FIVHeMA: Intraventricular fibrinolysis versus external ventricular drainage alone in aneurysmal subarachnoid hemorrhage: A randomized controlled trial

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FIVHeMA: INTRAVENTRICULAR FIBRINOLYSIS VERSUS EXTERNAL VENTRICULAR DRAINAGE ALONE IN ANEURYSMAL SUBARACHNOID HEMORRHAGE: A RANDOMIZED CONTROLLED TRIAL

FIVHeMA: FIBRINOLYSE INTRAVENTRICULAIRE VERSUS DÉRIVATION VENTRICULAIRE EXTERNE SEULE DANS LA PRISE EN CHARGE DES HÉMORRAGIES SOUS ARACHNOÏDIENNES PAR RUPTURE D'ANÉVRISME: UN ESSAI CONTRÔLÉ RANDOMISÉ

Intraventricular fibrinolysis in aneurysmal SAH

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FIVHeMA: Intraventricular fibrinolysis versus external ventricular drainage alone in aneurysmal subarachnoid hemorrhage: a randomized controlled trial

FIVHeMA : Fibrinolyse intraventriculaire versus dérivation ventriculaire externe seule dans la prise en charge des hémorragies sous arachnoïdiennes par rupture d'anévrisme : un essai contrôlé randomisé.

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ABSTRACT

Introduction: Aneurysmal subarachnoid hemorrhage (SAH) is a devastating form of stroke, which often causes acute hydrocephalus requiring the insertion of an external ventricular drain (EVD). A major complication of aneurysmal SAH is delayed cerebral ischemia (DCI). As DCI is linked to the presence of blood within the subarachnoid space, it has been hypothesized that removing this blood may decrease the risk of DCI. This could be achieved by injecting a fibrinolytic agent through the EVD, a strategy called intraventricular fibrinolysis (IVF). Here, we propose to conduct a phase III trial to directly evaluate the impact of IVF after aneurysmal SAH.

Materials and methods: We will perform an open-label randomized controlled trial comparing the standard of care, i.e. EVD alone, to the experimental treatment, i.e. IVF. We plan to include 440 patients to be able to show a 10% increase in the rate of good functional outcomes in the EVD+IVF group compared to the EVD alone group (α=0.05 and β=0.8). To obtain such sample, a multicenter trial is required, and to date 17 research sites in France have agreed to participate.

Perspective: FIVHeMA would be the first phase III trial evaluating the relevance of IVF in aneurysmal SAH. If IVF is shown to be beneficial, then a new therapeutic tool will be available to improve the outcomes of aneurysmal SAH patients.

Keywords: subarachnoid hemorrhage, intracranial aneurysm, external ventricular drainage, intraventricular fibrinolysis, tissue plasminogen activator, delayed cerebral ischemia

RESUME

Introduction : L'hémorragie sous arachnoïdienne (HSA) par rupture d'anévrisme est une forme grave d'accident vasculaire cérébral, entraînant souvent une hydrocéphalie qui nécessite la pose d'une dérivation ventriculaire externe (DVE). Une complication majeure de l'hémorragie méningée est l'ischémie cérébrale retardée (ICR). Cette dernière étant liée à la présence de sang dans les espaces sous-arachnoïdien ; le drainage de ce sang pourrait permettre une diminution du risque d'ICR. Cela peut être fait en injectant un agent fibrinolytique dans la dérivation ventriculaire externe, ce qui s'appelle la fibrinolyse intraventriculaire (FIV). Nous proposons de réaliser un essai thérapeutique de phase III afin d'évaluer l'impact de la fibrinolyse intraventriculaire après une HSA par rupture d'anévrisme.

Matériels et méthodes : Nous réaliserons un essai contrôlé randomisé ouvert comparant les soins courants actuels, comprenant une DVE seule, au traitement expérimental qui est la FIV. Nous prévoyons d'inclure 440 patients afin de montrer une augmentation de 10% du taux de bons résultats fonctionnels dans le groupe dérivation DVE+FIV comparé au groupe DVE seule (α=0,05 et β=0,8). Pour obtenir ce nombre de patients, un essai multicentrique est obligatoire, et à ce jour 17 centres ont accepté d'y participer.

Perspectives : FIVHeMA est le premier essai randomisé évaluant l'intérêt de la FIV dans l'HSA anévrysmale. S'il est démontré un bénéfice de la FIV, alors une nouvelle arme thérapeutique sera disponible pour améliorer le devenir des patients présentant une HSA anévrysmale.

