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'SPOT Sign' seLection of Intracerebral haemorrhage to Guide Haemostatic therapy

Submission date 06/10/2010	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 12/11/2010	**Overall study status** Completed	
Last Edited 20/01/2017	**Condition category** Circulatory System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
210358

Study information

Scientific Title
'SPOT Sign' seLection of Intracerebral haemorrhage to Guide Haemostatic therapy: a randomised controlled trial

Acronym
SPOTLIGHT

Study objectives
1. Primary objective:
To investigate the haemostatic effects of recombinant activated factor VIIa (rFVIIa) in spot-sign positive intracerebral haemorrhage (ICH) patients. The study will compare the effects of rFVIIa versus placebo on attenuating ICH growth, and identify variables that modify treatment response.

Hypothesis:
rFVIIa-treated patients will have significantly less ICH growth compared to placebo-treated patients, as measured by the average ICH volume on computed tomography (CT) scan at 24 hours post-treatment and the average absolute change in ICH volume (ml) from baseline to 24 hours. We expect the greatest efficacy in patients treated early (less than 3 hours post-onset) and quickly (less than 40 minutes after CT angiography [CTA]), and without baseline intraventricular haemorrhage.

2.1. Secondary objective 1:
To obtain feasibility data and safety data for this emergency rFVIIa treatment protocol in spot-sign positive ICH patients.

Hypothesis:
2.1.1. Target numbers will be met
2.1.2. Sites able to scan patients with CTA rapidly, with greater than 80% achieving a target time of less than 45 minutes from emergency department arrival to the start of the scan
2.1.3. Enrolling physicians will interpret the presence/absence of a spot sign on CTA in the context of the trial with greater than 90% accuracy, as compared to blinded over-read by the 'gold standard' study neuroradiologist
2.1.4. Sites are able to randomise and treat patients rapidly, with greater than 80% achieving a target time of less than 60 minutes from the end of the CT angiogram to administration of study drug
2.1.5. Low rate of major protocol violations (less than 5%) during the first 18 months and thereafter
2.1.6. Ability to control blood pressure acutely, defined as achieving systolic blood pressure (BP) less than 180 mmHg within 1 hour post-randomisation, will be achieved in greater than 90% patients using a standard protocol. This will be an important demonstration that will have relevance for other future studies of ICH management.
2.1.7. The incidence of myocardial infarction and ischemic stroke within 4 days, and 90-day mortality rate, in the rFVIIa group will not exceed the rates observed in previous trials based on our stricter eligibility criteria

2.2. Secondary objective 2:
To evaluate the acceptability and effects of implementing a waiver of consent for CTA in this

emergency stroke trial, and to evaluate the applicability, acceptability and effects of a waiver of consent for randomization to treatment in this trial.

Hypothesis:
2.2.1. Site REBs will approve the proposed inclusion of a waiver of consent policy for CTA in the study protocol, and this waiver of consent policy will be acceptable to patients/LARs
2.2.2. Sites in this trial will have significantly shorter door-to-CTA times and door-to-needle times and greater efficacy for this time-sensitive treatment versus patients in other trials (e.g. STOP-IT) using standard consent for CTA and randomisation
2.2.3. The majority of site REBs will approve the proposed option of a waiver of consent for randomisation to treatment in this trial, and the majority of patients/LARs surveyed will be in favour of such a waiver of consent option for randomisation to treatment in a future hypothetical trial

2.3. Secondary objective 3:
To evaluate cognition and quality of life as endpoints in an ICH trial.

Hypothesis:
Survivors of ICH will have cognitive impairments and reduced quality of life, measurable on the Montreal Cognitive Assessment (MoCA) and Stroke Impact Scale at 90 days and 1 year.

2.4. Secondary objective 4:
To obtain preliminary clinical efficacy data for rFVIIa treatment in spot sign positive patients (a pooled analysis with other similar trials is planned).

