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Recombinant Factor VIIa for Hemorrhagic Stroke Treatment at Earliest Possible Time (FASTEST): Protocol for a Phase III, Double-Blind, Randomized, Placebo-Controlled Trial

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Abstract

Introduction: Intracerebral hemorrhage (ICH) is the deadliest form of stroke. Hematoma expansion (HE), growth of the hematoma between the baseline computed tomography (CT) scan and a follow-up CT scan at 24±6 hours, predicts long-term disability or death. Recombinant Factor VIIa (rFVIIa) has reduced HE in previous clinical trials with a variable effect on clinical outcomes, with the greatest impact on HE and potential benefit when administered within two hours of symptom onset.

Methods: Factor VIIa for Hemorrhagic Stroke Treatment at Earliest Possible Time (FASTEST) is a randomized controlled trial that will enroll 860 patients at ~100 emergency departments and mobile stroke units in five countries. Patients are eligible for enrollment if they have acute ICH within two hours of symptom onset confirmed by CT, a hematoma volume of 2 to 60

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mL, no or small volumes of intraventricular hemorrhage, do not take anticoagulant medications (antiplatelet medications are permissible), and are not deeply comatose. Enrolled patients will receive rFVIIa 80 mcg/kg or placebo intravenously over 2 minutes. The primary outcome measure is the distribution of the ordinal modified Rankin Scale at 180 days. FASTEST is monitored by a Data Safety Monitoring Board. Safety endpoints include thrombotic events (e.g., myocardial infarction). Human subjects research is monitored by an external Institutional Review Board in participating countries.

Discussion: In the US, FASTEST will be first NIH StrokeNet Trial with an Exception from Informed Consent which allows enrollment of non-communicative patients without an immediately identifiable proxy. FASTEST will use ultra-early hemostatic treatment to reduce HE and improve patient outcomes.

Keywords

cerebral hemorrhage; hemorrhagic stroke; Factor VII; hemostasis; clinical trial; randomized controlled trial

INTRODUCTION AND RATIONALE

Intracerebral hemorrhage (ICH), unprovoked bleeding into brain tissue, often leads to disability or death at follow-up.(1) Developing treatments for ICH is urgent. Factor VIIa for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) is a clinical trial intended to reduce hematoma expansion (HE), disability, and death. HE indicates increased volume of the intracranial hematoma from a diagnostic (baseline) computed tomography (CT) scan of the head to a CT scan obtained at follow-up.(2) HE predicts disability or death.(3-6) A strategy of reducing HE to reduce disability and death is rational, but strategies of acute hemostatic treatment have had inconsistent results. Some patients (e.g., hematoma ≥60 mL at presentation) have a poor outcome regardless of HE.(7, 8) Selection of patients who are likely to have HE but could still could be independent at follow-up is challenging.

Minimizing time to effective interventions is crucial. HE occurs in nearly 50% for patients who undergo CT scanning within an hour of symptom onset, and then rapidly declines.(9) Mobile stroke units are particularly useful for early diagnosis and treatment.(10, 11)

Several hemostatic treatments are available for consideration in ICH. rFVIIa activates coagulation and platelet activity(12) and reduced HE in phase II and phase III trials,(7, 13, 14) A trial of tranexamic acid found a small reduction in HE.(15) Desmopressin improves platelet activity in patients known to take aspirin,(16-18) however, prospective data are lacking.(19) Thus, rFVIIa seems to be the treatment most likely to reduce HE in patients with acute ICH.

DESIGN

FASTEST is a randomized, placebo-controlled trial, double-blind, parallel group trial. Patients will be enrolled by site investigators at ~100 mobile stroke units or emergency departments in the US, Canada, Japan, Germany, Spain, and the United Kingdom.

Wherever possible, consent will be obtained from the patient or a proxy prior to enrollment. In the US, an Exception From Informed Consent (EFIC) allows enrollment of non-communicative patients without an immediately identifiable proxy. Community consultation must be approved in advance, and mandates meaningful efforts to consult with the community from which persons could potentially be enrolled in FASTEST. An external Institutional Review Board will approve all EFIC plans for communication with local stakeholders. These communication plans are designed to collect feedback and advise potential patients how to preclude their enrollment in FASTEST. Patients enrolled through EFIC or consent by a proxy will be asked for consent to continue through study follow-up if they return to a communicative state.

