splenectomy is protective and prevents a higher prevalence of AVD in the entire ITP population.

The current literature on the effect of splenectomy on cardiovascular risk of any type in ITP patients is scarce. A 10-year cohort study by Thomsen et al. reported a 2.7-fold (95% CI, 1.1-6.3) increased risk of venous thromboembolism in patients splenectomized for ITP compared to their age-matched controls [15]. Similarly, the aforementioned retrospective cohort study by Chandan et al. showed a higher risk of developing ischemic heart disease, heart failure, and stroke/TIA in ITP patients who had a splenectomy than in ITP patients who did not (adjusted IRR, 1.69; 95% CI, 1.22-2.34; P = 0.001) [14]. Studies have reported elevated levels of procoagulant cell-derived microparticles (C-MPs) and significantly shortened activated partial thromboplastin time (aPTT) in ITP patients without a spleen [16]. Additionally, patients were found to have significant thrombocytosis beginning at 48 to 72 hours post splenectomy, gradually returning to normal levels over weeks to months [17, 18]. Without the spleen as a major clearance site, these C-MPs, platelets, and damaged erythrocytes may promote hypercoagulability and an increased risk of thromboembolic events [19].

This study is the first to assess the association of AVD risk and splenectomy in patients with ITP. Our findings suggest a possible protective effect from AVD for ITP patients who undergo splenectomy. The reason for this is unclear. Diehl et al. and other researchers have proposed that circulating platelet microparticles lead to activation of monocytes and leukocyte microparticles, and subsequent activation of endothelial cells in the pathogenesis of AVD based on flow cytometry studies in patients with severe aortic valve stenosis [19]. Thus, the significant elevation in C-MPs that has been observed in ITP patients post-splenectomy would be expected to be associated with increased rates of AVD [16]. Perhaps after splenectomy, the reduction in pro-atherosclerotic factors that may be associated with higher AVD risk in ITP patients at baseline outweigh the damage caused by C-MPs. There is evidence to suggest that splenectomy decreases the production of anti-platelet autoantibodies, which may result in less endothelial damage due to cross-reaction with endothelial cells in ITP patients post-splenectomy [10, 11]. Likewise, the reduction in inflammatory cells may allow upregulation of factors that inhibit calcification of the aortic valve leaflets [12].

Limitations

There are some limitations to this study. There may be inaccuracies in the ICD-9-CM coding used to identify primary and secondary diagnoses and procedures in the NIS database. Furthermore, the inpatient sample may not be fully representative of the general population. Future cohort and laboratory studies are needed to establish the protective effect of splenectomy against AVD in ITP patients and the possible mechanisms behind such effect.

Conclusion

Based on a large inpatient database, our previous finding of ITP patients' association with AVD is only present in patients without splenectomy, and splenectomy appears to exert a protective effect on developing aortic valve disease in ITP patients, warranting further investigation.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Mehrnoosh Hashemzadeh, University of Arizona, 6119 N. Pinchot Rd, Tucson, AZ 85750, USA. Tel: 949-374-1501; E-mail: mhashemz1@yahoo.com

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