Hypothesis:
Spot-sign patients treated with rFVIIa will have a lower probability of poor outcome compared to placebo-treated patients, as measured by the proportion with modified Rankin score 5-6 (death or severe disability) at 90 days and 1 year. ICH survivors who received rFVIIa will have a greater probability of good recovery compared to placebo, defined as the proportion with modified Rankin Score 0 - 2 at 90 days and 1 year.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Sunnybrook Health Sciences Centre Research Ethics Board, amendment approved 23/04/2014, ref: 255-2010.
All other centres will seek ethics approval before recruiting participants.

Study design
Phase II multicentre two-arm double-blind placebo-controlled randomised trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Intracerebral hemorrhage (ICH)

Interventions
Patients randomised (1:1) to receive either a single intravenous bolus of 80 ug/kg rFVIIa (intervention group) NiaStase RT®, or placebo (control group).

Treatment is administered one time. Total duration of follow up is 1 year, with follow-up assessments post-treatment and at 24 hours, days 1, 2, 3, 4, hospital discharge, day 30, day 90 and 1 year.

Intervention Type
Other

Phase
Phase II

Primary outcome measure
ICH growth within 24 hours between the active drug and placebo. The ICH volume will be measured by analysing the baseline CT scan compared to the CT scan at 24 hours, by means of linear regression. The 24-hour ICH volume will be summarised for each group by descriptive statistics and the adjusted treatment effect and 95% confidence interval will be obtained from the regression model.

Secondary outcome measures
Measured by completing CRF forms to capture date and time of study-related assessments such as:
1. Blood work
2. Informed consent processes
3. Vitals
4. Well-established grading scales, occurring at regular intervals. The grading scales are already used clinically by many sites, and are all incorporated into this trial. Patients will be assessed at baseline, immediately after dosing, days 1 - 4, 30, 90 and 1 year post based on the following scales:
4.1. Glasgow Coma Scale
4.2. NIH Stroke Scale
4.3. Barthel Index
4.4. Modified Rankin Score
4.5. MoCA cognitive assessment
4.6. Stroke Impact Scale
4.7. EQ-5D

Overall study start date
03/01/2011

Completion date
30/06/2017

Eligibility

Key inclusion criteria
Current inclusion criteria as of 24/04/2014:
1. Acute spontaneous primary supratentorial ICH diagnosed by CT scan
2. Presence of a spot sign within the hematoma on CTA (single-phase, multi-phase, or dynamic CTA). [Note: CTA should ideally be performed immediately after the baseline CT scan. If CTA is going to be delayed more than 20 minutes after the baseline CT, then a new plain head CT must be obtained immediately prior to CTA which will serve as the baseline CT for the study]. A spot sign must meet the following criteria:
2.1. One or more foci of contrast enhancement within the margin of a parenchymal hematoma
2.2. Any size or morphology (shape may be spot-like, linear or serpiginous)
2.3. Spot sign(s) must not have any connection to vessels outside the hematoma
2.4. Hounsfield unit density greater than background hematoma density (density of spot sign is typically >120 Hounsfield units)
2.5. No corresponding density present within the hematoma on non-contrast CT
3. Baseline ICH volume 3-90 ml, estimated using the standard 'abc/2' calculation on the baseline plain head CT
4. Age 18 years or over
5. Investigator is able to randomize and administer study drug as soon as possible within a target of 60 minutes after CT angiogram and no later than 6 hours after stroke symptom onset (using the 'last seen normal' principle)
6. Plan to provide full medical care for at least 24 hours
7. Consent from patient or LAR prior to enrolment (or a waiver of consent if patient/LAR assent-consent is not possible prior to enrolment, and if REB approved at your site). [Note: full informed consent to be obtained as soon as possible after study treatment administered].

