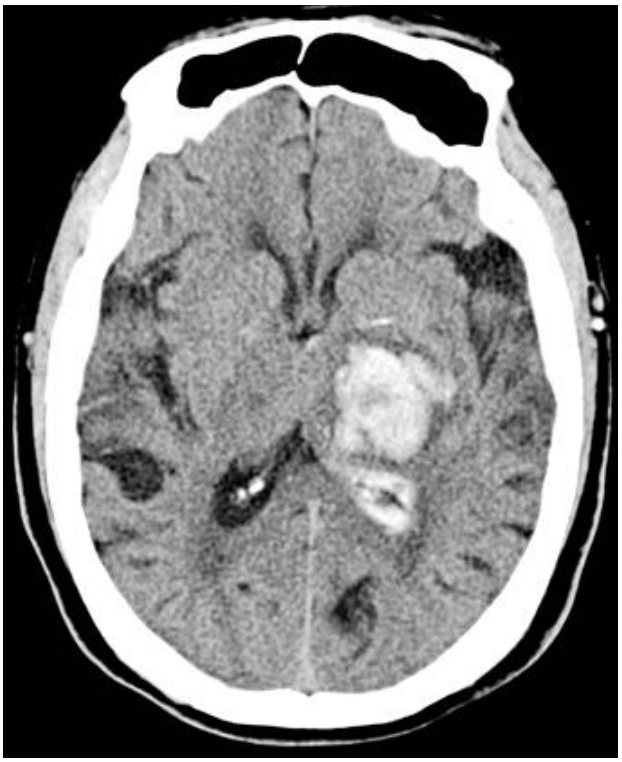
Universitat de Girona

Efficacy of rFVIIa (NiaStase RT ®) on haematoma growth reduction and clinical evolution in patients with intracerebral haemorrhage with non-contrast CT radio-markers of haemorrhage expansion

A randomized, controlled, double-blind trial

Final degree project



MARC DELGADO ROMEU

6th Year Medical Student
Facultat de Medicna UdG

TUTOR: Dr. Yolanda Silva Blas

Neurology Department,
Hospital Dr. Josep Trueta

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1 ABSTRACT

Background Haematoma expansion has been associated with early neurological deterioration, mortality and worse functional outcome in patients with intracerebral haemorrhage (ICH). rFVIIa (*NiaStase RT*®) has shown promising results in avoiding early haematoma growth, but previous studies have been done in all patients regardless of their risk for haematoma expansion. Some studies have isolated patients with high risk for haematoma expansion (SPOTLIGHT), but they used CT angiography (CTA) techniques (not available in all hospitals) and had long therapeutic windows. Therefore, evidence of the drug's effectiveness up until now has been unclear.
Some non-contrast computerized tomography (NCCT) characteristics of ICH have been associated with this early haematoma expansion. These radio-markers could be used in all hospitals with available CT, and might guarantee a correct therapeutic window for the drug.

Purpose The aim of this study is to evaluate the effect of rFVIIa (*NiaStase RT*®) on patients with high risk of haematoma growth evaluated with NCCT radio-markers. We will assess its effects on mortality and morbidity on the patients it is given to.

Design Multicentre, double blind, placebo-controlled randomized clinical trial in the tertiary centres of the *Institut Català de la Salut (ICS)*.

Population Patients admitted to tertiary centres within the Institut Català de la Salut (ICS) with the diagnosis of acute primary spontaneous ICH (nontraumatic and non-anticoagulant-related ICH), with NCCT radio-markers of haemorrhage growth. A non-probabilistic consecutive sampling will be performed expecting to gather a minimum sample of 148 patients. These patients will be randomized in two groups, one for intervention (NiaStase RT®) and the other for control.

Methods The patients will be administered either 80 µg/kg dose of rFVIIa (NiaStase RT®) or placebo. The CT scan will be repeated after 1 hour of drug infusion and 24 hours post dosing to assess the rate and degree of ICH growth. Likewise, neurological status measured by NIHSS and disability degree measured by mRS will be evaluated during the hospital stay and in the follow-up visits, which will be at 3 and 6 months and 1 year after the event. Mortality will be assessed for up to a year after the event.

Key words Intracerebral haemorrhage Haematoma expansion NNCT rFVIIa (NiaStase RT®) Clinical outcome

2 INTRODUCTION/JUSTIFICATION

A stroke, as defined by the American Heart Association/American Stroke association (AHA/ASA), is an episode of acute (or, in certain cases, chronic) neurological dysfunction of vascular origin not due to trauma.

Strokes are divided between ischaemic strokes and haemorrhagic strokes.

Ischaemic strokes are caused by the blockage of blood flow to a certain area of the brain, causing first tissue ischaemia, and then tissue infarction. They are the most common form of stroke, accounting for about 80% of cerebral vascular accidents. When the ischaemia is resolved before infarction can establish itself (generally within the first hour) and the neurological focality disappears, we talk about a transitory ischaemic accident. When the neuronal damage is established and the clinical features (or some of them) remain, we talk about an established ischaemic stroke.

On the other side, haemorrhagic strokes represent about 20% of strokes. Within these, we distinguish two types.

First, intracerebral haemorrhages (ICH) are focal collections of blood within the brain parenchyma or ventricular system which is not due to trauma. This excludes other entities such as subdural and epidural haematomas due to their traumatic origin.

Second, we have subarachnoid haemorrhages (SAH). These are bleedings in the subarachnoid space, generally with an aneurismatic origin.

Within haemorrhagic strokes, about 15% are intracerebral haemorrhages and the remaining 5% are subarachnoid haemorrhages. (1)

2.1 EPIDEMIOLOGY

ICH accounts for 15% of all strokes (2) and, while not being as frequent as ischaemic stroke, its annual incidence is significant, with reports varying between 10-30 per 100.000 habitants. This incidence can increase up to 30% in Asiatic and Afro-American populations (3). Incidence in this disease is also linked with age, being higher in patients older than 85 years old (309.8 per 100.000) (4).

Thirty day mortality has been reported to be 30-50%, with half of it being on the first two days (5), with an overall 10-year survival of 24,1% (4). Morbidity is also high, as only 20% of patients live independently 6 months after the event (5).

Risk factors for ICH are shown on Table 1 (6).

The most common risk factor for ICH is arterial hypertension, especially in those patients with deep haemorrhages (4).

Alcohol consumption has also been associated with ICH, albeit with a complex and multifactorial relation. Acute alcohol consumption has been associated with blood pressure peaks, which can explain part of the association. Furthermore, chronic alcohol consumption has an effect on platelet adhesion and coagulation factor production (chronic liver damage) (7).

TABLE 1 RISK FACTORS FOR ICH

Modifiable risk factors
- Hypertension
- Current smoking
- Excessive alcohol consumption
- Decreased Low-density lipoprotein cholesterol, low triglycerides
- Anticoagulation
- Use of antiplatelet agents
- Sympathomimetic drugs (cocaine, heroin, amphetamine, PPA and ephedrine)
- Alcohol
Non-modifiable risk factors
- Old age
- Male sex
- Asian and Afro-American ethnicity
- Cerebral amyloid angiopathy
- Cerebral microbleeds
- Chronic kidney disease
Other factors suggested to be related to risk
- Multi-parity
- Poor working conditions (blue-collar occupation, longer working time)
- Long sleep duration
PPA, Phenylpropanolamine

Other risk factors, such as low cholesterol levels and smoking have been associated with IHC but evidence about the association is unclear.

Identifying the modifiable risk factors for ICH is vital, as a preventive approach is necessary to reduce ICH incidence in our population.

2.2 AETIOLOGY

We have several ways to classify ICH causes. Generally we differentiate between primary and secondary causes. Primary causes are mainly hypertension and cerebral amyloid angiopathy. These pathologies create a direct damage to brain blood vessels which causes ruptures, and therefore bleeding. On the other hand, secondary causes are those that create a predisposition for haemorrhage, such as tumours or vascular malformations.

Another classification for ICH is based on its location, distinguishing between deep and lobar haematomas. Deep haematomas, also called ganglionic haematomas, are the characteristic location of hypertensive ICH, whereas lobar (or extraganglionic) haematomas are more typical of cerebral amyloid angiopathy. Obviously, secondary causes have a location depending on where they are situated and where the blood vessels are more susceptible to damage. (7)

Now we will review the main causes of ICH.

2.2.1 HYPERTENSION

This represents the most important cause of ICH, as it is the most common one, accounting for up to 70-80% of all ICHs (4). It is also a relevant cause because it falls in the category of modifiable risk factors for ICH, making it an ideal target for both primary and secondary prevention interventions. We have two main mechanisms for ICH due to hypertension. The first one, associated with chronic hypertension and age, and the second one associated with acute blood pressure spikes on healthy blood vessels that are not used to such circulatory changes.

Chronic hypertension, a common finding in patients with old age, has been associated with the apparition of deep haematomas. This has been attributed to the lipohyalinosis of small arterioles, with the subsequent apparition of Charcot Bouchard microaneurysms (8).

Lipohyalinosis is the term for the vascular remodelling due to the constant high pressure that arterioles endure. The loss of smooth muscle and the exchange elastin for collagen weakens the wall of the arterioles, to the point of creating fusiform aneurisms (Charcot Bouchard microaneurisms), and when the right conditions are met (mainly a high spike of arterial blood pressure), they rupture (7). It has been found that when this happens, most bleeding occurs at

perforating arterioles, as these vessels are subjected directly to blood pressure changes, while cortical blood vessels are protected of said changes by collateral circulation.

ICH can also occur in patients with normal vascular structure, albeit with significantly less frequency. When this happens, the cause of the bleed is attributed to an excessively high blood pressure peak. Causes of said tension peaks can be the manipulation of the carotidal bulb during endarterectomy, sympathomimetic drugs, trigeminal stimulation, Valsalva manoeuvres or cold exposition (7).