Mots clés : hémorragie méningée ; anévrisme cérébral ; dérivation ventriculaire externe ; fibrinolyse intraventriculaire ; activateur tissulaire du plasminogène ; ischémie cérébrale retardée.

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a devastating form of stroke, caused by intracranial aneurysm rupture. A few days after the initial hemorrhage, delayed cerebral ischemia (DCI) can develop, which is one of the main phenomenon affecting SAH outcomes (1). DCI has a multifactorial origin which includes arterial vasospasm, microthrombosis, inflammation, spreading depolarization, and excitotoxicity (2). No theory so far has connected these phenomenon together; consequently we have no way to prevent DCI from developing.

We propose a new theory to explain the origin of DCI: glymphatic system impairment. The glymphatic system plays a key role in the brain's metabolite clearance through the intracerebral circulation of cerebrospinal fluid (CSF). In a rodent model, we have shown that SAH severely impairs the glymphatic system (3). We hypothesize that this glymphatic dysfunction leads to accumulation of several brain metabolites, which in turn activate the phenomenon involved in DCI (4). We have also shown that injection of a fibrinolytic agent within the CSF—a technique called intraventricular fibrinolysis (IVF)—restores the function of the glymphatic system after SAH. IVF has already been investigated in humans in a Phase I trial, which demonstrated good safety (5). A few series have been published since then with good results but inadequate methodology (6). In 2013, a phase II trial was performed in 60 patients suffering from aneurysmal SAH who required external ventricular drain (EVD) insertion for acute hydrocephalus (7). Thirty patients received IVF, 30 others had only CSF drainage through the EVD. This trial reported a 15% decrease in the risk of DCI in IVF patients, and a 10% decrease in the rate of severe disability in the same group. Therefore, it makes sense to perform a phase III trial with appropriate power to determine the relevance of IVF in aneurysmal SAH.

METHODS

Design

We plan to perform a randomized controlled phase III trial to compare the standard of care, i.e. EVD alone, to the experimental treatment, i.e. EVD+IVF. Our trial will be a multicenter trial. As the standard treatment does not include injection within the EVD, the trial will not include injection through the EVD in the control group, thus the trial will have an open design. To minimize bias, the 6-month outcome assessment (in which the primary outcome will be assessed) will be performed by an independent investigator, blinded to the treatment received. We will analyze the outcome measures on the intent-to-treat population (namely, all patients who were randomly assigned to treatment and had any post-randomization data recorded). We also plan to perform a secondary analysis on the per-protocol population.

Setting and trial committees

The study protocol was approved by the "Sud-Ouest et Outre-Mer 4" Ethics Committee (CPPSOOM4 - Ref. CPP17-035a). It is included in the French public register of clinical trials, number 2017-000429-10. It is also registered on ClinicalTrials.gov under the identifier NCT03187405.

At the launch of the study on February 21, 2018, a total of 17 hospitals in France have started randomization for the FIVHeMA trial. It is expected that two additional study sites will start randomization in the near future.

Sponsor: Caen University hospital, France

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Participants and participant information and consent

The criteria for study participation are listed in Table 1.

Free, clear, and express consent will be collected after the patient has been informed of the goals of the research, the progress and duration of the study, the benefits, potential risks and limitations of the study, as well as the nature of the product studied and the opinion given by the ethical committee (art. L.1122-1) and after he/she has had adequate time to consider this information. The consent form will be signed and dated personally by the patient and the investigator before any procedure linked to the research is performed. The patient's participation in the study will be recorded in the patient's medical record at the time of the baseline visit.

We expect that a large portion of the patients included will have an altered level of consciousness, which could impair their ability to consent to participate in the study. In this case, a relative will be asked to provide consent. If no relative can be contacted, an emergency consent procedure will be applied. In the two latter cases, the patient will be

asked to provide consent as soon as his/her clinical condition allows him/her to understand the procedure and to provide a post-hoc consent to participate in the study.

Patients may terminate their participation in the study if they wish to do so, at any time and for any reason, or upon the decision of the investigator. This will be recorded in the patients' medical record. Any departure from the protocol will be documented and justified by the investigator. The observations folder must be filled out for the duration of the patient's participation. Those who leave the trial will not be replaced because the number of subjects to be included was maximized. The departures will be included in the final statistical calculation which will be done with the intent to process the data.

