Review Article

Safety of Recanalization Therapy in Patients with Acute Ischemic Stroke Under Anticoagulation: A Systematic Review and Meta-Analysis

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Background: Intravenous thrombolysis treatment (IVT) and endovascular therapy (EVT) have been proved as fist-line beneficial option for eligible patients who have acute ischemic stroke (AIS) with major safety concern of symptomatic intracranial hemorrhage (sICH). Unfortunately, the emergency management of patients with AIS taking vitamin K antagonists and with international normalized ratio higher than 1.7 or taking new oral anticoagulants (NOACs) represents a great challenge. We aim to comprehensively determine the safety of EVT in patients under prior-stroke anticoagulants and IVT in patients under NOAC use. *Methods:* Clinical researches published in the Embase, PubMed, and Cochrane Library electronic databases up to December 2017 were identified for analysis. Subgroup and sensitivity analyses were also conducted to evaluate the robustness of the conclusions. *Results:* Overall, 9 studies involving 3885 patients met the inclusion criteria. The rate of sICH (risk ratio [RR] = .94, 95% CI = .61-1.47, P = .799), mortality (P = .495), and recanalization (P = .655) after EVT did not differ between patients under and those who were not under anticoagulants, although patients under anticoagulants were less likely to achieve good functional outcome (P < .001) than those who were not. Moreover, prior NOAC therapy was not significantly associated with increasing sICH in patients with AIS after IVT (RR = .79, 95% CI = .41-1.53, P = .492). *Conclusions:* Patients under anticoagulation appear to be safe after EVT with relatively lower rate of good outcome; furthermore, prior NOAC therapy was not associated with an increasing sICH rate after IVT. This offered a practical information to select appropriate therapeutic strategies for patients under anticoagulation, although the level of evidence seems to be quite shaky. **Key Words:** Stroke—anticoagulation—recanalization therapy—safety.

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Introduction

Atrial fibrillation (AF) is a serious risk factor for ischemic stroke,[1] and accounts for 25%-40% of all large vessel occlusion strokes.[2] To decrease the incidence of stroke in patients with AF, anticoagulant therapy with vitamin K antagonists (VKAs) or new oral anticoagulants (NOACs) like dabigatran, rivaroxaban, edoxaban, and apixaban[3-5] are essential. Despite anticoagulation, 1.11%-3.24% of patients with AF may still develop

thromboembolic events annually.[6] Furthermore, intravenous thrombolysis treatment (IVT) with alteplase is currently an effective clot-eliminating treatment for acute ischemic stroke (AIS), although it carries a risk of life-threatening symptomatic intracranial hemorrhage (sICH) ranging from 5% to 7% in certain conditions.[7,8] However, because of the increased bleeding risk in patients pretreated with VKA, the American Stroke Association guidelines suggested that IVT is formally contraindicated if international normalized ratio (INR) is higher than 1.7 in patients presenting within 3 hours from symptom onset and in all patient with AIS regardless of INR during the time window of 3-4.5 hours,[9] whereas the European Stroke Organization guidelines discourage IVT in patients treated with VKA regardless of INR.[10] Recently, with the advent of endovascular therapy (EVT), it has been a beneficial option for patients who have contraindications of IVT to have local thrombolytic therapy or mechanical thrombectomy. Unfortunately, there is lack of information on whether patients previously under VKA anticoagulant with elevated INR or patients taking NOAC allow the use of EVT in recent guidelines.[2,10] To date, no randomized controlled trial has been conducted but only several small-scale observational studies have been reported to evaluate the safety of EVT in patients with AIS under anticoagulation.[11-18] Whether prior anticoagulant therapy additionally increased the risk of bleed, unfavorable outcome, and mortality after EVT for stroke is still largely unclear and controversial to our knowledge.

NOACs have been validated in phase III clinical trials to at least match the efficacy of VKA with a significant superiority in safety, leading to their exponentially increasing use.[3,4] However, it remains uncertain how patients with AIS while taking NOACs should be treated. Some studies demonstrated devastating sICH event after IVT, while others showed safe thrombolysis in patients with AIS on NOAC in limited evidence of 29 case reports and 2 cohort studies.[19,20] In addition, current guidelines recommend that only patients who have taken NOAC beyond 48 hours of onset or have entirely normal coagulation tests are candidate for IVT (Class III, Evidence C).[21] Nevertheless, NOAC-specific coagulation assays are more complex with limited availability and the time of last dose may not be a reliable indicator of coagulation activity due to renal impairment, older ages, or concomitant use of P-glycoprotein inhibitors, and even do not obtain the time of receiving drugs. This could result in withholding or denying IVT in otherwise eligible patients who may eventually benefit from timely IVT.

In light of aforementioned uncertainty, we therefore pooled all results of observational studies available and conducted a substantial meta-analysis to evaluate the safety of EVT in patients under prior stroke anticoagulant therapy and IVT in patients with NOAC use.

Methods

We conducted our systematic review and meta-analysis according to the Preferred Reporting Item for Systematic Reviews and Meta-analysis[22] guideline.

Search Strategy

Potential relevant studies were identified by systematically searching PubMed, Embase, and Cochrane Library from inception up to December 2017 without language restriction. The keywords such as "endovascular treatment", "IVT," and "anticoagulants" in combination with "stroke" were searched across all databases (details of search strategies are shown in Supplementary Table S1). Conference abstract and reference lists of available records identified in the initial publications were also manually searched to avoid omitting relevant researches.

Study Selection

The inclusion studies in present meta-analysis met all the following criteria: (1) cohort study focus on the comparison of patients with AIS who underwent EVT (pharmacologic or mechanical or both) in receiving prior-stroke full dose anticoagulant therapy (defined as IV heparin with elevated partial thromboplastin time, full dose low molecular weight heparin, VKA with INR >1.7 or regardless of INR if the study was conducted in Europe, a NOAC regardless of coagulation test) with that in control group, or comparing IVT in patients with and without NOAC; (2) adults (>18 years) were diagnosed with ischemic stroke in original study; and (3) the study reported available safety outcome.

The following exclusion criteria were applied for subsequent analysis: (1) editorial, case report, systematic review, meta- or pool analysis, letters to the editors, conference abstract, studies on animals model, basic science studies; (2) repeated population or article with overlapping data; and (3) unable to extract relevant data.

Outcome Measure

The primary outcome was safety outcome (sICH), and additional outcome was good functional outcome at 3 months, mortality at 3 months, and arterial recanalization. sICH was defined according to the criteria used in the original studies. Good functional outcome at 3 months was defined as a modified Rankin Score of 0-2 at 3 months after stroke onset. Recanalization was defined as patients with any thrombolysis or mechanical therapy, had a Thrombolysis In Myocardial Infarction in myocardial ischemic grades 2b or 3 by computed tomography or magnetic resonance imaging or digital subtraction angiograph scans.