2.2.2 Cerebral Amyloid Angiopathy (CAA)

CAA-related haematomas are generally located in extraganglionic areas (lobar haematomas). It is the second most frequent cause of spontaneous ICH, with a high incidence in elderly patients, as it is associated with Alzheimer's disease.

The cause of the blood vessel wall weakening is the deposition of amyloid-beta peptide (Aß). It begins with an accumulation of congophilic material between the media and adventitia layers, with a progression through the media. In later stages the amyloid replaces the smooth muscle layer. Finally, these deposits lead to vasculopathic changes, such as microaneurysms, concentric splitting of the vessel wall, chronic perivascular inflammation, and fibrinoid necrosis. The same deposit of amyloid substance cause Alzheimer's disease in these patients (7,9,10).

2.2.3 Tumours

ICH due to brain tumours is mainly found in multiform glioblastoma and melanoma, bronchogenic carcinoma, hypernephroma and choriocarcinoma metastases. Another brain tumour associated with ICH is the pituitary adenoma.

The reason for the predisposition these tumours have to bleed is the presence of aberrant angiogenesis. Angiogenesis is one of the hallmarks of cancer, and advanced brain tumours (such as multiform glioblastoma) and brain metastases tend to cause this process. When tumours cause angiogenesis, the newly formed vessels are not well formed, thus having a

tendency to bleed. Another cause of haemorrhage caused by brain tumours is the invasion of normal blood vessels by the tumour (11).

2.2.4 ANTICOAGULANT, ANTIAGGREGATING AND FIBRINOLYTIC DRUGS

Oral anticoagulants have been associated to ICH, but their role in the creation of the initial haemorrhage is unclear. It is commonly thought that an underlying mechanism will cause the initial bleeding, and the fact that the patient is taking these drugs causes the haemorrhage to grow more than it would be expected otherwise. This is supported by the fact that ICH in patients with oral anticoagulation therapy have ICH of greater volume and more associated mortality (12).

Heparin-related ICH are less common, and are observed mainly in heparinized patients with acute ischaemic stroke, who then suffer haemorrhagic conversion (13).

Antiaggregating therapy also increases risk for ICH, especially in elderly patients, and independently of the dose (14).

Fibrinolytic agents have also been related to ICH, especially in ischaemic stroke, where rtPA therapy can cause a haemorrhagic conversion of the stroke (15).

2.2.5 VASCULAR MALFORMATIONS AND ANEURISMS

Vascular malformations and aneurisms are a common cause of ICH in young patients without hypertension. Vascular malformations include Arterio-Venous Malformations (AVMs), cavernomas, venous angiomas and telangiectasia. The most common vascular malformation is the AVM, which typically produces lobar haemorrhages. AVMs have an annual secondary haemorrhage risk of 18%. They are diagnosed by angiographic studies and can be treated by surgery, embolization and radiosurgery (alone or in combination) (16).

The other vascular malformations have less prevalence and a lower annual risk of rupture and secondary haematoma.

Intracranial aneurisms tend to produce subarachnoid haemorrhages (SAH), but some of them can cause ICH. Isolated ICH due to aneurisms (without SAH) is an extremely rare finding (17).

Aneurismatic ICH is diagnosed with an angiographic study (but can be suspected by angio-MRI), and the treatment requires either endovascular coils or surgical clipping of the aneurism (to reduce the chance of another bleed), with a following medical treatment to avoid the main complications (vasospasm and hydrocephalus) (18).

2.2.6 CEREBRAL VENOUS THROMBOSIS (CVT)

CVT is a relatively uncommon cause of ICH, with an incidence of 0,5% from all strokes. Risk factors for CVT are: older age, female sex, acute onset (48h), headache, decreased level of consciousness, seizure, elevated blood pressure and papilledema. Its diagnosis depends on the clinical suspicion, as we have to check the venous phase of the contrast MRI to see the thrombus in the cerebral venous system (delta sign). Treatment will be done initially with heparin, and later with oral anticoagulants, with mechanical thrombectomy reserved to patients with neurological deterioration despite the medical treatment. ICH due to CVT generally have poorer outcomes. (19)

2.2.7 SYMPATHOMIMETIC DRUGS

Cocaine, phenylpropanolamine, amphetamines and other illegal drugs are a common cause of ICH in younger patients. They cause lobar ICH, especially when the patients already have a predisposing cause (such as an AVM). (20)

2.2.8 INFLAMMATORY VASCULITIS

When the blood vessels in the brain are inflamed its rupture is more likely when there are tension spikes. Vasculitis can be infectious (bacterial, fungal or viral) or non-infectious (such as CNS granulomatous angiitis).

2.2.9 MISCELLANEOUS

Less common causes of ICH can be considered when other causes are discarded and a temporal relation between the exposure and the ICH is confirmed. They include: Moya-Moya

disease, hematologic diseases (leukaemia, thrombocytopenic thrombotic purpura, afibrinogenemia, Von Willebrand Factor deficiency, multiple myeloma, disseminated intravascular coagulation…), migraine, Spät apoplexy (delayed ICH after traumatic brain injury), methanol intoxication, wasp and scorpion bite, trigeminal nerve stimulation, exposure to cold, break-dance, electroshock, and roller coaster rides. (21)

2.2.10 CRYPTOGENIC

Patients without a possible, probable or definite aetiology of ICH (with the basic study being completed) (21).

2.3 PATHOPHYSIOLOGY

After the initial vessel rupture, the haematoma has two effects on the normal function of the brain: the mechanical effect (amplified by the haematoma growth) and the toxic effect.

2.3.1 MECHANICAL EFFECT

When blood leaks out of the brain vessels it causes a direct mechanical lesion to the brain tissue. This has several implications for the CNS. As intracranial pressure (ICP) depends on an equilibrium between its container (the skull) and its contents (blood, LCR and brain tissue), an increase of one of the latter will cause an increase in ICP. The rate at which this happens and how much this happens will determine the effect of the expanding lesion on the brain tissue surrounding it, which is why ICHs tend to have a more progressive onset of symptoms when compared to ischaemic stroke, where onset is sudden due to a lack of blood flow to a determined section of the brain.

Another mechanical effect on the brain is the ischaemic effect the haemorrhage has on the surrounding brain tissue. This effect contributes to secondary neuronal damage due to the compression of the peri-haemorrhage microvasculature. It has been shown with both pathological and radiological evidence, but its clinical repercussions are variable and not clear at the moment.

Radiologically, this ischaemic area is shown in CT as a hypodense area. It corelates with the area with perihematomal oedema, which is why it is thought that these effects overlap in the creation of the secondary neuronal damage of ICHs. (22)

2.3.2 TOXIC EFFECT

Another cause of secondary neuronal damage is the perihematomal oedema. This is created within the first 3 hours after the onset of the ICH, peaking at 72 hours and usually persisting for 5 days, although it has been reported for up to 2 weeks. This is caused by blood and plasma products mediating secondary injury processes, including an inflammatory response, activation of the coagulation cascade and iron deposition from haemoglobin degradation. This creates a

cytotoxic oedema that disrupts the blood-brain barrier, causes sodium-pump failure and, ultimately, neuronal death. (22)

2.3.3 HAEMATOMA GROWTH

Initially, it was thought that the haematoma volume was static after the first few minutes. Nevertheless, it has been proven that after the onset of the neurological deficit there is a risk for haematoma expansion. This is defined as a ≥6mL or ≥33% increase in volume. After the vessel rupture and within the first 3 hours, 38% of patients have a continued haematoma growth from continuous bleeding, being one of the main causes of early neurologic deterioration, especially when the haematoma expansion is of more than 20 mL (10). The cause for this phenomenon is unclear. Acute hypertension, local coagulation deficit or both may be associated. (22)

This is related with the aim of this project, as the intended therapeutic window for rFVIIa has changed over the years. It was previously thought that the first 24 hours were the most critical for haematoma expansion, and, while it is true, even more critical are the first 3 hours, as about 1/3 of ICH patients will have this haemorrhage expansion within those hours. This means that previous studies on rFVIIa done with wider therapeutic windows that did not find significant differences could be improved by a therapeutic window within the first 3-4 hours, which is the aim of this study.

This early haematoma growth is thought to occur because of bleeding into the necrotic layer of tissue that forms acutely at the margin of the haematoma (7). It was previously thought that the bleeding came from the same artery that started the haemorrhage, but evidence suggests otherwise. As we will see in later sections, neuroimaging techniques it is possible to predict whether the haemorrhage will grow or not (23–25). This is important because not all patients with ICH have the same risk for haematoma expansion, and thus, they are not all eligible for a treatments like rFVIIa. In these neuroimaging techniques we can see that the risk of haematoma growth is related either to the evidence of an active bleeding site (spot sign) or indirect evidence of several bleeding sites (irregular shape, heterogeneities in density…), which correlates with the theory of different bleeding points instead of just one initial bleeding artery. (7)

2.4 CLINICAL CHARACTERISTICS

The presentation of ICH does not differ from that of ischaemic strokes. Both clinical presentations depend mainly on their anatomic location. Nevertheless, ICH neurological focality is not usually as well defined as the signs and symptoms of ischaemic stroke. That is because the infarcted area of an ischaemic stroke is limited by the CNS surface that is irrigated by the blocked artery. On the other hand, ICH depends more on its mass effect to produce its clinical features, making its syndromes less well defined.

Some stroke traits are more characteristic of ICH, such as its progressive onset (neurologic deficits that evolve gradually over 5-30 min strongly suggest ICH) and the absence of fluctuation or rapid recovery. Headache, vomiting and loss of consciousness are more frequent in ICH than in ischaemic stroke. (6)

While ICH can develop anywhere in the CNS, it typically occurs in the following locations with the corresponding clinical features:

- Putamen: Contralateral hemiparesis often with homonymous hemianopsia.
- Thalamus: Hemiparesis with prominent sensory deficit.
- Pons: Quadriplegic, “pinpoint” pupils, impaired horizontal eye movements
- Cerebellum: Headache, vomiting, gait ataxia.