Everything possible will be done to contact those who are lost to follow-up, either through the patient's family doctor or through the mayor of the patient's residence and birthplace.

The study will be stopped if the benefit-risk balance becomes unfavorable during the trial, if the sponsor requests it based on an IMC opinion or upon request of the competent authorities.

Randomization

Patients will be randomly allocated (1:1) to receive either EVD alone or EVD+IVF (72 hours, 9 doses). We will use a computer-generated randomization code to randomize them.

In order to optimize the distribution in each group, a minimization procedure will be used on the following levels:

- Center
- Major prognostic factor for aneurysmal SAH (World Federation of Neurosurgery scale, WFNS scale): I, II, III, IV
- Age

- Classification of SAH seen on CT scan (Fischer scale): II-III vs IV

Interventions

Control group: EVD alone

As explained in the inclusion criteria section, all patients will have an external ventricular drain inserted. In the control group, the EVD will only be used to drain CSF. EVDs will be inserted using an aseptic technique via a frontal twist drill craniotomy. The catheter will be tunneled under the skin for approximately 4 cm and connected to the external CSF drainage system.

A brain CT scan will be performed immediately to ensure the catheter is in the correct position. The EVD will be left open, with the 0-level positioned approximately 15 cm above the tragus. The intracranial pressure (ICP) will be monitored every 30 minutes until the EVD is removed. The EVD will be clamped when the CSF becomes clear and the ICP is stabilized. After clamping, the ventricular catheter will be removed after 48 hours of monitoring to determine whether the clinical status and ICP remain stable.

After 3 failures of EVD clamping, an internal CSF shunt will be inserted.

Experimental group: EVD + IVF (Alteplase)

Alteplase will be dispensed by patient name/inclusion code in accordance with the protocol and the prescription prepared by the local investigator. A model prescription will be supplied by the sponsor. The prescription and dispensing information will be recorded for each patient.

<u>Methods of administration</u>:

Prior to administration, the 2 mg vial (with contains a total amount of 2.2 mg Alteplase, including 0.2 mg overage that will remain in the transfer syringe so the amount actually administered is 2 mg Alteplase) will be reconstituted to a final concentration of 1 mg/ml

Alteplase. To do so, 2.2 mL of sterile saline will be injected in the vial containing the Alteplase powder using a suitable precision measuring syringe under aseptic conditions. The EVD inserted and managed exactly as described in the control group. After the ruptured aneurysm is excluded and a brain CT scan is performed to ensure the catheter is inserted in the lateral ventricle, the IVF protocol will be started.

Justification of the dose and duration:

The effects of IVF have been extensively studied in another indication, spontaneous intraventricular hemorrhage (IVH), by the CLEAR study group (8). It has been shown in a phase II study that the best dose regimen of rtPA to ensure clot lysis without inducing symptomatic intracranial hemorrhage was 1 mg every 8 hours (9). This dose regimen was used in a recent large phase III trial, with good safety and efficacy (10). We hypothesized that this finding could be translated to our indication, which is very close to the previously studied one, thus we plan to use this dose. We chose a fixed dosing regimen of 9 doses over 72 hours for every patient, which is different from some previous studies that stopped IVF once no more blood was visible on the follow-up CT scans. However, the exact cut-off to stop IVF in SAH is difficult to define, contrary to IVH. Thus, we chose a pragmatic design to make IVF usable as a routine treatment. This approach was the same one adopted in the previously published phase II trial (7).

Description of other treatments

General management

The patients will be systematically admitted to a neuro-intensive care unit for at least 10 days. Analgesics will be administered to relieve pain as best possible (including opioids if necessary). To prevent DCI, all the patients will receive oral Nimodipine at a dose of 2 pills (30 mg) every 4 hours for 21 days. If the oral route is not feasible, the treatment will be administered through a nasogastric tube.

The aneurysm will be excluded as soon as possible (i.e. within 24 hours of admission). The type of exclusion procedure (i.e. clipping or coiling) will be chosen after a multidisciplinary team discussion. If both exclusion methods are feasible, the endovascular method will be preferred. Digital subtraction angiography (DSA) will be performed after the exclusion procedure to ensure the aneurysm is fully excluded before beginning IVF. In case of high ICP, the objective will be to maintain an ICP under 20 mmHg and a cerebral perfusion pressure (CPP) between 50 and 70 mmHg. To achieve these goals, three levels of treatment can be used:

-Rest in silence and in the dark, in the 30-degreeTrendelenburg position, head and neck in the axis of the trunk, avoiding cervical or abdominal compressions. Control of temperature, blood pressure, glycemia and natremia.

