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REVIEW

Anticoagulation for the Acute Management of Ischemic Stroke

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Few prospective studies support the use of anticoagulation during the acute phase of ischemic stroke, though observational data suggest a role in certain populations. Depending on the mechanism of stroke, systemic anticoagulation may prevent recurrent cerebral infarction, but concomitantly carries a risk of hemorrhagic transformation. In this article, we describe a case where anticoagulation shows promise for ischemic stroke and review the evidence that has discredited its use in some circumstances while showing its potential in others.

INTRODUCTION

A 43-year-old man with diabetes mellitus presented to the emergency department with 5 hours of aphasia. Physical exam was notable for 2+ pitting lower extremity edema extending above the knee, an S3 gallop, and expressive aphasia. Magnetic resonance imaging (MRI†) revealed a subacute infarct in the distribution of the left middle cerebral artery (MCA). Transthoracic echocardiography demonstrated global hypokinesis, a left ventricular (LV) ejection fraction of 20 percent, and a large, pedunculated, 2.2 x 2.9cm, mobile thrombus within the LV. Cardiology consultants recommended anticoagulation to prevent recurrent embolism of a high-risk intracardiac

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†Abbreviations: AF, atrial fibrillation; CI, confidence interval; LV, left ventricle; MRI, magnetic resonance imaging; MCA, middle cerebral artery; MI, myocardial infarction; OR, odds ratio.

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thrombus and a potentially catastrophic occlusion of a major blood vessel. However, the neurology service opposed anticoagulation due to concern that it may precipitate hemorrhagic transformation of the existing infarct.

TREATMENT OF ISCHEMIC STROKE

Optimal management of patients in the aftermath of ischemic stroke is an area of ongoing, active investigation [1-4]. Treatment strategies include intravenous thrombolysis, endovascular interventions, systemic anticoagulation, and antiplatelet therapy, among other pharmacologic and non-pharmacologic approaches. This review will focus primarily on the data and issues surrounding the use of heparin-based anticoagulants in acute ischemic stroke.

Researchers have studied the role of anticoagulation in ischemic stroke for more than 50 years, after autopsy analysis of basilar artery thrombi demonstrated an evolution in clots over time [5]. This, along with our conception of the pathogenesis of thrombotic arterial occlusion, suggested that early anticoagulation for ischemic stroke may likewise allow for endogenous mechanisms of thrombolysis to proceed unopposed, preventing clot propagation and even hastening its resolution and tissue reperfusion [6,7]. Despite this, anticoagulation has not shown benefit as a treatment for acute cerebral ischemia [8-11]. Furthermore, treatment with heparin has failed to halt neurologic deterioration even in the subset of patients with progressing strokes [12].

There are significant risks associated with the use of anticoagulants in the immediate aftermath of ischemic stroke as well. In this setting, anticoagulation is a potential precipitant for hemorrhagic transformation, where it may allow for the typical peri-infarct processes of micro-extravasation through ischemic capillaries and blood brain barrier disruption to crescendo into significant parenchymal bleed and additional tissue necrosis [13,14]. In an effort to characterize this risk, Sandercock et al. conducted a Cochrane review of 16 trials of anticoagulation early after ischemic stroke that demonstrated a more than twofold increase in the rate of symptomatic intracranial hemorrhage among patients receiving anticoagulants: 1.44 percent compared to 0.48 percent of controls [15]. Consequently, a great deal of caution is exercised before anticoagulation is undertaken in the context of nascent cerebral infarction and, even then, only when a specific indication exists for its use.

PREVENTION OF ACUTE RECURRENCE

Ischemic stroke is a heterogeneous entity with diverse causes, including lacunar infarction, cerebrovascular stenosis, and emboli of sundry types, including fat, air, atheromata, septic vegetations, and calcific debris from left-sided heart valves in addition to thromboemboli originating from a variety of sources [16,17]. However, atrial fibrillation (AF) with thromboembolism from the left atrium or its appendage is one of the most common such contributors and is responsible for approximately 20 percent of all ischemic strokes [18]. AF may also result in multiple successive cardioemboli and repeat infarction. This risk of recurrent ischemic stroke in the wake of a first event is much higher than in comparable patients with AF. Data has varied between studies, but the risk of recurrent thromboembolic event within 14 days of a first ischemic stroke is estimated to be between 0.1 percent and 1.3 percent per day [19-23]. Although it is not helpful for treatment of the initial event, anticoagulation may prevent acutely recurrent cardioemboli [21]. It is this therapeutic use for anticoagulation that must be weighed against its potential for hemorrhagic transformation.