The evaluation of patients with ICH must be performed methodically, and scores such as the NIHSS help to keep track of the patient’s signs and symptoms. The. Modified Rankin scale (mRS) is also helpful to evaluate the previous state of the patient, and therefore helps to assess their disability status before and after the event. (See Annex)

2.5 PROGNOSIS

2.5.1 PROGNOSTIC FACTORS

Factors related to poor prognosis and mortality in ICH are low Glasgow Coma Scale score, age ≥80 years, infratentorial origin of ICH, large ICH volume (>30mL),the presence of intraventricular haemorrhage and early haematoma growth (26,27).

Early haematoma growth of more than 33% occurs in one third of patients with ICH within the first 3 hours of onset. For every 10% increase in ICH size, mortality increases by 5% and 16% of patients will worsen by 1 point on the mRS (27). This is critical, as any treatment that aims to prevent this should be performed as early as possible to have an impact on mortality and morbidity in patients with ICH.

2.5.2 PROGNOSTIC SCORES

When talking about diseases with the morbidity and mortality that ICH has, it is important to have tools to assess the chances the patient has to survive. This is essential for three reasons. First, keeping patients and their families well informed. Second, clinical grading scales are useful as a framework for clinical decision making; and finally, they are also vital to provide reliable criteria for assessing efficacy of new treatments.

TABLE 2 ICH SCORE

Component	ICH Score Points
GCS score	
3–4	2
5–12	1
13–15	0
ICH volume, cm^3	
≥30	1
<30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age, y	
≥80	1
<80	0
Total ICH Score	0–6

GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using *ABC*/2 method; and IVH, presence of any IVH on initial CT.

In this line of thought, the ICH-Score was created as a simple, reliable grading scale for ICH (See Table 2). This score was created keeping in mind that clinical scores should be able to be used without significant special training or extensive time commitment. The results for this score are correlated with 30-day mortality in ICH patients, with mortality rates of 13% for scores of 1, and up to 97% for scores of 5 or 6. (26)

2.6 DIAGNOSTIC MANAGEMENT

When a patient presents with sudden neurological focality, a vascular origin must be assumed until proven otherwise. As we have said, it is not possible to distinguish between an ischaemic or haemorrhagic origin of the stroke with enough confidence to initiate the corresponding treatment. It is, therefore, necessary to perform neuroimaging studies, which will be able to determine the etiologic origin of the event (28). Both computerized tomography (CT) and magnetic resonance imaging (MRI) are good tools to perform this evaluation.

It is also important to evaluate familiar background for stroke or other diseases associated with strokes. A thorough anamnesis will be performed, asking about toxic habits (alcohol, smoking and drugs, specifically sympathomimetic drugs), chronic hypertension, systemic diseases (vasculitis, cancer and hematologic and hepatic diseases) and other neurological conditions (epilepsy and previous neuropsychiatric status).

A physical examination will be performed, and besides evaluating the neurological condition (NIHSS), we'll look for signs of hypertension (fundus exam: hypertensive retinopathy) and other systemic diseases.

Other tests will be done to complete the initial evaluation: laboratory tests (hemogram, coagulation, hepatic and renal function, glycaemia, ionogram and drugs/toxicants levels), EKG and chest x-ray. We will also measure the arterial blood pressure, temperature and oxygen saturation.

This procedures will be performed in the emergency department, and the order to follow will depend on the availability of resources. Nevertheless, neuroimaging is the priority here, because its result will determine the following treatment, and will provide an initial prognosis of the patient.

2.6.1 COMPUTERIZED TOMOGRAPHY (CT)

CT is very sensitive to acute haemorrhages, and is therefore considered the gold standard, but some sequences of MRI are just as sensitive for acute haemorrhage, and even better to detect prior haemorrhages. In clinical practice, most hospitals (including those in Catalonia) perform a

CT scan in the situation of acute neurological focality, as cost and proximity might make it difficult to get access to an emergent MRI scan.

Acute ICH is identified in a CT-scan as an intraparenchymal hyperdense region of haemorrhage, with a location that will depend on the aetiology of the bleed. In hypertensive ICH, it has been classically described to be located within the basal ganglia, cerebellum or occipital lobes. Other ICH causes will give different locations, such as in CAA, which will tend to cause ICHs adjacent to the cerebral cortex, generally sparing the basal ganglia, posterior fossa and brainstem (29).

2.6.1.1 CT ANGIOGRAPHY (CTA)

Other causes of ICH (such as AVMs and aneurisms) tend to remain hidden in non-contrast CT scans. For these aetiologies, (CTA) will allow a better approach, even though a diagnostic angiography might be necessary to perform a definitive diagnostic.

CTA also has an emergent role in the acute evaluation of ICH, as CT images obtained in the late arterial phase of CTA might show contrast extravasation in what is known as the “Spot Sign”. The presence of spot sign in CTA has been shown to predict haematoma expansion, which is related to END. It is, therefore, a useful parameter in order to evaluate the prognosis of ICH patients (23,30,31).

Nevertheless, CTA, as it is the case with MRI, can be limited in its access. It is for this reason, that the use of non-contrast CT (NCCT) to predict haematoma growth is necessary, especially in order to start treatments such as the one this project focuses on as soon as possible.

2.6.1.2 NON-CONTRAST CT (NCCT) RADIO-MARKERS FOR HAEMORRHAGE GROWTH

2.6.1.2.1 HAEMORRHAGE VOLUME

This parameter is measured using the ellipsoid approximation method ABC/2, where A, B and C represent the 3 maximal orthogonal dimensions of the haemorrhage, as it is shown in Figure 1 (32). This method can accurately measure smaller, more regular ICH, but it loses accuracy with larger, more irregular haemorrhages (33). Nonetheless, larger haemorrhages have a higher risk of expansion, and the inverse holds true, with smaller haemorrhages having less risk of growth (25).

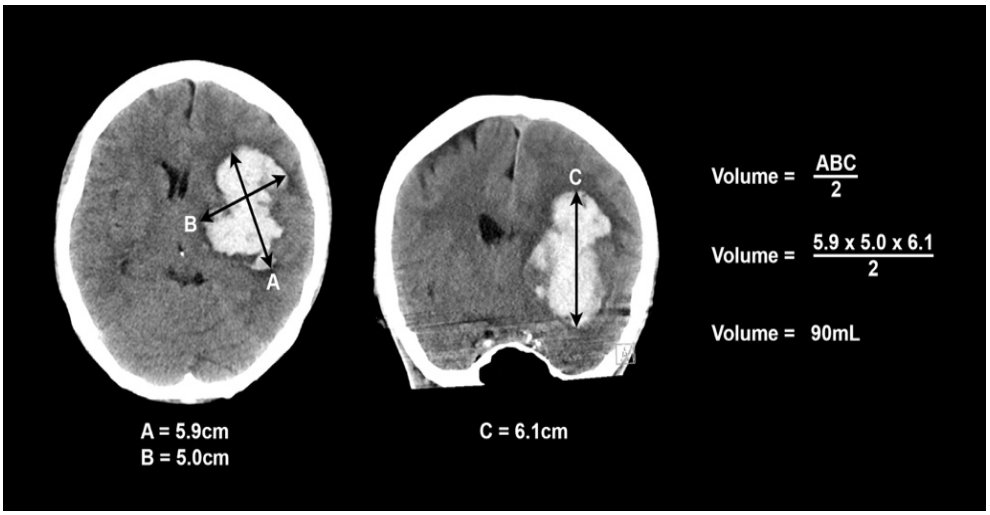

FIGURE 1 ICH VOLUME CALCULATION

2.6.1.2.2 HAEMORRHAGE SHAPE IRREGULARITY

More irregular margins are associated with haemorrhage-expansion. This irregularities are thought to be the reflection of peripheral sites of secondary bleeding (24). This parameter is assessed on the axial slice showing the largest hematoma cross-sectional area (34). In Figure 2 we can see a categorical scale to evaluate ICH margins This score allows to categorize haemorrhages with a good agreement value (85%) for within and inter-rater reliability. The patients that have a high score in the scale (3-5) had a higher risk of

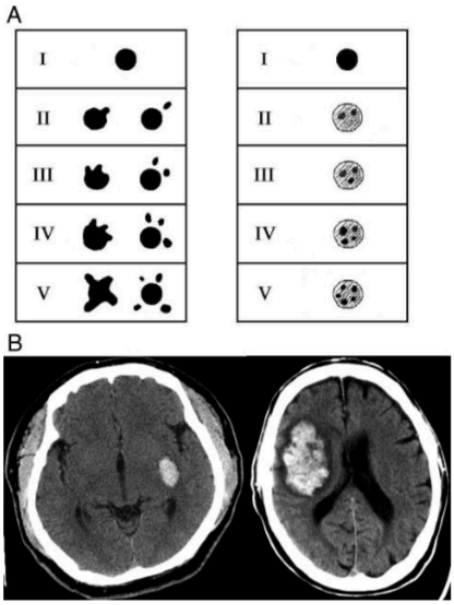

FIGURE 2 A, SHAPE (LEFT) AND DENSITY (RIGHT) CATEGORICAL SCALES AND (B) EXAMPLES OF HOMOGENEOUS, REGULAR ICH (LEFT) AND HETEROGENEOUS, IRREGULAR ICH (RIGHT).

haematoma expansion, especially for scores 4 and 5, which is why for this study we chose this cut-off point. This is valid also for the heterogeneity score. (35)

2.6.1.2.3 HAEMORRHAGE DENSITY HETEROGENEITY

Several representations of this concept have been used. We will explain the main methods available in the following sections.

Heterogeneous density is defined as the apparition of at least three foci of hypodensity within the haematoma (which will show as an hyperdense image). In Figure 2 we can see a categorical scale to evaluate ICH heterogeneity (35).

The “Swirl sign” is defined as irregular or streak-like regions of hypo/iso-attenuation (compared to the brain parenchyma). The swirl can be found adjacent to the haemorrhage margin, and even connect with the surrounding brain structures. It can be seen on both axial and coronal images (25,34).