-Increase the volume of CSF drained. Increase the sedation. Use of curare.

-Osmotherapy by macromolecules and/or hypertonic saline. In case of intractable high ICP, potential use of barbiturates or decompressive craniotomy.

In conscious patients, the monitoring will mainly be based on the clinical examination; transcranial Doppler will be used at discretion of the local investigator. In a comatose patient, transcranial Doppler will be performed daily. In case of suspicious findings, a perfusion CT scan will be performed. In case of DCI, the primary treatment will be controlled high blood pressure. If there is no response to HBP, in-situ intra-arterial treatments will be performed. Medical complications such as seizure will be treated by Levetiracetam. Deep vein thrombosis will be prevented by the introduction of prophylactic low molecular weight heparin 3 days after exclusion of the ruptured aneurysm and at least 24 hours after the last dose of IVF. High or low glycemia will be avoided. As with every patient in neuro-intensive care, several laboratory tests will be performed; their prescription will be at discretion of the physician in charge of the

patient. These could include measurements of blood electrolytes, glycemia, blood oxygen level, bacterial examination of CSF, etc.

List of authorized treatments

Most of the medications used to manage aneurysmal SAH will be allowed, including analgesic therapy, antihypertensive drugs, vasopressive drugs, antibiotics, and anesthetic drugs. However, anticoagulant and antiplatelet therapy will be prohibited before and during the period when IVF therapy will be performed. But 24 hours after the last injection of Alteplase in the ventricular drain, these medications will be allowed as needed. In the EVD alone group, low molecular weight heparin therapy will be used if necessary, once the aneurysm has been excluded.

List of prohibited treatments during IVF

-Systemic antifibrinolytic therapy, including Tranexamic Acid and Ɛ-Aminocaproic Acid before the ruptured aneurysm is excluded and during IVF (3 days)

-Antiplatelet drugs, including acetylsalicylic acid (Aspirin®, Kardegic®) and its derivates, and Clopidogrel (Plavix®) before or during IVF therapy

-Anticoagulant drugs, including heparin therapy (Heparin) and low molecular weight heparin therapy (Lovenox®, Innohep®), vitamin K antagonists (Previscan®, Sintrom®, Coumadin®) and the newer oral anticoagulants (Dabigatran®, Rivaroxaban®).

Primary outcome measure

The primary endpoint is the patients' functional outcome evaluated on the modified Rankin Scale (mRS) 6 months after the aneurysm rupture. We will compare the proportion of patients in each group without severe disability: mRS = 0–3.

Secondary outcome measures

The secondary endpoints are:

- Mortality rate 3 weeks, 3 months and 6 months after the aneurysm rupture

- DCI occurrence rate (brain CT scan) or clinical deterioration caused by DCI
- Internal CSF shunt surgery rate (chronic hydrocephalus) 3 and 6 months after the aneurysm rupture
- Number of permanent catheter obstructions requiring insertion of a new EVD catheter
- Complication rate: rebleeding, bacterial meningitis, and aseptic meningitis
- Return to work at 6 months' follow-up
- Evaluation of quality of life at 6 months follow-up: MOS SF-36 scale, Pichot scale

Practical roll-out of the study

The inclusion procedure and follow-up schedule are summarized in Figure 1.

Anticipated number of patients to be included in the study

The main objective is to demonstrate the efficacy of IVF on the patients' outcome, i.e. functional outcome better with EVD+IVF than with EVD alone (control group).

The difference between the two groups will be studied based on the percentage of patients with a good functional outcome at 6 months' follow-up. The functional outcome will be evaluated using the mRS; a good functional outcome will be defined as a mRS score between 0 and 3. Since the primary outcome is binomial, we based our sample size calculation on the percentage of good functional outcomes in the control group and an effect size of the treatment of interest, namely EVD+IVF. Using PROC POWER (SAS 9.4), we calculated that a fixed sample size of 390 patients was necessary to detect a 10% absolute increase in good functional status, from 75% in the control group (7) to 85% in the EVD+IVF group with a power of 80% and a type I error of 5% (one-sided hypothesis). Because the effect size is largely unknown, we considered a sequential plan with two interim and one final analysis, with each step having the possibility of stopping the trial for futility or efficacy (PROC SEQDESIGN