In order to capture its role after AF-associated stroke, a meta-analysis was conducted of early heparin administration after cardioembolic ischemic stroke. The analysis, which aggregated data from seven trials and 4,624 patients, 82.1 percent of whom had AF as the cause of their stroke, failed to show a net benefit for anticoagulation [21]. The pooled outcomes demon-

strated a significant increase in symptomatic intracranial hemorrhage (OR 2.89; 95% CI: 1.19 to 7.01) and no significant difference in the rate of death or disability (73.5 percent vs. 73.8 percent, OR 1.01; 95% CI: 0.82 to 1.24) [21]. The reduction in recurrent ischemic stroke was non-significant, but this may have been an issue of sample size, as the larger analysis by Sandercock of 21,605 patients revealed a significant reduction of recurrent ischemic strokes with early anticoagulation [15]. However, the Cochrane review of all ischemic strokes, like the meta-analysis of cardioembolic strokes, showed no clear association with respect to death and dependency [15]. Accordingly, there are no data to support a net benefit for early anticoagulation in this setting, and guidelines by the American Heart Association, American Stroke Association, and American College of Chest Physicians all recommend deferring anticoagulation in the management of ischemic stroke with AF [11,24].

TIMING

Despite the unanimity on postponing anticoagulation after ischemic stroke, there is little consensus on the specifics. A sizeable portion of patients with AF-associated stroke will require resumption or initiation of indefinite anticoagulation, which would ideally take place as soon as is safe. However, earlier anticoagulation may overlap with a period of vulnerability to reperfusion injury, theoretically predisposing to hemorrhagic transformation [13,14]. Empiric data on timing is scant, and head-to-head comparisons are lacking entirely. In this regard, there was notable variability among the trials incorporated in the Cochrane review by Sandercock. Half of the 16 included studies randomized patients within the first 48 hours after stroke, with the remainder enrolling at various time points over the ensuing 14 days [15]. The resulting chronologic window is broad enough to frustrate the identification of an ideal time for safe use of anticoagulants [15].

This uncertainly is canonized in the major society guidelines. The 2012 evidence-based practice guidelines of the American College of Chest Physicians, for example, recommend beginning anticoagulation "within 1 to 2 weeks" after stroke onset [24]. While there are certainly clinical parameters that may guide the decision-making process, including arterial blood pressure, age, cerebral vasculopathy, and infarct size (discussed below), their use to systemically stratify patients and guide the therapeutic calendar is poorly delineated. Thus, proper timing for the initiation of anticoagulation after ischemic stroke remains a question without clear answers.

INFARCT SIZE

Another important consideration regarding hemorrhagic potential is the size of existing ischemic infarct. More proximal vascular occlusions with larger infarcted territories incorporate greater quantities of friable vasculature and are thus considered higher risk for hemorrhagic transformation. Much of the data on size-dependent, iatrogenic hemorrhagic transformation has resulted from work on the post-stroke administration of fibrinolytics, but it is clear that the correlation exists for anticoagulants as well [25]. However, the mantra that infarcts greater than 1/3 MCA territory pose a particularly high risk of hemorrhagic transformation is specific to fibrinolytic use and thus extrapolation to settings of anticoagulation may not be prudent [26].

Other clinical guidelines surrounding infarct size and anticoagulation have arisen without the benefit of being substantiated by thorough investigation. One example is the clinical rule of the thumb to start anticoagulation 72 hours after a small infarct, 1 week after a moderate-sized infarct, and 2 weeks after a large infarct [27]. This is based on expert opinion, without a clear definition of what constitutes a small, moderate or large infarct [27]. The European Stroke Organization has adopted a single, size-based guideline, recommending infarction of 50 percent MCA territory or greater as a contraindication to anticoagulation [10]. However, it is not clear that there are any specific

data to support this threshold. As such, the role for measuring infarct territory to inform clinical decision-making regarding anticoagulation in individual cases of ischemic stroke is difficult to determine beyond the extremes of size.