The “Black hole sig” is a well-defined area of hypoattenuation within the haematoma. Unlike the swirl sign, it cannot be connected with the haematoma outer surface and can have any dimension and morphology. The margin between the two regions must be clear to the rater, and a difference of at least 28 Hounsfield units (HU) must be identified (25,34).

The “Blend sign” is an hypoattenuating area next to the haematoma. The margin between the areas has to have a density of at least 18HU at any point of the border. One region cannot encapsulate the other, and both should be big enough as to not need zoom to see them (25,34).

The apparition of a fluid level also represents a higher risk of haematoma expansion. It is seen as an area of low attenuation above and an area of high attenuation below a discrete straight line of separation (25,34).

In Figure 3 (25) we can see examples of NCCT markers of haemorrhage expansion.

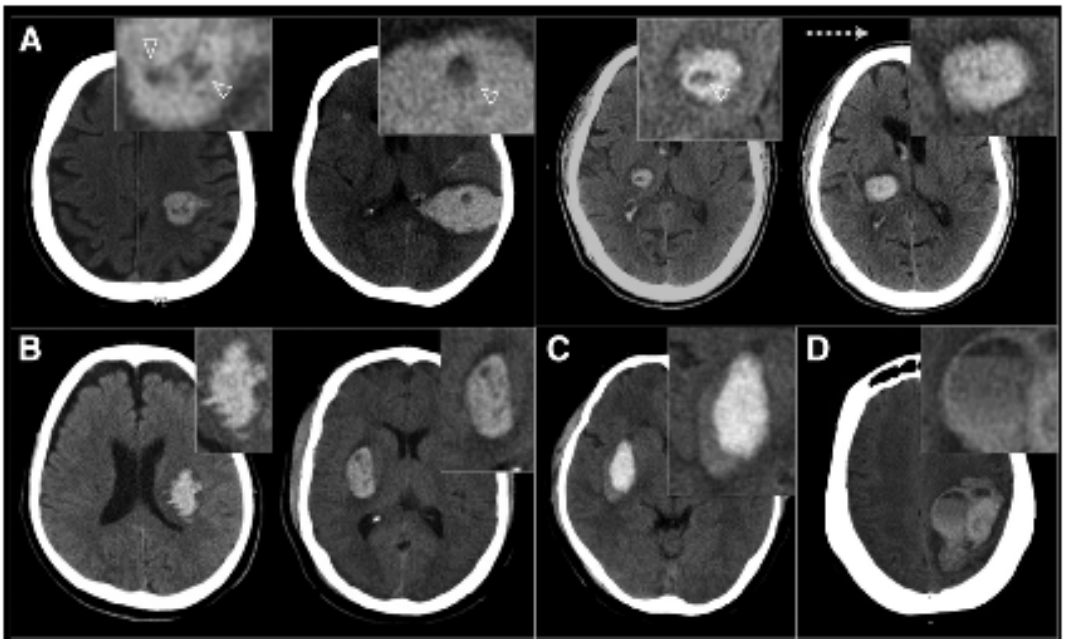

FIGURE 3 EXAMPLES OF REPORTED NCCT MARKERS OF HAEMORRHAGE EXPANSION. AXIAL SLICES OF ACUTE NCCT IN ICH. A, HYPODENSITIES INCLUDING FROM LEFT TO RIGHT, A SWIRL SIGN, A BLACK HOLE SIGN, AND A CENTRAL HYPODENSITY IN AN ICH DEMONSTRATING SIGNIFICANT EXPANSION ON REPEATED CT AFTER 8H. B, ICH WITH IRREGULAR MARGINS AND ICH WITH HETEROGENOUS DENSITY (ALSO QUALIFYING FOR HYPODENSITIES AND SWIRL SIGN. C, BLEND SIGN. D, FLUID LEVEL.

2.6.1.2.4 OTHER SIGNS

The “Island sign” consists of ≥3 small haematomas separated from the main haematoma or ≥4 small haematomas with some or all of them being connected to the main haematoma in at least one plane (34).

The “Satellite sign” depicts a small haematoma that is separated from the main haematoma, while being close enough (maximum distance 20 mm). This should not be confused with multiple spontaneous ICH, usually located in bilateral deep structures. (34)

2.6.2 MAGNETIC RESONANCE IMAGING (MRI)

MRI can identify ICH through the magnetic resonance properties of haemoglobin degradation products, more precisely deoxyhaemoglobin, which becomes a paramagnetic substance when it is deposited in the brain tissue, with a rapid dephasing of proton spins. This is viewed in T2, and more so in T2*-weighted images and susceptibility weighted images (SWI) (36).

MRI is also helpful due to its ability to detect chronic microbleeds. Cerebral microbleeds are well-demarcated, hypointense, rounded lesions on SWI sequences, and they represent cumuli of hemosiderin-laden macrophages. These microbleeds can help with the initial etiologic diagnosis, as a finding of chronic microbleeds in the cortical area is suggestive of cerebral amyloid angiopathy. On the other hand, it is typical to find the same microbleeds in a deeper location in patients with chronic hypertension.

The use of MRI in ICH can also help identify tumours or AVMs that might be the cause of the haemorrhage, as well as provide indication of haematoma growth through an analogous sign to the CTA spot sign. This is performed with contrast MRI (gadolinium), and the presence of contrast extravasation indicates greater risk of haematoma expansion (37).

MRI is especially sensitive to detect cavernomas, as they are a kind of vascular malformation that is not directly connected to the circulation, thus not showing up with ACT (as contrast can't reach the malformation) (38).

However, MRI availability can be a difficult aspect of early ICH evaluation, which is why most centres rely on CT scan to identify ICH in early stages, and will later perform the MRI to complete the etiologic studies.

2.6.3 TRANSCRANIAL ULTRASOUND (TCU)

The role of TCU in the management of ICH is not yet established, but some characteristics of this technique are helpful for this pathology.

Native transcranial B-mode ultrasound can be used to identify structural abnormalities (such as ICH), as well as their repercussion on the normal architecture of the CNS, such as midline shift (39).

Nonetheless, at the moment the diagnostic accuracy of TCU (even with the newer perfusion imaging studies) is not precise enough to support therapeutic decisions. This is due to the limitations of TCU, such as limited temporal bone window in about 15% of patients, and the inability of TCU to diagnose lesions in the upper part of the parietal and frontal bones (39).

While the diagnostic capability of TCU is unclear, its role in controlling for ICH complications is more established. Several variables that can be found with TCU have shown a correlation with poor outcome and haemorrhage expansion. These variables are midline shift, third ventricle (IIIV) diameter and haemorrhage volume (40). The possibility of performing this procedure at the bedside gives TCU an important role within ICH management.

2.6.4 ARTERIOGRAPHY

The role of conventional angiography has shifted over the last years, mainly due to the development of angiographic imaging through MRI and CT. Nowadays, conventional angiography should be performed in patients with ICH without an established etiologic diagnosis, particularly in young patients with clinical stability (41).

The goal with these patients is to find or confirm vascular malformations or tumours, and in some cases (such as with some AVMs) provide treatment.

2.7 TREATMENT

2.7.1 MEDICAL TREATMENT FOR ICH (INITIAL ACUTE MANAGEMENT)

The measure that has shown a better improvement on patients' outcomes, both in terms of mortality and morbidity, is the admission of the patient in a Stroke Unit or a neurocritical ward. This is necessary because these patients require constant monitoring to be able to detect fluctuations in their vital constants and clinical status. (42)

2.7.1.1 HAEMOSTASIS AND COAGULOPATHY, ANTIPLATELET AGENTS AND DVT PROPHYLAXIS

Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively, as soon as possible.

If the INR is elevated because of oral anticoagulants (ACO; vitamin K antagonists), therapy will be initiated with intravenous vitamin K and the replacement of the vitamin K-dependent factors. This should be done with prothrombin complex concentrates (PCCs), as it corrects the INR more rapidly than the alternative, fresh frozen plasma (FFP).

If the patient was taking the new oral anticoagulants (NACO: Dabigatran, Rivaroxaban or Apixaban), therapy should be performed with the respective antidote if it is available. For Dabigatran, the available antidote is Idarucizumab, and for Rivaroaban and Apixaban we can use Andexanet (even though the last one is not as widely available as Idarucizumab). We can also add PCCs to speed up the recuperation of the blood's coagulability. Another option, if the latest dose of the NACO was taken <2 hours earlier, is giving activated charcoal. Finally, dabigatran reversion can be done with haemodialysis.

When the patient is being treated with sodic heparin, protamine sulphate should be given to limit haemorrhage growth.

ICH patients are at risk for deep venous thrombosis, due to the extended immobilization time. This is why measures such as intermittent mechanic compression should begin the day of hospital admission. When the cessation of the bleeding is confirmed, we can start to give

subcutaneous low-molecular-weight heparin in prophylactic doses, especially in patients that are expected to have a lack of mobility after 1 to 4 days from onset.

If, despite this measures, the patient develops DVT or a pulmonary embolism (PE), measures such as systematic anticoagulation or an inferior vena cava (IVC) filter should be established. The decision of which treatment to perform depend on the days from ICH, the documentation of a stable haematoma size on neuroimaging and the practicality of removing the IVC filter on a later date. (28,42)

2.7.1.1.1 Recombinant activated coagulation factor VII (rFVIIa)

Treatments directed to avoid the haemorrhage are currently being investigated. One such treatment is the recombinant activated coagulation factor VII (rFVIIa). It is a fast-acting procoagulant drug, previously developed for the treatment of Haemophilia-related bleeding. rFVIIa as a haemostatic treatment has been the first intervention proven to significantly reduce haematoma groth in ICH. Clinical trials of dose scalation and safety have been performed, with the results showing that rFVII reduces ICH expansion in a dose-dependent fashion, especially when given within 4 hours of onset (43).

Nevertheless, most studies have had a difficult time proving rFVIIa's effectiveness. This is because most phase III studies up until now did not differentiate between patients with high risk for haematoma expansion (those that might benefit the most from rFVIIa's effects) from patients with a lower risk. Differences, therefore, were not as significant as expected (43,44).