in SAS 9.4). Following an O'Brian and Fleming plan, with one interim analysis after 50% of the data is collected (220 patients) and a second interim analysis after 75% of the data is collected (330 patients), the total sample size for the final analysis is 440 patients. The study will be terminated for futility if nominal p-values are above 0.31665 and 0.12459 at stages 1 (220 patients) and 2 (330 patients), respectively. The study will be terminated for efficacy if nominal p-values are below 0.0095 and 0.02774 at stages 1 and 2, respectively. If the study goes to the final analysis (i.e. stage 3, 440 patients), the p-value for statistical significance will be 0.0486. These analyses will be conducted independently from investigators and presented to the Data and Safety Monitoring Board.

Anticipated statistical methods

A flow chart will summarize the number of screened, randomized and analyzed patients according to CONSORT guidelines. Baseline characteristics will be described by counts (percentages), mean (standard deviation) and median (interquartile range), as appropriate, according to their randomized group. Regarding the primary outcome, the percentage of patients with good functional status (0,1,2,3) based on to the mRS 6 months after the aneurysm rupture will be compared between groups by a stratified Chi-square test accounting for the factors used in the randomization (WFNS= 1-2 *versus* WFNS= 3-4). The statistical tests performed will be unilateral to limit the number of patients needed for the study and because we want to test a specific hypothesis—IVF+EVD is superior to EVD alone. According to this one-sided superiority hypothesis, the absolute difference of the primary outcome between groups will be computed with 100% minus 2*nominal alpha confidence intervals, stratified by design factor used for the randomization (WFNS= 1-2 *versus* WFNS= 3-4). The 100% minus nominal alpha lower bound of this difference will demonstrate superiority if above 0. The full-set

analysis will include all randomized subjects. The analyses will be carried out in the intention to treat population to minimize potential bias. In case of missing data for the primary outcome measure, multiple iterations will be performed to comply with the intent to treat approach and the complete case analysis will be performed as a sensitivity analysis.

Three pre-planned subgroup analyses of the primary outcome will be performed:

(1) the first subgroup analysis will separate patients with severe intraventricular hemorrhage (Graeb score superior or equal to 6) from patients without severe IVH;

(2) the second subgroup analysis will separate patients with high grade SAH (WFNS score III-IV) from patients with low grade SAH (WFNS score I-II);

(3) the third subgroup analysis will separate patients who received the full IVF treatment (9 doses) versus patients who received an incomplete course of IVF treatments (≤ 8 doses). The statistical analysis will be done using SAS software version 9.4 by Prof. Jean-Jacques Parienti of the Unit of Biostatistics and Clinical Research of the Caen University Hospital, France.

Safety evaluation

The safety parameters were determined by considering the potential risks associated with the protocol (above):

-*Risk of intracranial bleeding*: during the 3 days of IVF treatment, the occurrence of ICH will be evaluated by continuously monitoring clinical parameters and ICP in the neuro-intensive care unit. In case of suspicion (i.e. appearance of new neurological symptoms) the treatment will be suspended until a new brain CT scan can be performed on an emergency basis to confirm the occurrence of a new ICH. If no ICH is identified, the treatment will be continued. If a new ICH is detected, the treatment will be stopped permanently. Moreover, a daily CT scan will be performed during the treatment period

(D1 to D3) to rule out any asymptomatic ICH. Finally, a brain CT scan 24 hours after the last injection of Alteplase will be performed to detect any delayed asymptomatic ICH.

-*Risk of catheter-related bacterial meningitis*: the occurrence of bacterial meningitis will be based on standard examination, including clinical parameters (cranial nerve signs, headache, photophobia, seizures, stiff neck, altered mental status, irritability, inflammation at the catheter site, and fever) and blood sample analysis (elevated neutrophil levels, elevated C-reactive protein, etc.). If catheter-related bacterial meningitis is suspected, CSF sampling through the EVD and laboratory testing will be performed on an emergency basis (CSF culture) to allow antibiotic treatment to be initiated as soon as possible.