Previous inclusion criteria:
1. Acute spontaneous primary supratentorial ICH diagnosed by CT scan
2. Evidence of active contrast extravasation within the haematoma as defined by the presence of a spot sign on CTA source images. [Note: CTA should ideally be performed immediately after the baseline CT scan. If CTA is going to be delayed more than 20 minutes after the baseline CT, then a new baseline plain head CT must be obtained immediately prior to CTA]. A spot sign must meet the following criteria:
2.1. One or more foci of contrast enhancement within the margin of a parenchymal haematoma
2.2. Any size or morphology (shape may be spot-like, linear or serpiginous)
2.3. Spot sign(s) must not have any connection to vessels outside the haematoma
2.4. Hounsfield unit density at least double that of background haematoma density (density of spot sign is typically greater than 120 Hounsfield units)
2.5. No corresponding density present within the haematoma on non-contrast CT
3. Baseline ICH volume 3 - 70 ml, estimated using the standard "abc/2" calculation on the baseline plain head CT
4. Age 18 - 85 years (participants must have had their 18th birthday and not their 86th birthday), males and females
5. Investigator is able to randomise and administer study drug within 60 minutes after CT angiogram and no later than 6 hours after stroke symptom onset (using the "last seen normal" principle)

6. Assent-consent from patient or LAR prior to enrolment, or a waiver of consent if patient/LAR assent-consent is not possible prior to enrolment. [Note: full informed consent to be obtained as soon as possible after study treatment administered].

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
N = 110, 55 patients per group

Key exclusion criteria
Current exclusion criteria as of 24/04/2014:
Diagnostic/imaging exclusions:
1. Brainstem or cerebellar hemorrhage
2. ICH secondary to known or suspected trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischemic stroke, venous sinus thrombosis, thrombolytic treatment, tumour, or infection; or an in-hospital ICH or ICH as a result of any in-hospital procedure or illness
3. Baseline brain imaging shows evidence of acute or subacute ischemic stroke (chronic infarcts are not an exclusion)
4. Contrast administration within the previous 24 hours

Clinical exclusions:
1. Evidence of thromboembolic risk factors, defined as any of the following: known history within the past 6 months of any of the following: myocardial infarction, coronary artery bypass surgery, angina, ischemic stroke, transient ischemic attack, carotid endarterectomy, cerebral bypass surgery, deep venous thrombosis, pulmonary embolism, vascular angioplasty, stenting (coronary, peripheral vascular or cerebrovascular) or filter (e.g. vena cava filter); prosthetic cardiac valve; and/or known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc)
2. Known hereditary (e.g. hemophilia) or acquired hemorrhagic diathesis or coagulation factor deficiency
3. Any condition known that the investigator feels would pose a significant hazard if rFVIIa were administered
4. Planned surgery for ICH within 24 hours (placement of intraventricular catheter is not an exclusion)
5. Planned withdrawal of care before 24 hours post-ICH onset
6. Known participation in another therapeutic trial
7. Known allergy or other contraindication to iodinated contrast dye
8. Known or suspected hypersensitivity to the trial product

Medication exclusions:
1. Known unfractionated heparin use must check PTT and exclude if elevated above upper limit

of local labs reference range
2. Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 7 days
3. Known GPIIb/IIIa antagonist use in previous 2 weeks
4. Known warfarin (or other anticoagulant) therapy with INR >1.40. Note: if the patient is suspected to have cirrhosis, study staff are to wait for the INR value prior to dosing, and ensure not to enroll the patient if the INR value is >1.40. Otherwise the physician should use their discretion if they believe the patient is not at risk for elevated INR
5. Concurrent or planned treatment with prothrombin complex concentrate, vitamin K, fresh frozen plasma, or platelet transfusion

Clinical/laboratory exclusions:
1. Pregnancy or lactation. Women of childbearing potential must have a negative pregnancy test prior to randomization
2. Current clinical symptoms suggestive of acute coronary ischemia (e.g. chest pain)
3. Baseline ECG evidence of acute coronary ischemia (e.g. ST elevation in 2 contiguous leads, new LBBB, ST depression)
4. Baseline platelet count <50,000 or INR >1.40 or elevated PTT [Note: participants can be enrolled without awaiting these results unless a bleeding abnormality or thrombocytopenia is suspected, the participant is known to have been taking warfarin, heparin, or other anticoagulant, or anticoagulation use is uncertain]