The SPOTLIGHT study did aim to select patients depending on their risk for haematoma expansion, by using the Spot Sign of CTA to classify the study participants. This study, however, did not find significant differences between intervention and placebo groups. The main problem with this study was its large therapeutic window they used on their patients (up to 6h 30') (45).

After pre-clinical and clincal trials, an 80 µg/kg dose of rFVIIa (NiaStase RT®) has been found to have the best security profile while maintaining its procoagulant effect on the haemorrhage site. If given to patients at risk of haematoma expansion within a small time frame, this dose has

the potential to avoid the growth of the ICH. This, if possible, will improve the prognosis for ICH patients who, up until now, have to face high mortality rates and even higher disability rates.
Its adverse effects are related to its procoagulant action, being mainly myocardial infarction, ischaemic stroke, deep-vein thrombosis and pulmonary embolism (43). Overall, the potential risks of rFVIIa are relatively small when compared to the much greater risks of death and disability due to the untreated ICH itself.

2.7.1.2 BLOOD PRESSURE MANAGEMENT

Most ICH patients will benefit from an aggressive reduction of blood pressure. Current guidelines support a systolic blood pressure (SBP) objective of 140 mmHg, especially for patients with SBPs of 150 to 220 mmHg. This has been shown to improve functional outcomes for these patients. (42)
The most optimal time to initiate intensive hypotensive treatments is unclear, but recent evidence from the INTERACT-2 trial has shown that reducing BP under 140mmHG (SBP) in the first hours after the event has benefits. (46)

2.7.2 HOSPITAL MANAGEMENT AND PREVENTION OF SECONDARY BRAIN INJURY

As we have said, hospital management of ICH should be done within an intensive care unit or a stroke unit with physicians and nurses specialized in neurocritical care. This is one of the best measures we currently have to improve outcomes for ICH patients.
To avoid worsening of clinical condition, several parameters will be managed in these stroke units. These parameters are: blood pressure, glucose levels and temperature. Routine clinical evaluations will also be performed following the NIHSS to provide an objective measure of the patients' evolution. (42)
Blood pressure management has already been talked about in an earlier section.
Glucose management should be performed to avoid both hyperglycaemia and hypoglycaemia, as both entities have been associated with poor outcomes independently of the presence of diabetes mellitus.

Temperature management is just as important. Fevers should be treated with antipyretic measures (Paracetamol).

Finally, the management in the stroke unit should focus on avoiding complications for patients after ICH. These complications are, mainly:

- Seizures: prophylactic antiseizure drugs are not indicated, but any clinical seizure should be treated and secondary prevention with antiseizure drugs should be initiated in these patients. In patients with a depressed mental status disproportionate to the brain injury degree, continuous EEG monitoring can help to identify seizures and indicate the appropriate treatment.
- Dysphagia and aspiration: dysphagia tests should be performed routinely to detect the patients at risk for aspiration. Adapting the patient's diet will help prevent the development of pneumonia.
- Cardiac complications: a continuous EKG should be performed to detect cardiac events of different aetiologies.

As all systems can be affected in the critical state of these patients, caregivers in the stroke unit should be alert for signs of other complications (pulmonary, renal, gastrointestinal, metabolic…). (28)

2.7.3 PROCEDURES/SURGERY

Intracranial pressure (ICP) management should be performed as it is done with other neurocritical patients. Patients with a GCS score of ≤8, clinical features of transtentorial herniation or those with significant intraventricular haemorrhage or ventriculomegaly should have ICP monitoring. If necessary, ventricular drainage as treatment for symptomatic hydrocephalus can be considered.

As for surgical options, haematoma evacuation should be considered in patients with cerebellar haemorrhages of >3cm and neurological deterioration or brainstem compression or signs of obstructive hydrocephalus. Lobar haematomas can be drained when they are of significant

volume (>30mL) and with a location near the cortical surface in patients with a clear neurologic deterioration. This treatment is not indicated in deep haemorrhages. (42)

There is not enough evidence to support minimally invasive evacuations over the current procedures, but they show promise in the management of ICH.

Finally, decompressive craniectomy can be useful in patients with supratentorial haematomas that are in a coma state, with a significant midline shift or an elevated ICP resistant to medical treatment. (28,42)

2.7.4 REHABILITATION AND RECOVERY

All patients with ICH should have access to rehabilitation therapy depending on the deficits that they have after the event. This can include physical, cognitive and/or logopaedic rehabilitation depending on the patients' needs, and it should be started as soon as the patients' state allows. (42)

2.7.5 PREVENTION OF RECURRENT ICH

Secondary prevention of ICH will depend mainly of the etiologic diagnosis that is given to the event. Lifestyle modifications such as reducing alcohol intake, tobacco use and illegal drugs use, as well as the treatment of concomitant diseases are obviously necessary.

For hypertensive ICH, the obvious treatment should include an strict control of blood pressure, ideally below 130/80 mmHg. This BP management should also be done even if the cause is found to not be directly hypertensive. (46)

Secondary ICH causes should be treated if the risk of recurrence is considered too high. As always, a risk-benefit analysis will tell us the need of more intensive and/or aggressive treatments. An example of this risk-benefit analysis is whether to reintroduce anticoagulants or antiaggregating treatments to patients that have suffered ICH. The evidence is unclear, but if the risk of a thrombotic event is high, they should be reintroduced. (28,42)

A follow-up visit will be performed initially 3 months after the onset of ICH. Further visits will depend on the neurologist view of the patient and his control on risk factors for ICH recurrence.

Justification

As we have discussed, intracerebral haemorrhages have a great impact on society, especially in western populations, where risk factors such as hypertension are very prevalent.

Its significant incidence amplifies the fact that it has a very high mortality and morbidity associated. This is also worsened by the lack of an effective treatment, as the current management is largely supportive.

However, new treatments are on the horizon. Drugs such as rFVIIa have shown promise in the first studies, but at the moment the indication of rFVIIa for ICH is not clear, mainly due to the lack of clinical significance of the results of said studies. Some limitations for them are their population of study, and the wide therapeutic window used.

As for population, some studies (43,44) performed their trial on patients with ICH, independently of their risk of haemorrhage growth. This limits the studies clinical applicability, as not all patients with ICH are at risk of hematoma expansion, and a drug that aim to reduce this risk will not have any impact on them, while maintaining its risk for thrombotic adverse effects.

Therapeutic window is also critical for this drug. It has been shown that one third of patients with ICH will develop haematoma growth within the first 3 hours. This has been lacking in one study that did try to approach the lack of use of risk factors for haematoma growth, the SPOTLIGHT trial, which used the CTA “spot sign” to select its population (45). In this trial, the therapeutic window was of 6,5 hours, one that the authors remarked as a variable in need of improvement.

In conclusion, for the development of strategies to limit the effect it has on patients who suffer ICH we need to solve these problems. In this study we will use radio-markers for haemorrhage growth measured with NCCT to have a population of study at risk of haematoma expansion.

We also intend to have a therapeutic window of less than 4 hours from symptoms onset (shorter than previous studies with rFVIIa). We think that the use of NCCT, a more available tool than CTA, will allow more patients to have access to this treatment within the time where it is more effective, magnifying the effect of this trial in clinical practice.

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4 HYPOTHESIS

rFVIIa can significantly reduce haemorrhage expansion in patients with ICH and risk of haematoma expansion dictated by NCCT biomarkers of haematoma growth, when applied within a 4 hours margin from the onset of symptoms.

5 OBJECTIVES

Main objective:

- To evaluate whether rFVIIa reduces haematoma expansion in patients with risk of haematoma growth.

Secondary objectives:

- To investigate the effect rFVIIa has on short term clinical status (early neurological deterioration) of the patients it is given to.
- To investigate the effect rFVIIa has on the long term disability status of the patients it is given to.
- To investigate the effect rFVIIa has on the mortality of the patients it is given to.

6 METHODOLOGY

6.1 STUDY DESIGN

Multicentre, double blind, placebo-controlled randomized clinical trial.

6.2 STUDY SUBJECTS

Patients admitted to tertiary centres within the Institut Català de la Salut (ICS) with the diagnosis of acute primary spontaneous ICH (nontraumatic and non-anticoagulant-related ICH).

6.2.1 INCLUSION CRITERIA

- Patients above 18 years old.
- Baseline ICH volume 3-70 ml, estimated using the standard ABC/2 calculation on the NCCT.
- NCCT radio-markers for ICH growth: shape or density categorical score of 4 or 5.
- Previously independent (mRS of ≤2).
- Investigator is able to randomize and administer study drug within 60 minutes after NCCT and no later than 4 hours after stroke symptom onset.
- Assent-consent from patient or legally authorized representative (LAR) prior to enrolment, or a waiver of consent if patient/LAR is not possible prior to enrolment (Note: full informed consent to be obtained as soon as possible after study treatment administered).

6.2.2 EXCLUSION CRITERIA

Diagnostic/imaging Exclusions

- Brainstem or cerebellar ICH.
- Known or suspected secondary causes of ICH (trauma, aneurysm, vascular malformation, haemorrhagic 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).

- Baseline brain imaging showing evidence of acute or subacute ischaemic stroke (chronic infarcts are not an exclusion).

Clinical Exclusions

- Unknown time of symptom onset (wake up strokes will be excluded).
- Glasgow score <8 at time of initial screening by the enrolling team
- Evidence of thromboembolic risk factors, with a history within the past 6 months of any of the following: (a) myocardial infarction, (b) coronary artery bypass surgery, (c) angina, (d) ischemic stroke, (e) transient ischemic attack, (f) carotid endarterectomy, (g) cerebral bypass surgery, (h) deep venous thrombosis, (i) pulmonary embolism, (j) any vascular angioplasty, stenting (coronary, peripheral vascular or cerebrovascular) or filter (e.g. vena cava filter); and/or known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc.).
- Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis or coagulation factor deficiency.
- Any condition known that the investigator feels would pose a significant hazard if rFVIIa were administered.
- Planned surgery for ICH evacuation within 24 hours (not including ventricular drains).
- Known terminal illness or planned withdrawal of care or comfort care measures.
- Known participation in another therapeutic trial.
- Known or suspected hypersensitivity to the trial product.