-*Risk of Alteplase-related aseptic meningitis*: monitoring for aseptic meningitis will be based on standard examination, including clinical parameters (cranial nerve signs, headache, photophobia, seizures, stiff neck, altered mental status, irritability, inflammation at the catheter site, and fever) and blood sample analysis (elevated neutrophil levels, elevated C-reactive protein, etc.). In this case, CSF sampling through the EVD and laboratory testing will be performed on an emergency basis (CSF culture) to differentiate between septic and aseptic meningitis. The diagnosis of aseptic meningitis will be made based on three negative CSF cultures.

<u>IVF will be stopped in case of</u>:

-intracranial rebleeding, confirmed on brain CT scan

-suspicion of meningitis, septic or aseptic, even before the CSF culture results are available.

The IMC will perform three interim safety assessments to evaluate the risk of IVF, after 50, 220 and 330 patients have been included. The study will be stopped if the frequency

of the three above-mentioned complications (symptomatic ICH, bacterial meningitis, aseptic meningitis) in the IVF group exceeds the one in the EVD alone group. Arms will be unblinded for members of the IMC. The following data will be extracted after 50 (after the Day 4 monitoring of the 50th patient), 220 and 330 patients (after the 6-month assessment of the 220th and 330th patient, respectively) have been included:

- serious adverse events, including the expected complications,
- neurological outcomes (if available), including clinical examinations and the mRS
- data provided by the repeated brain CT scan.

The IMC has an advisory role for our study: the sponsor decides whether or not to implement the recommendations made by that committee. The committee can be also consulted by the sponsor at any time (for example to analyze new safety information). All of the committee's analyses and conclusions will be sent to the French competent authority (ANSM).

DISCUSSION

FIVHeMA will be the first phase III trial to evaluate the relevance of IVF in aneurysmal SAH. While many phase III trials have been performed in aneurysmal SAH to find an effective neuroprotective treatment, most of them have failed. The impact of our study in the neurosciences field could be considerable: if positive, this could be the first neuroprotective treatment validated in brain injury in the past 20 years. In France, about 1000 patients each year would benefit from IVF. If 10% fewer patients experienced severe disability, then 100 patients each year would be saved from it. Moreover, we believe that IVF, by acting on the glymphatic system—the brain's waste clearance system—may also improve patients' quality of life. Lastly, the economic benefit

associated with our study could be considerable. If IVF is proven to be effective, it could save up to 2 million Euros each year.

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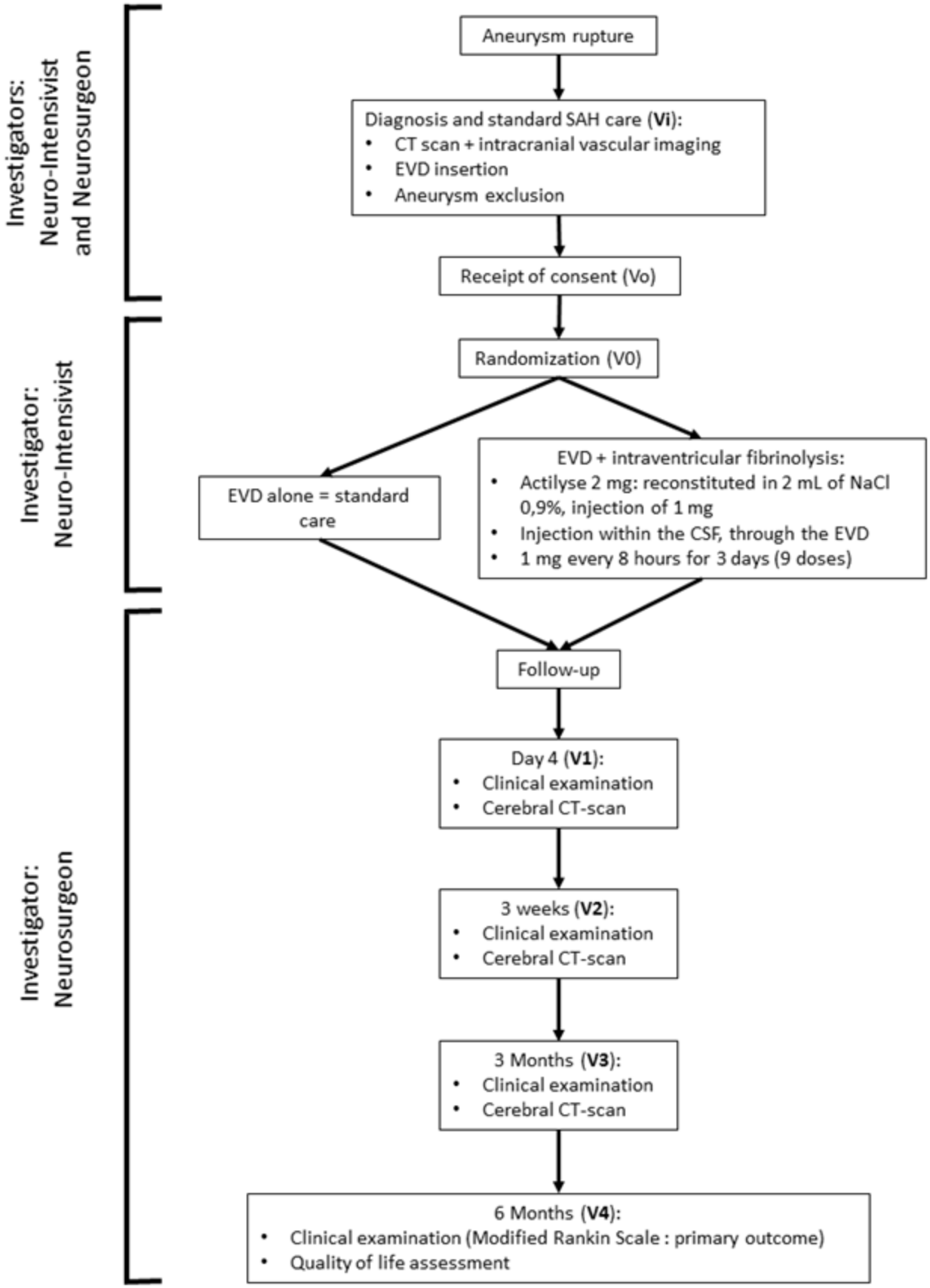
TABLE LEGENDS

