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Symptomatic thromboembolic events in patients treated with intravenous-immunoglobulins: Results from a retrospective cohort study

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ABSTRACT

Aims: To estimate the incidence and predictors of symptomatic arterial and venous thromboembolic events (TEE) from intravenous immunoglobulin (IVIg) therapy according to its indications.
Methods: We performed a retrospective cohort study of patients seen at our institution and treated with IVIg over a 36-month period. Indications, comorbility and comedication associated with TEE were identified by a stepwise logistic regression analysis.
Results: Of 303 patients included with at least one infusion of IVIg over three years, TEE were identified in a total of 50 patients treated with IVIg, for an incidence of 16.9% (CI 95%: 13.0–21.6); 27 (54%) arterial (9.1%;CI 95%: 6.3–13.0%) and 23 (46%) venous TEE (7.8%; CI95%: 5.2–11.4%), overall mortality was 32%. Per indication there were more patients with autoimmune conditions, secondary immunodeficiency, dysimmune neuropathies, acute rejection of solid organ transplantation and sepsis. Patients with TEE were significantly older, were more likely to be men, they had more comorbid conditions; the doses of IVIg were high (589.4 mg/kg/day vs 387.0 mg/kg/day, $p < 0.001$) and differences in comedication were found. The stepwise logistic regression analysis retained high doses of IVIg (OR 3.03; CI 95%: 1.49–5.67) and diuretics therapy (OR 1.69; CI 95%: 1.06–3.97) when combined with the usual comorbid confounders.
Conclusions: The incidence of TEE from IVIg therapy remains high at one in six patients treated. The most remediable factor is a high daily IVIg load. Decreasing the daily IVIg dose together with carefully weighing diuretics therapy and comorbid risk factors may be the keys to saving lives.

Introduction

The reported incidence of adverse events from intravenous immunoglobulin (IVIg) therapy varies widely, from 1% to 81% of patients; [1] most studies report adverse events between 30% and 40% of the infusions [2]. Immediate adverse reactions following IVIg administration are usually mild and transient flu-like symptoms, changes in blood pressure and tachycardia [3,4]. These reactions improve or wane following a reduction in the flow rate of IVIg infusion and pretreatment with analgesic, nonsteroidal anti-inflammatory drugs, antihistamines or intravenous glucocorticoids [5]. Severe anaphylactic/anaphylactoid reactions following IVIg administration are rare [6]. The role of anti-IgA antibodies in causing anaphylaxis in IgA-deficient patients receiving IVIg therapy is still controversial [7]. Late adverse events may be severe: acute renal failure, aseptic meningitis, neutropenia, autoimmune hemolytic anemia, skin reactions, arthritis and pseudohyponatremia. Probably the most important of the late events are thromboembolic events (TEE) including myocardial infarction, cerebrovascular accidents, deep vein thrombosis, pulmonary emboli, central retinal vein occlusion and hepatic veno-occlusive disease [8–12]. In 2002 the FDA required updated package labeling to include a warning about the risk of thrombotic events [13]. In limited retrospective series, the incidence of thrombotic events varies from 3% [14] to 11.2%. [15] Some authors have described a higher risk with increasing age, hypertension and dyslipidemia [8] or vascular risk factors [16]. However, no study has attempted to determine the frequency and predictors of TEE with IVIg according to the indication and taking into account comedication. As a result of the persistent uncertainties, appropriate clinical risk-assessment and consideration of alternative treatments are currently inadequate.

We studied a retrospective cohort of patients who received IVIg over a 3-year period. Our objective was to estimate the incidence of IVIg-

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related TEE in our patients, as well as to attempt to establish the predictors and differential characteristics between venous and arterial events.

Methodology

Study Design

This was an observational, retrospective cohort study of patients treated with IVIg. We identified patients who had a TEE within 30 days of IVIg treatment completion. The needed sampling was determined to be 280 patients (margin of error ± 10%, 95% CI). The sample size for logistic regression showed that accepting alpha risk of 0.05 and a beta risk of 0.2, for a proportion of events between 10% and 16%, between 192 and 271 subjects were needed to recognize as statistically significant odd ratio greater than or equal to 1.7 [17]. Information was collected according to protocol. A case report form was completed with these details. Approval was obtained from the Institutional Review Board at La Paz University Hospital, protocol PI-1090.

Setting and Participants

This study was conducted at La Paz University Hospital in Madrid, Spain, a tertiary-care teaching hospital with 1,365 care beds. It serves a population of 787,000, plus 550,000 additional children (reference population) and 1,089,472 additional women (gynecology and obstetrics). In addition, it is a national referral hospital for certain clinical situations (Immunodeficiency syndromes, critically burned patients, solid and alogenic organ transplantation, pediatric ophthalmology, pediatric hemato-oncology), but we cannot attribute a precise reference population for those conditions. We identified patients who had a prescription for IVIg between January 1, 2008, and December 31, 2010.