Medication Exclusions

- Known unfractionated heparin use (check PTT and exclude if elevated above upper limit of local laboratory's reference range.
- Known low-molecular weight heparin, heparinoid, factor X inhibitor or direct thrombin inhibitor use within previous 24 hours.
- Known GPIIb/IIIa antagonist use in previous 2 weeks

- Known acenocumarol (or other anticoagulant) therapy with INR>1.40. Also applied for suspected cirrhosis.
- Concurrent or planned treatment with prothrombin complex concentrate, vitamin K, fresh frozen plasma, or platelet transfusion.

Tests/Laboratory Exclusions

- Pregnancy or lactation. Fertile women must have a negative pregnancy test prior to randomization.
- Current clinical symptoms suggestive of acute coronary ischaemia (e.g. chest pain).
- Baseline EKG evidence of acute coronary ischaemia (e.g. ST elevation in 2 contiguous leads, ST depression, new left bundle branch block).
- Baseline troponin T or troponin I >0.1 ng/ml.
- Baseline platelet count <50,000 or INR >1.4 or elevated PTT. (Note: Patients can be enrolled without waiting for results unless a bleeding abnormality or thrombocytopenia is suspected, the patient is known for acenocumarol, heparin or other anticoagulant, or anticoagulation use is uncertain.).

6.3 SAMPLE AND SAMPLING

A non-probabilistic consecutive sampling method is used.

Sample size calculations are based on data from the SPOTLIGHT study regarding ICH volume variation depending on rFVII administration in spot-sign positive patients, which according to the literature correlates well with NCCT radio-markers of haemorrhage expansion. The median growth of ICH volume at 24 hours is of 41mL. According to the current data, haematoma growth reduction of 20mL can be expected from the treatment, and this difference with the base group would be significant. We require 80% power to detect this difference. The calculations will be made accepting an alpha-risk of 0,05 in a bilateral contrast. With a 1:1 allocation ratio and

assuming a 10% follow-up loss rate, a sample size of 74 rFVIIa and 74 placebo is needed to detect a statistically significant difference between the groups.

A computer-generated randomization schedule will be created for the trial to ensure that the number of patients are equal in each group. The randomization will be performed after the informed consent has been acquired.

6.4 VARIABLES

6.4.1 SOCIODEMOGRAPHIC VARIABLES

- *Sex*: expressed as categories of woman and man.
- *Age*: expressed as the number of years.

6.4.2 CLINICAL VARIABLES

- *Date and time of stroke onset*, defined by the moment the symptoms are observed by the patient or by a witness.
- Presence of *vascular risk factors*: hypertension, diabetes, coagulopathy, smoking and alcohol habits, coagulopathy, dementia. They will be expressed as Yes or No.
- *Neurological state*: measured with NIHSS (see Annex) and recorded during stay in the Hospital and after 3 and 6 months and 1 year. It will be expressed as <4 Mild, <16 Moderate, <25 Moderate-Severe and ≥25 Severe.
- *Early neurological deterioration*. We will consider that a patient has suffered END when they have an increase in their NIHSS of >4 points within the first 48 hours. It will be expressed as Yes or No.
- *Disability status*: measured with mRS and recorded during stay in the Hospital and after 3 and 6 months and 1 year. It will be expressed as Independent (0- 2) and Dependent (3-5).
- Patient *mortality*: failure to follow up will be investigated and deaths will be recorded. We will consider mortality within the *stay on the hospital* and within the *first year* after the event. It will be expressed as the percentage of deaths during these periods.

- Hemodynamic parameters: they will be collected at baseline, and will be expressed as beats per minute for *heart rate,* number of mmHg for *blood pressure* (both systolic and diastolic), *temperature* as centigrade degrees and *oxygen saturation* as a percentage measured in capillary blood.

6.4.3 LABORATORY VARIABLES

- *Glycaemia* on admission measured in mg/dL.
- *Haemoglobin*, expressed as g/dL
- *Platelet count* will be expressed as number $x10^9$/L.
- Coagulation parameters: *INR* as a whole number, and as seconds for both *prothrombin time* (PT) and *activated partial thromboplastin time* (aTTP).

6.4.4 NEUROIMAGING VARIABLES

- *Haemorrhage location*: expressed as *deep* (for basal ganglia and thalamus), *lobar*, *brainstem* or *cerebellum*.
- *Initial haematoma volume* measured with a head CT scan using the ABC/2 formula.
- Haematoma growth: haematoma volume variation as measured with a head CT scan using the ABC/2 formula. It will be expressed in absolute values (mL) and relative values (%). We will consider that the haematoma has had significant growth with >20mL increase from the initial haematoma volume.
- *NCCT radio-markers of ICH growth*: shape or density categorical score (See Annex). Brain imaging will be performed with a NCCT scan at baseline and will be repeated 1 hour after drug administration, and at 24 hours post dosing to assess the rate and degree of ICH growth.

  NCCT scan will be performed with a standard 5-mm thickness axial slices.
- *Intraventricular hematoma (IVH)*. It will be expressed as Yes or No.

6.4.5 TREATMENT VARIABLES

- *rFVIIa administration*: a 80 µg/kg dose of rFVIIa (NiaStase RT®). Reconstitution and administration should be performed using the following procedures and using aseptic technique:
    - Storage: NiaStase RT® powder and histidine solvent should be stored between 2°C and 30°C, protected from light and not be frozen.
    - Reconstitution: NiaStase RT® powder and histidine solvent vials should be at room temperature and diluted to achieve a concentration of 1.0 mg/mL after reconstitution.
    - Administration: It should take place immediately. NiaStase RT® is intended for intravenous bolus injection only, and should not be mixed with infusion solutions or be given in a drip.
- General ICH treatment: the management of the patients will be recorded, including:
    - *Stroke unit admission*: It will be expressed as Yes or No.
    - *Hypotensive treatment*: Drugs taken (which ones and doses) will be recorded.
    - *Glycaemic control*: Drugs taken (which ones and doses) will be recorded.
    - *Antipyretic treatment*: Drugs taken (which ones and doses) will be recorded.
    - *Ventricular drain placement*: It will be expressed as Yes or No.

7 STATISTICAL ANALYSIS

Independent variable

- *rFVIIa (NiaStase RT®) administration* presented as a dichotomous variable.

Dependent variables

- Haematoma growth, expressed in absolute values (mL) and relative values (%)
- Clinical outcome, expressed as:
    - Early neurological deterioration within the first 48 hours.
    - Disability status (mRS) at 3 and 6 months and 1 year.
    - Mortality during hospitalisation and at 1 year.

Co-variables

- Age
- Gender
- Hemodynamic parameters heart rate, blood pressure oxygen saturation and temperature
- Laboratory variables: glycaemia, haemoglobin, platelet count, INR, PT and aTTP
- Cardiovascular risk factors
- Onset-to-baseline CT time
- Haemorrhage location
- Baseline haematoma volume
- Presence of IVH
- Baseline NIHSS
- Baseline mRS
- Stroke unit admission
- Ventricular drain placement
- Antihypertensive treatment

Analyses will be performed considering p values of ≤0.05 being statistically significant and p≤0.001 being highly significant. Confidence intervals (CI) will be expressed as 95%.

7.1 UNIVARIATE ANALYSIS

Results will be presented as mean and standard deviation (SD) for normally distributed continuous variables, as median and range for non-normally distributed continuous variables and as frequencies and percentages for categorical variables. mRS will be presented as quartiles.

7.2 BIVARIATE ANALYSIS

A comparison between the intervention and the placebo group will be established in order to evaluate differences and possible confusion variables. The potential confounders that we expect might play a role in differences between the groups are age, gender, medical history, toxic habits, baseline NIHSS and mRS , laboratory parameters, stroke unit admission, antihypertensive treatment, blood pressure, onset-to-baseline CT time, haematoma location, IVH, ventricular drain placement and baseline haematoma volume. For quantitative variables it will be done by means of T-Student tests, and for qualitative variables it will be done through $\chi 2$ tests.

7.3 MULTIVARIATE ANALYSIS

To evaluate the effect of rFVIIa between groups, accounting for the effect of confusion variables, a multivariate analysis will be executed.

To evaluate the effect of the drug on the degree of haematoma growth, an analysis of variance (ANOVA) will be done.

For the secondary dependent variables, which are all qualitative variables, a Cox model will be applied to estimate the hazard ratios between the intervention and the control group for each of the variables.

Once the hazard ratios are obtained, we will be able to calculate the absolute risk reduction (ARR) associated with taking rFVIIa, and from there we will obtain the necessary number to treat (NNT).

8 ETHICAL AND LEGAL ASPECTS

In order to enter in the trial, the patient or the legal authorized representative will have to agree to the informed consent given (see Annex). The informed consent is made in accordance with national regulations ("*Ley Orgánica 15/1999, del 13 de diciembre, de Protección de Datos de Carácter Personal", "Real Decreto Legislativo 1/2015, de 24 de Julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios"* and "*Real Decreto 1090/2015, de 4 de Diciembre, por el que se regulan los Ensayos Clínicos con Medicamentos, los Comités de Ética de la Investigación con Medicamentos y el registro español de estudios clínicos"*). Furthermore, the trial will have to be approved by the ethics committee in each of the ICS tertiary centres that will be involved in this trial.

Anonymity will be guaranteed at all costs. Data related to the trial will use the medical record numbers instead of the patients' names.

This study also respects the *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. June 1964. Last revision, October 2013*.

The authors declare that they have no conflict of interest.