Table 1: Inclusion and exclusion criteria for the study

FIGURE LEGENDS

Figure 1: Practical roll-out of the study.


Investigators: Neuro-Intensivist and Neurosurgeon
Investigator: Neuro-Intensivist
Investigator: Neurosurgeon
Aneurysm rupture
Diagnosis and standard SAH care (Vi):
• CT scan + intracranial vascular imaging
• EVD insertion
• Aneurysm exclusion
Receipt of consent (Vo)
Randomization (V0)
EVD alone = standard care
EVD + intraventricular fibrinolysis:
• Actilyse 2 mg: reconstituted in 2 mL of NaCl 0,9%, injection of 1 mg
• Injection within the CSF, through the EVD
• 1 mg every 8 hours for 3 days (9 doses)
Follow-up
Day 4 (V1):
• Clinical examination
• Cerebral CT-scan
3 weeks (V2):
• Clinical examination
• Cerebral CT-scan
3 Months (V3):
• Clinical examination
• Cerebral CT-scan
6 Months (V4):
• Clinical examination (Modified Rankin Scale : primary outcome)
• Quality of life assessment

Inclusion criteria

- Patients (age 18–75) with SAH on initial CT scan examination
- SAH associated with hydrocephalus requiring external ventricular drainage
- Confirmation of an associated intracranial aneurysm by vascular imaging
- Less than 24 hours from onset to admission
- Exclusion of the ruptured aneurysm by surgical clipping or endovascular coiling before IVF
- Oral information about study and informed consent from the patient and/or a relative
- Patient affiliated with the French health insurance scheme
- Patient or a relative who speaks French fluently

Exclusion criteria

- Patient with severe clinical presentation on admission: WFNS score = 5
- Associated intracerebral hematoma of more than 2 cm at its widest
- Minor SAH diagnosed on lumbar puncture: original Fisher grade = 1
- Fisher Grade II to IV SAH not requiring the insertion of an EVD (with good clinical presentation and without hydrocephalus on the initial CT scan)
- Aneurysm cannot be excluded within 72 hours of its rupture
- Patient with platelet anomaly: patient previously treated with antiplatelet therapy or treated with antiplatelet therapy after exclusion of the ruptured aneurysm or platelet count < 100,000/mm^3
- Severe coagulopathy: heparin therapy with a TCA up to 1.3, oral vitamin K antagonist therapy without reversion, new oral anticoagulant, constitutive coagulopathy (hemophilia)
- Pregnant or lactating woman (systematically assessed by a pregnancy test—β-HCG—for women under 65 years of age)
- Person under guardianship