PATIENT POPULATION

Inclusion criteria include age 18-80 years, CT-confirmed ICH, and enrollment within two hours of last known well. Exclusion criteria include Glasgow Coma Scale <8, a secondary cause of ICH (e.g., vascular malformation), hematoma volume <2 or >=60 mL, pre-existing mRS>2, ischemic event (e.g., myocardial infarction) or revascularization within 90 days, acute myocardial ischemia, brainstem hematoma, thrombocytopenia, other severe illness, heparin use with elevated PTT, low-molecular weight heparin within 24 hours, refusal to participate, limitations in medical care, pregnancy, or previous enrollment.

RANDOMIZATION

Patients will be randomly allocated in a 1:1 ratio. Each site will receive numbered, blinded, matching study drug kits. A participant is considered to have been randomized/enrolled upon infusion of the study drug.

INTERVENTION

The study intervention is rFVIIa 80 μg/kg or matching placebo as study drug, intravenously once over two minutes. The volume administered will depend on the patient's weight. The maximum dosage is 10 mg, the maximum amount of study drug per study kit.

Clinical data will be recorded onto case report forms (CRFs). Imaging studies will be anonymized and uploaded to a secure web-based platform. If the patient undergoes an unanticipated neurosurgical procedure the head CT immediately before the procedure will be uploaded. Hematoma volumes will be centrally measured.

PRIMARY OUTCOME

The primary outcome measure is the distribution of the mRS at 180 days. Per recommendations from the US Food and Drug Administration, the mRS will be categorized as 0-2, 3, or 4-6. The primary safety outcome is the rate of life-threatening thromboembolic complications within four days (acute myocardial infarction, cerebral infarction, or pulmonary embolism) and mortality at 90 days.

SECONDARY OUTCOME

Secondary analyses of the mRS outcome include a per-protocol sample; ordinal regression of the seven steps of the mRS; analysis of the dichotomous mRS (0-2 vs. 3-6); analysis of the utility-weighted mRS, and; analysis for participants aged <70 years.

Adverse events (AE) and serious adverse events (SAE) will be prospectively documented on case report forms. All AEs will be screened to determine if they meet the criteria for a SAE by an independent medical safety monitor.

DATA MONITORING BODY

A Data Safety and Monitoring Board (DSMB) appointed by the US National Institutes of Health will monitor SAEs. FASTEST will be conducted by the National Coordinating Center of the NIH StrokeNet. Data will be held by the StrokeNet National Data Management Center.

SAMPLE SIZE ESTIMATE

With a total sample size of 776, a two-sample test of proportions will have 80% power to detect a clinically important absolute difference of proportions of 10% of patients with mRS 0-2 (40% placebo versus 50%) at alpha of 0.05 two-sided. This was inflated for 10% lost to follow-up, missing data, and one interim analysis.

STATISTICAL ANALYSIS

The primary analysis will be conducted according to the Intent-to-Treat principle. One interim analysis is planned after approximately one-half patients have been evaluated. An alpha-spending function with O'Brien-Fleming stopping boundaries (two-sided) will be used.

STUDY ORGANIZATION AND FUNDING

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DISCUSSION

FASTEST maximizes the likelihood that rFVIIa will reduce HE and improve patient functional outcomes. The protocol requires only an abbreviated history and a standard-of-care CT scan. A positive trial would bolster rapid diagnosis and treatment of ICH, potentially before hospital arrival.

FASTEST will be the first large multicenter interventional trial to capitalize on mobile stroke units,(10) which are already familiar with rapid treatment of ischemic stroke.(20)

SUMMARY AND CONCLUSIONS

FASTEST represents a global effort to show that a precisely targeted, potential medical treatment can reduce HE and improve patient outcomes after acute ICH.

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