9 STUDY LIMITATIONS

- Due to the acute characteristics of ICH, it is necessary to use a non-probabilistic consecutive sampling method. Nevertheless, the sample size is large enough to guarantee a good variable distribution in our groups.
- The sample size for this study would be quite big for a single hospital to assume within a small time frame. This is resolved by the fact that we will have a multi-centre approach to this study.
- One of the main limitations for the intervention variable is the time window for administration. Nevertheless, a short window is needed to evaluate the effectiveness of the drug, as wider windows have already been proven to not be effective. This short treatment window is one of the main limitation of the study, but the fact that we will use NCCT variables to select patients will make the results of this study applicable to smaller centres that only have access to NCCT, making the treatment administration feasible within the time given by the study.
- The lack of a consensus of a cut-off point for significant haematoma expansion creates a problem for the study. The 20mL growth cut-off point has been used in previous rFVIIa studies such as the SPOTLIGHT and STOP-IT, making it a good starting point for this study.
- The follow up for this study is of one year for each patient because of the need to evaluate the long-term effects that the therapy has in our patients. Dropout rates are expected to be low, as deaths are included within the data needed to collect.
- Systematic and information biases have to be taken into account. For this, the CT scans used in the study fulfil the highest criteria for quality, and all the scales used are validated and are applied in clinical practice throughout the world.
- The rates of adverse effects from both the CT scans used and the rFVIIa administered are expected to be limited. The imaging protocol's dose radiation is small, as we are talking about a NCCT. For the rFVIIa, the dosage used has been shown to have the best risk-benefits profile for patients with ICH.

- The fact that our study population is based only in Catalonia might make it difficult to generalize to other populations with different demographic characteristics. Nevertheless, most developed countries share demographic characteristics with our target population, making this limitation a minor one.

10 SCHEDULE

For this clinical trial we aim to recruit a minimum of 148 patients in the tertiary centres of the ICS. Based on current epidemiological data, the estimated recruitment time will be of one year. The healthcare staff involved will include: the neurologists of each hospital as the main investigators and neuroradiologists, pharmacists and nursing staff as co-investigators. A statistician will also be required to analyse the results, and an informatic technician will be hired in order to create the randomization software needed for the trial.

10.1 STAGE 1: COORDINATION AND REDACTION OF THE STUDY PROTOCOL

1) The first step is to elaborate the study protocol. After an extensive literature research, the study objectives will be established and the main variables will be defined. Based on this, the methodology for the study will be defined.
2) Following the redaction of the protocol, it will have to be evaluated by the relevant ethical committees (CEIC) and the pertinent administrative authorizations will have to be obtained (AEMPS).
3) The third step will involve several meetings in order to coordinate the participating hospitals. A system to notify the inclusion of pertinent patients will be established.
4) At the same time, the chronogram will be elaborated.

The estimated duration of this phase is of 4 months.

10.2 STAGE 2: SAMPLE COLLECTION, DRUG ADMINISTRATION, FOLLOW UP VISITS AND DATA COLLECTION

1) Recruitment of patients using a consecutive sampling method. Patients that meet the inclusion and exclusion criteria will be asked to participate and an informed consent will be obtained before they can be randomized in the trial.
2) Collection of baseline characteristics of the enrolled patients: baseline NCCT, NIHSS and mRS and blood tests.

3) Randomization between the two groups. This will be performed by a software developed for this study. Afterwards, the neurologists will administer the drug (*NiaStase RT®*) or placebo without knowing which one he or she is administrating.
4) Follow-up visits: a NCCT will be performed 1 hour after drug administration and 24 hours after drug administration. The clinical status will be evaluated during the hospital stay and 3 and 6 months and 1 year afterwards.
5) Data collection: neurologists will collect the information of each visit.
6) Coordination meeting: the main investigators will meet in order to assess if the protocol is well executed and to determine if procedural modifications are needed.

This phase will involve both investigators and co-investigators. The estimated duration of this stage is of 2 years according to the time needed to recruit and follow-up all 148 patients.

10.3 STAGE 3: STATISTICAL ANALYSIS AND INTERPRETATION OF RESULTS

In this phase the collected data will be processed and the required statistical analyses will be performed. Both the investigators and the statistician will participate in this stage.
After the results are obtained, they will be interpreted and conclusions will be drawn.

10.4 STAGE 4: PUBLICATION OF RESULTS

Finally, the results of the study will be prepared for publications. This is expected to take two months, and will be done by the investigators. The data will be summarized in the format of scientific papers and will be sent to medical journals for publication.

10.5 CHRONOGRAM

Stages	2019				2020												2021												2022				
	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M
STAGE 1: Coordination and redaction of the study protocol																																	
Scientific research and protocol elaboration																																	
Ethical (CEIC) and AEMPS aproval																																	
Initial coordination meeting																																	
Chronogram elaboration																																	
STAGE 2: Sample collection, drug administration, follow up visits and data collection																																	
Recruitment, data collection and study interventions																																	
STAGE 3: Statistical analysis and interpretation of results																																	
Statistical analysis																																	
Analyisis and interpretation of results																																	
STAGE 4: Publication of results																																	
Final article elaboration																																	
Results publication																																	

11 BUDGET

For the budget of this project procedures already included in the standard of care in ICH patients will not be reflected, as they are already accounted for in the national health system budget.

		QUANTITY	COST	TOTAL
Personnel cost	Neurologists	2 extra follow-up visits for 148 patients	25€/visit	€ 7.400,00
	Statician consultant	100h	35€/h	€ 3.500,00
	Informatic technician	10h	20€/h	€ 200,00
Executive expenses	Patient insurance	148 patients	50€/patient	€ 7.400,00
Neuroimaging expenses	Head NCCT	2/patient	154€/scan	€ 54.842,00
Material expenses	NiaStase RT®	80µg/kg in 74 patients (expected average dose: 6,4mg)	2.349€/mg	€ 1.112.486,40
	Placebo	10mL saline solution (0,9%) in 74 patients	13,89€/50 units	€ 20,55
Printing expenses	Informed consent	178 copies, each 4 pages	0,04€/page	€ 28,48
Publishing expenses	Publication in the Stroke AHA journal	70$ each printed page. Papers exceeding 4.500 words: 425$ per additional 1.000 words		€ 1.965,00
Presentation expenses	Inscription to national congress	2 investigators	400 €	€ 800,00
	Transport		180€ pp	€ 360,00
	Accomodation		150€ pp	€ 300,00
	Meals		200€ pp	€ 400,00
TOTAL				**€ 1.189.702,43**

12 ANNEX

12.1 THE NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

The NIHSS is a quantitative score that measures neurological deficits related to strokes. It focuses in key aspects of the neurological physical exam of stroke patients: level of consciousness, language function, neglect, visual fields, eye movements, facial symmetry, motor strength, sensation, and coordination.

Initially visualized as a tool for clinical trials, the NIHSS has become a wide spread clinical tool in the field. Its usefulness comes from its easy application (it can be performed in a mean of 6.6 minutes independently of severity and its outstanding inter-rater (mean k = 0.69) and intra-rater (mean k = 0,77) agreement, especially when used by vascular neurologists [1]

[1] Kasner SE, Chalela JA, Luciano JM, Cucchiara BL, Raps EC, McGarvey ML, et al. Reliability and Validity of Estimating the NIH Stroke Scale Score from Medical Records. Stroke [Internet]. 1999 Aug [cited 2019 Oct 16];30(8):1534–7. Available from: https://www.ahajournals.org/doi/10.1161/01.STR.30.8.1534

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

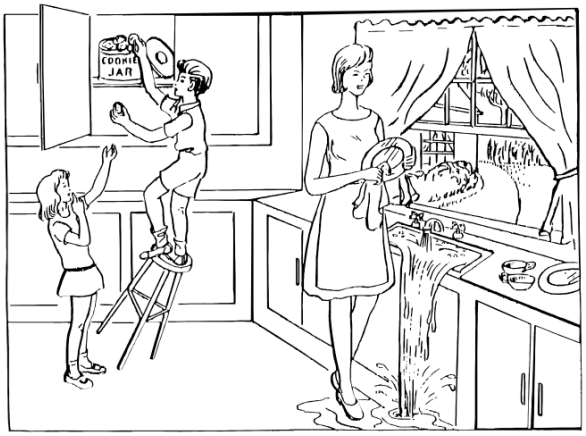
Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____



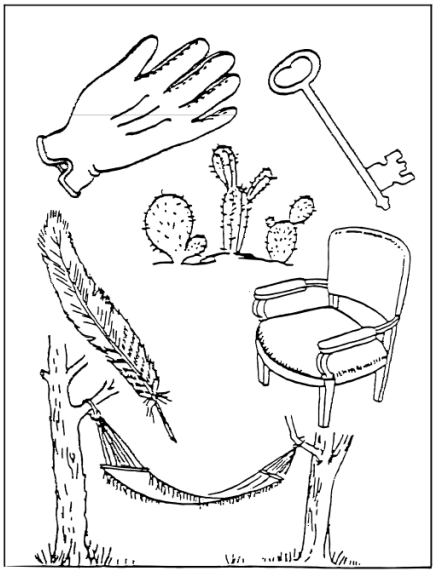
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

12.2 MODIFIED RANKIN SCORE (MRS)

The mRS is a clinician-reported measure of global disability. It is usually used to evaluated the long-term recovery from stroke (as it has no validity in the acute assessment of stroke). This score is simple, quick to apply and easy to interpret, something useful both in clinical practice and in the context of stroke trials (where it is widely used).

It consists of 7 categories (grades 0 to 6, with grade 6 being the death of the patient).

With respect to the original Rankin Score, some changes were made. The grade 1 of the RS ("no significant disability") was replaced by two grades: 0 for patients without symptoms, and 1 for patients without significant disability "despite symptoms". Additionally, grade 2 of mRS ("unable to perform all previous activities") is more conclusive than the previous grade of the RS ("unable to carry out some of previous activities").