Previous exclusion criteria:
Diagnostic/imaging exclusions:
1. Brainstem or cerebellar haemorrhage
2. ICH secondary to known or suspected trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischemic stroke, venous sinus thrombosis, thrombolytic treatment, tumour, or infection; or an in-hospital ICH or ICH as a result of any in-hospital procedure or illness
3. Baseline brain imaging shows evidence of acute or subacute ischaemic stroke (chronic infarcts are not an exclusion)

Clinical exclusions:
4. Glasgow Coma Scale score less than 8 at time of proposed enrolment
5. Known pre-existing dependence or moderate or severe disability, defined as pre-admission modified Rankin Scale score greater than 2. [Note: Patients must be independent in all basic activities of daily living and are excluded if they cannot walk independently without the assistance of another person (use of a cane or walker is not an exclusion) or if they require assistance from another person for basic activities of daily living (e.g. dressing, transfers, feeding, bathing, toileting)]. Patients with advanced dementia or admitted from a nursing home are excluded (cognitive impairment alone, without dementia, is not an exclusion to enrolment).
6. Evidence of thromboembolic risk factors, defined as any of the following: known history within the past 6 months of myocardial infarction, coronary artery bypass surgery, angina, ischemic stroke, transient ischemic attack, carotid endarterectomy, cerebral bypass surgery, deep venous thrombosis, pulmonary embolism, or any vascular angioplasty or stenting (coronary, peripheral vascular or cerebrovascular) or filter; or known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc.)
7. Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis or coagulation factor deficiency
8. Any condition the investigator feels would pose a significant hazard if rFVIIa were administered
9. Planned surgery for ICH within 24 hours (placement of intraventricular catheter is not an

exclusion)
10. Terminal illness or planned withdrawal of care or comfort care measures
11. Known participation in another therapeutic trial
12. Known allergic reaction or intolerance to recombinant activated factor VII, or iodinated contrast dye
13. Known or suspected hypersensitivity to trial product

Medication exclusions:
14. Known unfractionated heparin use must check PTT and exclude if elevated above upper limit of local lab's reference range
15. Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 24 hours
16. Known GPIIb/IIIa antagonist use in previous 2 weeks
17. Known warfarin use - must check INR and exclude if International Normalised Ratio (INR) greater than 1.50
18. Concurrent or planned treatment with prothrombin complex concentrate, vitamin K, fresh frozen plasma, or platelet transfusion

Clinical/laboratory exclusions:
19. Pregnancy or lactation [Note: women of childbearing potential must have a negative pregnancy test prior to randomisation]
20. Current clinical symptoms suggestive of acute coronary ischaemia (e.g. chest pain)
21. Baseline electrocardiogram (ECG) evidence of acute coronary ischemia (e.g. ST elevation in 2 contiguous leads, new LBBB, ST depression)
22. Baseline troponin T or troponin I greater than 0.1 ng/ml
23. Baseline blood work platelet count less than 50,000 or INR greater than 1.50 or elevated PTT. [Note: participants can be enrolled without awaiting these results unless a bleeding abnormality or thrombocytopenia is suspected, the participant is known to have been taking warfarin or heparin, or anticoagulation use is uncertain].

Date of first enrolment
03/01/2011

Date of final enrolment
03/01/2016

Locations

Countries of recruitment
Canada

Study participating centre
University of Toronto
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M4N 3M5

Sponsor information

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Sponsor type
University/education

ROR
https://ror.org/03wefcv03

Funder(s)

Funder type
Research organisation

Funder Name
Canadian Institutes of Health Research (CIHR) (Canada) (ref: 210358, committee code RC2)

Alternative Name(s)
Instituts de Recherche en Santé du Canada, Canadian Institutes of Health Research (CIHR), CIHR_IRSC, Canadian Institutes of Health Research | Ottawa ON, CIHR, IRSC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Canada

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration