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Acute Management of Hemostasis in Patients With Neurological Injury

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ABSTRACT

Neurological injuries can be divided into those with traumatic and nontraumatic causes. The largest groups are traumatic brain injury (TBI) and nontraumatic stroke. TBI patients may present with intracranial hemorrhages (contusions, or subdural or epidural hematomas). Strokes are ischemic or hemorrhagic. In all these disorders, thrombosis and hemostasis play a major role. Treatment aims to either cease bleeding and/or restore perfusion. We reviewed hemostatic and thrombolytic therapies in patients with neurological injuries by MEDLINE and EMBASE search using various key words for neurological disorders and hemostatic therapies restricted to English language and human adults. Review of articles fulfilling inclusion criteria and relevant references revealed that, in patients with ischemic stroke, intravenous thrombolytic therapy with recombinant tissue plasminogen activator within 4.5-5 hours after onset of symptoms improves clinical outcome. In contrast, there are no hemostatic therapies that are proven to improve clinical outcome of patients with hemorrhagic stroke or TBI. In patients with hemorrhagic stroke who use vitamin K antagonist or direct oral anticoagulants, there is evidence that specific reversal therapies improve hemostatic laboratory parameters but without an effect on clinical recovery. In patients with hemorrhagic stroke or TBI who use concomitant antiplatelet therapy, there is evidence for harm of platelet transfusion. In patients with aneurysmal subarachnoid hemorrhage, tranexamic acid was shown to reduce rebleeding rate without improving clinical outcome. The effects of tranexamic acid in patients with TBI are still under investigation. We conclude that, in patients with ischemic stroke, thrombolytic therapy improves outcome when given within 4.5-5 hours. In hemorrhagic stroke and TBI, most hemostatic therapies improved or corrected laboratory parameters but not clinical outcome. Currently, in several trials, the effects of tranexamic acid are being studied of which the results are eagerly awaited. Because improving clinical outcome should be the goal of new therapies, we encourage to use clinical outcome scales as the primary outcome measure in trials that investigate effects of hemostatic therapies in patients with neurological injury.

Contents

Abbreviations: APT, antiplatelet therapy; CT, computed tomography; CTA, computed tomography angiography; DOAC, direct oral anticoagulant; DDAVP, desmopressin; FFP, fresh frozen plasma; ICH, intracerebral hemorrhage; INR, international normalized ratio; mRS, modified Rankin Scale; PCC, prothrombin complex concentrate; RBC, red blood cell; rt-PA, recombinant tissue plasminogen activator; SAH, subarachnoid hemorrhage; sICH, spontaneous intracerebral hemorrhage; TBI, traumatic brain injury; tICH, traumatic intracerebral hemorrhage; TXA, tranexamic acid; VKA, vitamin K antagonist.

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Causes of neurological injuries are varied and can be subdivided in traumatic and nontraumatic. Traumatic injury may cause hemorrhage or edema within the brain (contusions) and/or hemorrhage between the brain and skull (subdural or epidural hematomas). Nontraumatic injuries can be categorized into ischemic and hemorrhagic strokes. In patients with neurological injury, the maintenance or restoration of hemostatic balance plays an essential role. Therefore, treatment modalities to either restore blood flow by thrombolytics or prevent further hemorrhage with prothrombotic drugs is essential for neurological recovery.