LEFT VENTRICULAR THROMBI

In addition to left atrial thrombi forming in AF, cardioembolic stroke may result from thrombi within a hypokinetic LV, such as in acute myocardial infarction (MI), stress cardiomyopathy, or dilated cardiomyopathy [28-30]. Additionally, certain echocardiographic features portend a greater embolic risk. Intraventricular thrombi characterized by luminal protrusion or mobility on echocardiography undergo embolization in 41 percent and 60 percent of cases, respectively [31,32].

Anticoagulant use has been correlated with reduced incidence of mural thrombi after MI since the 1950s [33]. In cases of intraventricular thrombi, anticoagulation is also considered the best-established and initial therapy of choice for speeding resolution and preventing embolization [34-37]. While there has been some concern that dissolution of intracardiac thrombi may lead to segmentation and facilitate thromboembolism, the available data suggest that this is not the case [35,38]. In a meta-analysis of seven observational studies of mural LV thrombus after anterior wall MI, anticoagulation was associated with an 86 percent reduction in embolization [39]. More recent uncontrolled trials have demonstrated that low molecular weight heparin may be useful for the treatment of LV thrombi as well [40,41]. Despite this, concern has persisted that anticoagulation may not be aggressive enough for precarious thrombi at high risk of embolization [35,37]. However, in an uncontrolled case series of 23 consecutive patients with LV thrombi possessing the high-risk echocardiographic features described above, there were no documented embolic events during a course of intravenous unfractionated heparin pursued until resolution of thrombus or high-risk features [38]. Taken together, these data favor the use of anticoagulation to reduce systemic embolization of uncomplicated moderate and high-risk LV thrombi.

However, instances where acute cardioembolic stroke is complicated by residual intracardiac thrombus represent a perilous clinical situation. Whereas anticoagulation reduces the risk of repeat cardioembolism, it also promotes hemorrhagic transformation. Thus paradoxically, both treating and observing such a patient threaten further cerebral infarction. Moderating the embolic risk of an LV thrombus without treatment against the hemorrhagic risk of an infarct with anticoagulation is difficult and must be attempted without any head-to-head studies in the literature. In fact, major society guidelines explicitly avoid addressing this situation, given the absence of direct evidence [24]. However, an indirect comparison of complication rates from studies of isolated situations can be somewhat informative. According to the data from Sandercock et al., the pooled risk of intracranial hemorrhage in patients undergoing anticoagulation 1 to 2 weeks after ischemic stroke is 1.4 percent [15]. This is a seemingly low value compared to the embolic rates of high-risk LV thrombi, which exceed 50 percent [31]. However, the rates of cardioembolism were derived over much longer follow-up periods, sometimes as long as 188 days after precipitating MI [31]. The disparate follow-up periods, as well as the much smaller patient cohort used to determine embolic rates, caution against drawing premature conclusions [15,31]. If nothing else, the comparison further underscores the void of studies to directly evaluate the risk-benefit ratio of anticoagulation for this subpopulation of stroke patients.

SPECIAL SITUATIONS AND FUTURE DIRECTIONS

There are additional situations of high thrombotic risk after ischemic stroke where anticoagulation may be beneficial but for which there are little or no data. These include mechanical heart valves, carotid artery dissection, and large artery atherosclerotic stenosis [24,42,43]. An older study reported

improved neurologic outcomes 3 months after acute anticoagulation for ischemic stroke due to large artery stenosis, but this came after subgroup analysis and without a difference in the rate of recurrent stroke [44]. No subsequent data has emerged to support acute anticoagulation for ischemic stroke due to large artery atherosclerosis.

Regarding extracranial internal carotid artery dissection, a 2010 Cochrane review of observational studies failed to demonstrate appreciable differences in the rate of death, ischemic stroke, or the composite of death and disability between anticoagulation and antiplatelet therapy [45]. A more recent meta-analysis of treatment for ischemic strokes of this subtype yielded similar results [46]. As no controlled trials exist for the treatment of carotid artery dissection, there is also nothing to suggest that either anticoagulation or antiplatelet therapy is superior to placebo [45]. Experts differ on the recommended approach. The guidelines of the American Heart Association/American Stroke Association, for example, simply offer that 3 to 6 months of "antithrombotic" therapy is reasonable after extracranial internal carotid artery dissection, making no preference between anticoagulation and antiplatelet therapy [47].

