COVER LETTER

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PREVENTIHS STUDY
PREvention of VENous Thromboembolism In Hemorrhagic Stroke patients

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Introduction

Venous thromboembolism (VTE) is a common life-threatening complication in patients with stroke. In these patients, an average incidence of asymptomatic deep-vein thrombosis (DVT) of 50% has been reported (1). Additionally, pulmonary embolism (PE) has been reported to occur in 2% of patients with stroke (2) and 5% of early deaths after stroke is reported to be due to PE (3). Prospective trials have shown that both unfractionated heparin and low molecular weight heparin are effective in reducing VTE and PE in ischemic stroke patients (4). Current guidelines recommend the use of these agents in ischemic stroke patients with risk factors for VTE (5). The role of anticoagulants for the prevention of VTE in acute hemorrhagic stroke is uncertain and anticoagulant agents have not gained wide acceptance because of concern about possible increases in hematoma enlargement. To support this, a recent meta-analysis has indicated that in patients with hemorrhagic stroke, early anticoagulation is associated with a significant reduction in PE and a non-significant reduction in mortality, with the trade-off of a non-significant increase in hematoma enlargement (6). These meta-analysis results cannot be reliably applied to clinical practice due to the low quality of the studies included.

Objectives

In this multicenter, randomized trial, the use of standard treatment alone (compression stockings and /or intermittent pneumatic compression and /or early mobilization) will be compared with the use of standard treatment plus the

administration of the low molecular weight heparin enoxaparin for the prevention of VTE in patients with acute hemorrhagic stroke. Enoxaparin will be started after 72 hours from stroke onset and will be continued for 10 days. The principal outcome measures will be symptomatic, objectively confirmed VTE or asymptomatic DVT (proximal and/or distal) as assessed by ultrasound examination. Because the use of anticoagulants in patients with hemorrhagic stroke could be associated with a high risk of re-bleeding, the safety of enoxaparin in this clinical setting will also be assessed.

Methods

Study population

The study will be designed as a multicentre, prospective, randomised, open, blinded endpoint clinical trial. Consecutive bedridden patients (a score of 3 or 4 per item 6 of the NIHSS or the impossibility to maintain an upright position such as in the case of ataxia in patients with hemorrhagic cerebellar stroke) 18 years of age or older with primary intracerebral hemorrhage on CT scan or patients with intracranial hemorrhage during treatment with oral anticoagulants (after reversal), will be assessed for eligibility.

Exclusion criteria will include: intracranial hemorrhage due to vascular malformation, bleeding disorders (defined by a prothrombin time more than 30% longer than the control value or a platelet count of less than 100,000 per cubic millimetre), renal failure defined as a clearance of creatinine less than 30, severe hepatic failure, known neoplastic disease, pregnancy, necessity of therapeutic anticoagulant or antiplatelet agents for concomitant disease, participation in

other ongoing clinical trials or patient refusal to consent. The study protocol will be approved by the local ethics committees of the participating hospitals.

Study design and interventions

Patients will be randomized 72 h after the onset of symptoms after having undergone a brain CT scan which will be considered the baseline examination. This CT must exclude a re-bleeding compared to the CT at admission. In the face of re-bleeding, patients will be excluded from randomization. Re-bleeding will be defined as an increase of 10% in the basal volume measured by standardized and validated criteria (9).

Patients will be randomized over the phone using a random list of numbers (even numbers – treatment A; odd numbers – treatment B) to receive enoxaparin 0.4 ml die plus standard therapy (group A) or standard therapy alone (group B). Treatment with enoxaparin is scheduled to last 10±2 days. A venous eco-Color-Doppler examination with a compression test will be performed bilaterally on the lower limbs 10±2 days following the start of treatment. This exam will evaluate the following three points: the common femoral vein at the groin, superficial femoral vein at the mid-thigh and the popliteal vein at the popliteal fossa up until the trifurcation.

Included patients will be visited on a daily basis during their hospital stay in order to monitor any complications as well as check for symptoms and signs of venous thromboembolism. An ultrasound exam of the lower limbs will be performed expediently on any patient having clinical signs of suspected deep venous thrombosis. If this exam results being negative, the patient will undergo a second ultrasound exam according to the timetable set out in the protocol. An

ultrasound exam of the lower limbs and a CT thoracic angiography will be performed expediently on any patient having clinical signs of pulmonary embolism. If these exams result being negative, the patient will undergo a second ultrasound exam according to the timetable set out in the protocol.

A positive result from either the CT thoracic angiography or an ultrasound exam will necessitate a treatment with heparin (unfractioned or at a low molecular weight), warfarin or vena cava filter according to clinical need. Brain CT scan will be performed 10±2 days from the start of treatment or whenever there is a worsening of the clinical condition, defined as an increase of 4 points or more on the NIHSS score. Treatment with heparin will be suspended whenever CT shows an increase of at least 10% in the volume of cerebral hemorrhage, notwithstanding clinical condition. Lesion volume will be measured with the methodology elaborated by Broderick et al. (9). Antithrombotic treatment different from that which is planned by the protocol during the treatment period will be forbidden except in the case of clinical need (i.e. diagnosis of venous thromboembolism). Follow-ups at 30 and 90 days after cerebral hemorrhage will be performed either in-clinic or over the phone in order to monitor for any clinical signs of venous thromboembolism or re-bleeding. All deaths will be recorded.