Stroke is the most prevalent cause of neurological injury and has a high burden on society, contributing around 8% of total disability adjusted life years in developed countries, the highest percentage after ischemic heart disease [1]. Patients with stroke present with neurological deficit that can range from dysarthria to paralysis. Ischemic stroke has the highest prevalence in developed countries [1] and is caused by obstruction of arterial oxygen supply to the brain, and therapy is thus aimed at restoring perfusion. Hemorrhagic stroke is less prevalent than ischemic stroke but is more prevalent in individuals of African descent and has a higher mortality rate and a higher burden of disability adjusted life years compared with ischemic stroke [1]. Hemorrhagic strokes have several causes, each requiring different treatment strategies. Hemorrhagic stroke can be caused by rupture of an intracranial aneurysm, a so-called subarachnoid hemorrhage (SAH). Treatment of SAH is directed at the prevention of rebleeding from the aneurysm and at prevention of complications (mainly hydrocephalus and/or secondary ischemia). Another cause is bleeding from a vascular malformation, where treatment is aimed at occlusion of this malformation. Most hemorrhages are spontaneous, so-called spontaneous intracerebral hemorrhage (sICH). In case of sICH, the most important aim of treatment is prevention of hematoma growth [2] by continued bleeding. This type of bleeding may worsen by the use of concomitant antithrombotic medication. At presentation, no clinical distinction can be made between ischemic or hemorrhagic cause of neurological injury. Imaging, especially computed tomography (CT), is essential for diagnosis and to guide treatment modalities, which need to be given as soon as possible because neural tissue will become irreversibly damaged in a time-dependent fashion.

To date, many hemostatic therapies are available of which several have been introduced for neurological injury. In this article, we will review the role of thrombolytic therapy in patients with ischemic stroke. Furthermore, we will give an overview of the effectiveness of different hemostatic therapies in patients with hemorrhagic stroke, while using vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), antiplatelet drugs, or using no antithrombotic drugs. Finally, different hemostatic treatment options in traumatic brain injury (TBI) are discussed. It is not our aim to discuss other treatment options, such as blood pressure lowering, neurosurgical treatments, or intraarterial treatments.

Methods

We searched EMBASE and MEDLINE from 1946 limited to English language and human adults for search terms "hemostatic* or haemostatic*" and different terms for types of known hemostatic therapies (such as vitamin K antagonists, new or novel or non–vitamin K or direct oral anticoagulants, heparin, antifibrinolytic therapy, antiplatelet therapy, transfusion) in combination with terms for neurological injury: "intracerebral or intracranial hemorrhage," "subarachnoid hemorrhage," "traumatic intracranial hemorrhage," "ischemic stroke," "stroke," and "traumatic brain injury." We searched for ongoing trials on clinicaltrials.gov. References of found articles were screened for relevant other articles.

Thrombolytic Therapy in Ischemic Stroke

Results of Randomized Controlled Trials

The first large trials investigating thrombolytic therapy in ischemic stroke were conducted in the 1990s. A major concern was that thrombolytic treatment after ischemic stroke would cause intracerebral hemorrhage. A dose-finding study showed that dosages of approximately 0.95 mg/kg were effective and safe [3,4]. The National Institute of Neurological Disorders and Stroke (NINDS) and European Cooperative Acute Stroke Study (ECASS) trials followed and showed clinical effectiveness of thrombolytic therapy [5,6]. In these randomized trials, patients received recombinant tissue plasminogen activator (rt-PA) therapy in a dose of 0.9 mg/kg within 3 hours (NINDS) or 1.1 mg/kg within 6 hours (ECASS) of start of symptoms or placebo. Despite a significantly increased risk of symptomatic hemorrhage and death within 7-10 days in both trials, overall clinical recovery, measured on the modified Rankin scale (mRS) and Barthel index (Tables 1 and 2), was significantly better in patients who had received rt-PA. Several other trials followed in which other thrombolytic agents were tested such as streptokinase [7,8]. Because only rt-PA was shown to have beneficial effects on the combination of efficacy and adverse effects at follow-up, thrombolytic therapy with rt-PA was then approved for treatment of patients <80 years with ischemic stroke within 3 hours of symptom onset. Because several patient groups were excluded in these trials (especially patients >80 years), the International Stroke Trial – 3 (IST-3) was designed to study the effects of rt-PA with less strict inclusion criteria [9]. In this study, more than 3000 patients were randomized either to receive rt-PA treatment within 6 hours of onset of ischemic stroke or to a control group. The investigators found a

Table 1
Modified Rankin Scale score

Modified Rankin Scale	
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Most often, a score of 2 or less is considered a favorable outcome. Adapted from www.strokecenter.org.