The mRS has shown a good validity in relation to physiological indicators of stroke, such as stroke type, lesion magnitude and neurological impairment. It has also a good inter-rater reliability, especially in the context of a structured interview (k=0.78) and a strong re-test reliability (k=0.81-0.95). [2]

[2] Banks JL, Marotta CA. Outcomes Validity and Reliability of the Modified Rankin Scale: Implications for Stroke Clinical Trials. Stroke [Internet]. 2007 Mar [cited 2019 Oct 16];38(3):1091–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17272767

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____
Rater Name: _____
Date: _____

Score	Description
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

TOTAL (0–6): _____

12.3 SHAPE AND DENSITY NCCT CATEGORICAL SCORES

In order to provide an agreed visual representation of the terms “regular/irregular” and “homogeneous/heterogeneous”, Barras et al created two categorical scales reflecting the spectrum of appearance of ICH and Hounsfield unit density variation (Figure 2). They are ranged from category 1 (most regular shape and most homogeneous density) to Category 5 (most irregular shape and most heterogeneous density). They have to be evaluated by a trained neuroragiologist using the largest ICH slice (usually the central axial slice in the vertical dimension).
They found a correlation of the categories with the posterior haematoma growth, especially for categories 4 and 5, which is why in this study they are part of the main inclusion criteria. [3]

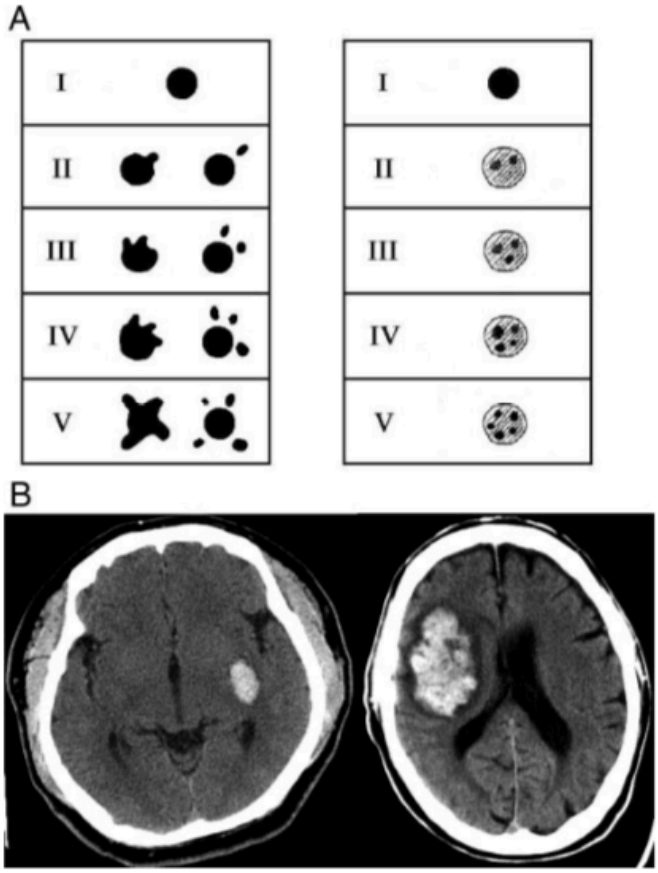


FIGURE 4 A, SHAPE (LEFT) AND DENSITY (RIGHT) CATEGORICAL SCALES AND (B) EXAMPLES OF HOMOGENEOUS, REGULAR ICH (LEFT) AND HETEROGENEOUS, IRREGULAR ICH (RIGHT).

[3] Barras CD, Tress BM, Christensen S, MacGregor L, Collins M, Desmond PM, et al. Density and Shape as CT Predictors of Intracerebral Hemorrhage Growth. Stroke [Internet]. 2009 Apr [cited 2019 Jul 29];40(4):1325–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19286590

12.4 INFORMED CONSENT

Títol de l'estudi: **Eficàcia del rFVIIa (NiaStase RT ®) en la reducció del creixement de l'hematoma i l'evolució clínica en pacients amb hemorràgia intracerebral amb radio-marcadors d'expansió d'hemorràgia en TC sense contrast**.

Aquest consentiment informat, del qual se li ha entregat una còpia, resumeix quins són els objectius de l'estudi i quina és la seva participació. Si vostè vol més detalls sobre l'estudi, pregunti lliurement a l'investigador i prengui's tot el temps necessari per a llegir i entendre aquest document.

L'hemorràgia intracerebral és una malaltia amb una gran mortalitat associada, i un risc elevat de presentar seqüeles greus en els pacients que la pateixen. Un dels principals factors pronòstics en les primeres hores des de l'inici de la clínica de l'hemorràgia cerebral és l'expansió de l'hematoma intraparenquimatós, ja que s'associa a un ràpid deteriorament neurològic. Determinades proves d'imatge, com la tomografia computeritzada (TC) o l'angiografia amb tomografia computeritzada (ATC) ens permeten fer una predicció de quins pacients tenen risc de creixement de l'hemorràgia. Aquesta predicció té una gran importància en el desenvolupament de nous fàrmacs i estratègies terapèutiques que tenen com a mecanisme d'acció la prevenció del creixement de la hemorràgia. Una d'aquestes estratègies és l'administració del factor VII activat recombinant (rFVIIa o NiaStase RT®). En aquest estudi es pretén esbrinar si l'administració del rFVIIa redueix el creixement de l'hemorràgia, i si això té un impacte en la mortalitat i les seqüeles derivades de l'hemorràgia intracerebral.

Vostè pot participar a l'estudi si, sent major de 18 anys, se li diagnostica una hemorràgia intracerebral mitjançant un estudi de TC cranial sense contrast, en el qual s'aprecien paràmetres que determinen un alt risc de creixement de l'hematoma. La seva participació durarà un any. Si compleix les característiques de la TC cranial i no té cap contraindicació, se li administrarà o bé el fàrmac NiaStase RT® o bé un placebo, de forma cega tant a vostè com a l'investigador. La TC cranial es repetirà a 1 hora i a les 24 hores de la infusió del fàrmac. Durant la seva estada a l'hospital, rebrà les cures normalment administrades i avaluacions normalment fetes als pacients amb hemorràgia intracerebral. També se li registrarà l'estat

clínic mitjançant l'escala NIHSS. A l'alta es registrarà el seu nivell de discapacitat mitjançant l'escala mRS. Es faran visites successives als 3 i 6 mesos i al cap de 1 any per avaluar tant les repercussions clíniques (NIHSS) com de discapacitat (mRS) que l'episodi d'hemorràgia intracerebral ha tingut en vostè.

Criteris d'exclusió:

Vostè no pot participar en l'estudi si:

- Té un volum d'hemorràgia de <3mL o >70mL, és a dir, o és molt petit i per tant té poques conseqüències o és massiu.
- Es sospita d'una causa secundaria de l'hemorràgia (tumors, malformacions vasculars…)
- S'evidencia una hemorràgia de tronc de l'encèfal o cerebel
- Ictus isquèmic agut o subagut concurrent
- Prèviament no era independent per les activitats de la vida diària (mRS de ≥3)
- Presenta una malaltia greu o terminal
- Estat de coma a l'avaluació inicial (mesurada per una puntuació al GCS de <8)
- Té factors de risc tromboembòlic o patologies que condicionen un risc elevat de sagnat (per exemple, hemofília)
- Està embarassada
- L'investigador no pot administrar el fàrmac abans de les 4 hores des de l'inici de la simptomatologia. De la mateixa manera, si no es coneix el moment de l'inici de la clínica (per exemple, si s'ha aixecat amb la simptomatologia establerta) no podrà participar a l'estudi.
- Es planeja una cirurgia d'evacuació de l'hematoma en les properes 24 hores (no incloent drenatges ventriculars)
- Pren fàrmacs que alteren el procés de coagulació (Heparina sòdica, heparina de baix pes molecular, antagonistes de GPIIb/IIIa o anticoagulants orals)

Riscs o efectes adversos

Tot i que la probabilitat és molt baixa, vostè pot presentar efectes adversos deguts a l'administració de NiaStase RT®, principalment infart de miocardi, ictus isquèmic, trombosi venosa profunda i embolisme pulmonar. La dosis donada ha estat provada per garantir un mínim risc d'efectes adversos mentre es manté l'eficàcia del fàrmac.

Donat que es faran diverses proves de TC cranial, rebrà una dosi de radiació superior a la que rep la població general. No obstant, el risc degut a la radiació és molt petit, ja que l'increment de dosi per TC cranial és comparable a 8 mesos de radiació per l'entorn que rep la població general.

Si participa a l'estudi, pot o no pot tenir efectes beneficiosos derivats de la inclusió a l'estudi. La informació que se'n deriva podrà ajudar a tractar pacients amb hemorràgia intracerebral en el futur.

Confidencialitat

Tota la informació que es recull de vostè serà confidencial. Les dades obtingudes, tant d'imatge com de valoració clínica, seran emmagatzemades en una base de dades per la seva divulgació amb fins científics i educatius. Se li reserva el dret de contactar amb els investigadors en qualsevol moment per retirar les imatges i la seva informació clínica de la base. En cas de mort, la seva família té el mateix dret de sol·licitar aquesta informació i retirar-la de la base si ho veu convenient.

Tot i que es podrà publicar la seva informació en congressos, la seva identificació no serà mai revelada.

La seva participació a l'estudi no comporta compensacions econòmiques. Si no compleix els criteris d'inclusió o té algun criteri d'exclusió, es continuarà amb el maneig diagnòstic i terapèutic habitual de la malaltia que presenta.

Consentiment

La signatura d'aquest document representa que ha entès la informació en relació a l'estudi i que està d'acord en participar. Si ho considera convenient, en qualsevol moment es pot retirar de l'estudi. En aquest cas, es prosseguirà amb el maneig habitual de la malaltia. Aquest document no allibera als investigadors o les institucions implicades de les seves responsabilitats legals i professionals. Qualsevol dubte o pregunta sobre l'estudi el podrà realitzar a l'equip investigador.

Signatura del participant o representant legal	Nom	Data
Signatura de l'investigador	Nom	Data