Safety of Endovascular Intervention for Stroke on Therapeutic Anticoagulation: Multicenter Cohort Study and Meta-Analysis

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Introduction: Intravenous (IV) tissue plasminogen activator (tPA) is contraindicated in therapeutically anti-coagulated patients. Such patients may be considered for endovascular intervention. However, there are limited data on its safety. *Patients and Methods:* We performed a multicenter retrospective study of patients undergoing endovascular intervention for acute ischemic stroke while on therapeutic anticoagulation. We compared the observed rate of National Institute of Neurological Disorders and Stroke defined symptomatic intracerebral hemorrhage (sICH) with risk-adjusted historical control rates of sICH after IV tPA using weighted averages of the hemorrhage after thrombolysis (HAT) and Multicenter Stroke Survey (MSS) prediction scores. We also performed a metaanalysis of studies assessing risk of sICH with endovascular intervention in patients on anticoagulation. *Results and Discussion:* Of 94 cases, mean age was 73 years and median National Institutes of Health Stroke Scale was 19. Anticoagulation consisted of warfarin (n = 51), dabigatran (n = 6), rivaroxaban (n = 13), apixaban (n = 1), IV heparin (n = 19), low molecular weight heparin (n = 3), and combined warfarin and IV heparin (n = 3). sICH was seen in 7 patients (7%, 95% confidence interval 4-15), all on warfarin. Predicted sICH rates for the cohort based on HAT and MSS scoring were 12% and 7%, respectively. Meta-analysis of 6 studies showed no significant difference in sICH between patients undergoing endovascular intervention on anticoagulation and comparator groups. *Conclusions:* Endovascular intervention in subjects on therapeutic anticoagulation appears reasonably safe, with a sICH rate similar to patients not on anticoagulation receiving IV tPA. **Key Words:** Endovascular treatment—anticoagulation—hemorrhage—ischemic stroke—safety—meta-analysis.

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Introduction

Therapeutic anticoagulation is considered an exclusion criterion for intravenous (IV) tissue plasminogen activator (tPA) for acute ischemic stroke. This is based on concerns for an increased risk of intracerebral hemorrhage (ICH) in patients receiving concomitant thrombolytic and anticoagulant therapy. As all of the major randomized trials of tPA for acute ischemic stroke excluded patients on therapeutic anticoagulation, there are few high-quality data on the relative risks and benefits of thrombolytic therapy in patients on anticoagulation. Mechanistically, post-thrombolysis ICH may occur due to 3 major mechanisms: (1) direct impairment of hemostasis due to the thrombolytic and coagulopathic effect of tPA, (2) recanalization of an occluded artery leading to reperfusion injury, and (3) direct disruption of blood–brain barrier integrity by tPA.[1] In any scenario, the presence of therapeutic anticoagulation might further increase the risk of intracranial bleeding; however, the degree of increased risk might vary substantially.

In the absence of pharmacologic thrombolytic therapy, anticoagulant therapy alone increases the risk of ICH compared with placebo or aspirin, but this risk is relatively low in absolute terms. In pooled analysis of parenteral anticoagulation trials, the risk of symptomatic intracerebral hemorrhage (sICH) was increased from .4% with placebo or aspirin to 1.4% with anticoagulation.[2] As many patients included in these studies likely had spontaneous reperfusion during the period of anticoagulation, the interaction of reperfusion and anticoagulation may not be associated with a dramatic excess risk of ICH. Recent data have established robust benefit for endovascular mechanical thrombectomy for patients with acute ischemic stroke, with a number needed to treat to reduce disability of just 2.6 despite a rate of major parenchymal ICH of 5.1%. Given the magnitude of this overall clinical benefit, the small incremental risk of anticoagulant therapy on ICH might be substantially outweighed by the benefit of early reperfusion.[3] However, if a substantial portion of the risk of post-thrombolysis ICH is due to reperfusion injury as opposed to impairment of hemostasis, then the presence of therapeutic anticoagulation might prohibitively increase the risk of ICH even with mechanical thrombectomy.

In this regard, several small case series have suggested that the risk of endovascular intervention is not increased in patients with acute ischemic stroke on therapeutic anticoagulation. The goals of the present study were to examine the risk of sICH following endovascular intervention in a multicenter cohort and to perform a systematic review and meta-analysis of all available studies to better estimate the risk of bleeding in this population.

Methods

Observational cohort data from 5 centers were pooled for this study. Centers reviewed internal databases to identify all endovascular cases for treatment of acute ischemic stroke in patients on therapeutic anticoagulation for the time periods accessible within their individual databases (Supplemental Table S1) and retrospectively retrieved data to complete a standardized case report form. Therapeutic anticoagulation was defined as current use of warfarin with an international normalized ratio (INR) greater than or equal to 1.7, IV heparin with an elevated partial thromboplastin time (PTT), full-dose low molecular weight heparin (LMWH), or current use of a direct oral anticoagulant (DOAC) (dabigatran, apixaban, or rivaroxaban). Patient selection for and type of endovascular treatment were performed according to local clinical practice. The primary outcome measure was sICH defined using National Institute of Neurological Disorders and Stroke (NINDS) criteria. Radiographic classification of hemorrhage type was also recorded by each site based on local review of imaging.

The rate of sICH in patients on anticoagulation undergoing endovascular therapy was compared with the predicted risk for patients receiving IV tPA not on anticoagulation using the Multicenter Stroke Survey (MSS) and the hemorrhage after thrombolysis (HAT) risk prediction scores. These scores are designed to predict risk of sICH following IV tPA, and incorporate clinical and diagnostic testing features known to be associated with hemorrhage risk after thrombolysis. We generated weighted averages for ICH risk for each score using the absolute hemorrhage rates per stratum reported in the original publications of both scores.[4,5] Global Use of Strategies to Open Occluded Arteries criteria were used to define systemic bleeding as mild, moderate, or severe.[6] Each institutional protocol was approved by the local institutional review board at each site.

Systematic Review and Meta-Analysis

We searched PudMed, Ovid Medline, and EMBASE from January 1, 2000 to September 15, 2016 using the following search terms: "Endovascular therapy," "Intra-arterial therapy," "Anticoagulation," and "Ischemic Stroke." We also hand-searched reference lists of identified studies for additional references. We extracted data from each publication regarding study methods, patient characteristics, definition of sICH, and number of patients and outcomes. A structured data abstraction form was used, and 2 authors abstracted data from the studies. Studies were included if patients underwent endovascular therapy and were on full-dose therapeutic anticoagulation, defined as INR $\geq$ 1.7 in the setting of a vitamin K antagonist (VKA), IV heparin with an elevated PTT, full-dose LMWH, or current use of a DOAC, and a comparison group was included. For subjects using DOACs, we did not exclude subjects based on coagulation test results. We included patients undergoing endovascular intervention of any type (mechanical or pharmacologic) and regardless of prior