Study Outcomes

We examined the following diagnoses and codes for venous thromboembolic disease: deep vein thrombosis (ICD-9-CM codes: 453.40 to 453.42) pulmonary embolism (415.19, 415.11 and 415.12), acute myocardial infarction (410.10 to 410.92), mesenteric thrombosis and embolism (557.0), arterial embolism and thrombosis (444.0 to 444.9), embolism and thrombosis portal (452), embolism and thrombosis of intracranial venous sinus (325), venous complications in pregnancy and puerperium (325), embolism or venous thrombosis in unspecified vein (453.9), other stroke and venous thrombosis (634.6, 635.6, 636.6, 637.6, 638.6 and 639.6), puerperal pulmonary embolism (673.2), thrombus (thromboembolism) following infusion, perfusion or transfusion (999.2), occlusion of central retinal vein (362.35) branch retinal vein (362.36). Diagnoses and codes of arterial thromboembolic disease: acute stroke (ICD-9-CM codes: 434.9X to 434.0X), transient ischemic attack (435.9), acute coronary syndrome (411.0 to 411.89), acute arterial ischemia (435.0 to 435.9), acute myocardial infarction (410.10 to 410.92), cardiogenic shock (785.51, as secondary diagnosis) and cardiorespiratory arrest (427.5). We included data for all study outcomes through January 31, 2011. The length of follow-up in all analyses was until discharge, transfer or decease after the index date.

Data Sources

We obtained IVIg prescriptions from the database of the hospital pharmacy department between January 1, 2008 and December 31, 2010. Clinical records were used to confirm the administration of IVIg and the clinical indication, the presence of TEE, its type, timing of confirmatory diagnostic tests performed and the outcome. Patients out of the reference population at the time of TEE were excluded from the cohort of IVIg. A review of records also noted the presence of the following risk factors for TEE: gender, age, comorbidity and comedication. The time of TEE in relation to the IVIg course of treatment was ascertained. The most frequent comedication of patients with TEE was compared with patients without TEE at the moment of onset. Drugs were categorized by Therapeutic Subgroups using the Anatomical Therapeutics Chemical (ATC) classification system.

Statistical Analysis

We describe the characteristics of the treatment groups on the index date by presenting the frequency distribution for categorical variables and the medians and ranges for continuous variables. The incidence rate of TEE in patients treated with IVIg was calculated by dividing the number of TEE by the number of patients treated with an IVIg during the period of the study. Uncertainty of estimation was assessed by calculation of the two-sided Wald 95% confidence interval. The χ^2-test or Fisher's exact test was performed for all categorical variables, and Student's t-test and the Mann Whitney test were employed, as appropriate, for continuous variables. Variables associated with a TEE at $p \leq 0.10$ in the univariate analysis were entered into a stepwise logistic regression model to obtain estimates effects; the rate of events per variable was at least 10. The age of adult patients and the dose of IVIg were dichotomized at the media for the analysis. We used commercially available software (SPSS, version 17, IL, US) for all statistical analyses.

Results

General Background

We identified 591 patients with at least one infusion of IVIg over three years. They were 49.8% females. The mean age of the patients was 41 years (SD, 27; range 0 to 94 years). Of them, 303 patients received their community-based health care from this hospital. Of those, TEE were identified in a total of 56 patients treated with IVIg; 6 patients were excluded because the TEE was before IVIg treatment and 50 patients had a TEE after IVIg therapy, representing an incidence of 16.9% (CI95%:13.0 to 21.6); 27 (54%) arterial TEE (9.1%;CI95%:6.3 – 13.0%) and 23 (46%) venous TEE (7.8%;CI95%:5.2 – 11.4%), overall mortality was 32% of cases.

Case Reports

Out of 50 affected patients, the mean age of affected patients was 60.6 years (SD 28.2), 66% males. The outcome of the TEE was fatal in 16 (32%) patients. TEE occurred with 3 different IVIg brands, all except one, at 5% concentrations. Arterial thromboembolic events included acute myocardial infarction (8 cases), acute stroke (5 cases), cardiorespiratory arrest (5 cases), cardiogenic shock (4 cases), acute arterial ischemia (3 cases), and transient ischemic attack (2 cases). Venous thrombosis events included deep vein thrombosis (11 cases), pulmonary embolism (7 cases), IVC thrombosis (3 cases), mesenteric thrombosis and embolism (2 cases). A summary of the demographic characteristics and indications for IVIg treatment for patients without TEE compared to those with TEE are shown in Table 1. Patients with TEE were significantly older, more were men, and the doses of IVIg were higher (589.4 mg/kg/day vs 387.0 mg/kg/day, $p < 0.001$). Per indication there were more patients with autoimmune conditions, secondary immunodeficiency, dysimmune neuropathies, acute rejection of solid organ transplantation and sepsis (Table 1). Significant risk factors for TEE included atrial fibrillation, coronary disease, diabetes, dyslipemia, hypertension, immobility neoplasia, recent surgery, solid organ transplantation and having four or more risk factors (Table 2). Comedication with diuretics, immunosuppressants, monoclonal antibodies and prepared hematinics was significant more frequent in TEE patients; treatment with antithrombotic and platelet aggregation inhibitors was less frequent in TEE patients (Table 2). Arterial TEE were documented in clinical records after a median of 1 day (0-20 days) after the