Finally, mechanical heart valves are considered to be of such high thromboembolic risk that they, like intraventricular thrombi, are often excluded from clinical trials for acute ischemic stroke [24]. The result has been an underrepresentation of these scenarios in the literature and little information to guide clinicians. The recent report indicating higher rates of both thrombotic and hemorrhagic complications with dabigatran for mechanical heart valves underscores the difficulties involved in appropriately anticoagulating this set of patients [48].

Another relevant point concerning the use of anticoagulants is the diversity of agents currently available. This review has focused on the use of intravenous unfractionated heparin, low molecular weight heparins, and heparinoids, treating them as a homogenous group. However, in a sign that all agents should not be regarded as interchangeable, the Cochrane review by Sandercock noted significant heterogeneity among anticoagulants with respect to death or dependency [15]. Low molecular weight heparins were associated with a non-significant reduction in this outcome, whereas treatment with the direct thrombin inhibitor argatroban was associated with a trend toward harm [15].

Furthermore, we have left unaddressed issues regarding other anticoagulants, specifically vitamin K antagonists and novel oral agents. The body of literature is sufficiently large on warfarin for secondary stroke prevention that it is beyond the scope of the present work. To date, there is almost no data on the use of newer factor Xa inhibitors or direct thrombin inhibitors after ischemic stroke. This lack of evidence, coupled with different pharmacokinetics and lack of reversal agents, cautions against their use. Their rapid achievement of therapeutic drug levels is a marked departure from the trajectory of established agents, complicating comparisons with the above discussion on timing of anticoagulation resumption after ischemic stroke [27].

There are other horizons for the use of anticoagulants in ischemic stroke. In accordance with the protocol of the seminal NINDS trial, anticoagulation is currently contraindicated during the 24-hour period following intravenous administration of tissue plasminogen activator in acute ischemic stroke [11,49]. However, there is presently some interest in adjunctive use of anticoagulants with or immediately after fibrinolytics for ischemic stroke in order to maintain patency after arterial recanalization. Again, concern regarding hemorrhagic complications is present, and the net benefit of such an approach is not yet clear [11,50,51].

As highlighted above, additional research is warranted into anticoagulation for alternative causes of ischemic stroke. There is currently little interest in exploring therapy for large artery stenosis and carotid artery dissection, but the recent failure of dabigatran for thromboprophylaxis of mechanical valves may spur further investigation into acute treatment of valve-associated

thrombi in addition to long-term prophylaxis. Of course, experimental studies for the treatment of intraventricular thrombi, alone or in the context of ischemic stroke are long overdue as well.

Perhaps one of the greatest unanswered questions in this area is that of optimal timing for anticoagulation after AF-associated stroke. With an estimated 138,000 such strokes in the United Sates annually, it is surprising that we have no answer to an empirical question so central to these patients' clinical management [18]. Possibly a future trial will directly compare the administration of anticoagulation at two different time points after cardioembolic ischemic stroke. Alternatively, large patient databases may lend themselves to the stratification of ideal anticoagulation onset times based on such variables as infarct size, blood pressure, age, and known vasculopathy, among others.

CONCLUSIONS

The patient described in the above vignette experienced an ischemic stroke due to cardioembolism, with a residual large thrombus located in the LV. The thrombus' protrusion into the ventricular lumen and mobility placed it in the highest-known risk category for subsequent embolism, at 60 percent, per the available literature [31]. Despite this, no consensus could be reached regarding anticoagulation and he remained untreated until the fifth day, when the thrombus again embolized. Fortunately, the destination was not the carotid or vertebrobasilar circulation, but the peripheral vasculature, where it resulted in a partial occlusion of the posterior tibial artery without serious ischemic sequelae.

This case underscores much of the uncertainty and nuance regarding anticoagulation for ischemic stroke. It is relatively well established that anticoagulation is, on the balance, a deleterious therapy for the general category of ischemic strokes and potentially for the subset associated with large artery stenosis as well. However, this relationship is poorly understood for other subpopulations, chiefly cases of residual intraventricular thrombi, as in our patient, or mechanical valves, where thromboembolic risk is also particularly high. Further, there is simply insufficient data to draw conclusions on anticoagulation for internal carotid artery dissection. Finally, though available data indicate a net neutral profile for early anticoagulation in AF-associated ischemic strokes, the details of timing of onset and stroke size are crucial but incompletely understood variables. These issues, as well as adjunctive anticoagulation with fibrinolysis and the role of novel oral anticoagulants, merit the careful consideration of future investigators.

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