The final follow-up, at 90 days, will be carried out over the phone by an independent physician blinded to the treatment received. After the treatment period outlined in the protocol (10±2 days), the treating physician will be able to determine future therapy.

In the event of positive ecographs, patients can be treated with heparin (unfractioned or low molecular weight heparin), warfarin or vena cava filter, according to necessity.

Neuroradiological exams as well as pulmonary angio-CTs will be evaluated by the study coordinating centre (University of Perugia) blinded to the clinical condition of the patients.

Venous thrombo-embolic and intra- and extra-cranial hemorrhagic events will be judged blindly on the type of treatment received by the following physicians from the University of Perugia: Giancarlo Agnelli, Andrea Alberti, Cecilia Becattini, Valeria Caso, Francesco Guercini e Michele Venti.

The study will be divided into 3 sections: I. Patients 1-120; II. Patients 121-240; III. Patients 241-406.

Given the complexity of the study, a data safety monitoring board (DSMB) will be responsible for evaluating the progress of the study after the closure of section I. The second evaluation will performed by the DSMB after the closure of section II. The DSMB will be composed of three independent and external physicians, one of which is a statistician, to the coordinating centre: Gualtiero Palareti, University of Bologna, Gian Paolo Reboldi, University of Perugia and Leandro Provinciali, University of Ancona.

Risks of treatments and procedures.

Risks include intra and extracranial hemorrhagic complications associated with heparin use and/or complications such as ulcers and subcutaneous hematomas due to the use of elastic stockings. There are no anticipated risks due to diagnostic procedures, given that all of the exams outlined in the protocol will be usually performed in clinical practice.

Risk-benefit evaluation

Patients with ICH have a reported risk of ~ 20% for thromboembolic complications. The use of prophylactic heparin, where it has been tested on cancer, orthopedic and neurosurgery patients, has reduced the incidences of these events and their respective mortality rates and hospital stays. These studies have also reported an increase in ICH in patients treated with heparin compared to placebo. Whereas, at the end of follow-up, a net benefit, which was statistically significant, remained for those patients treated with heparin compared to those on placebo.

End-points

The primary endpoint of this study will be made up of either: 1) symptomatic venous thromboembolism objectively documented as proximal/distal DVT or pulmonary embolism or 2) asymptomatic proximal/distal DVT documented by ultrasound at the end of follow-up. Diagnostic criteria which has already been validated will be utilized (10).

Secondary end-points:

1. The number of symptomatic and asymptomatic intracranial bleedings as described above in Methods;
2. The number of extracranial bleedings will be divided into two groups: major and minor. Major bleedings will be defined as 1) presence in critical organ sites including the retroperitoneal and intraocular spaces, 2) a reduction of 2 or more gr/dL of hemoglobin or the need to carry out a transfusion of 2 or more units of concentrate red blood cells or 3) fatal bleeding. Medical

intervention, including any interruption of study treatment, will be considered clinically relevant but not a major bleeding for all the events that do not satisfy the above described criteria. All other bleedings will be considered minor;

3. The combined end-point of disability (modifed Rankin Scale ≥ 3) and mortality for any cause at 90 days;
4. Mortality alone at 90 days.

For each endpoint event, centres will be required to submit adequate documentation which will be evaluated by the Adjudication Committee.

Statistical analysis

The primary and secondary endpoints will be evaluated with an intention to treat analysis that will include all the randomized patients in both groups which will be treated or not, depending on the randomized group. Differences between the two groups will be calculated using the Chi-square test. The odds ratio, as well as relative risk will be calculated with confidence intervals. All predefined endpoints will be assessed without adjusting for confounding factors. Post-hoc analysis (logistic regression) will be carried out, in the face off any possible un-matching between the two groups, by adjusting for the confounding factors. Logistic regression analysis will be performed by including all the variables and then retaining those having a statistical significance of $p<0.1$.

The same statistical analyses will be carried out on the per protocol population; that is, those patients that are randomized and assessed for type of treatment actually administered.

Sample size was calculated on the basis of an expected incidence of TVE equal to ~ 20% of non-treated patients, and ~ 10% of enoxaparin treated patients. Both groups will need approximately 203 patients each, in order to evidence a statistical difference of 50% with an alpha-value equal to 0.05 and a beta value of 0.20. The study will be multi-centered with an expected 20 Italian centers participating over a 2-year enrollment period.

Treatment of data

Data results will be published within 12 months of the study's termination. The principal investigator grants to every participating researcher the right to utilize all of the data and results for teaching and lecture purposes as well as scientific publications.

Ethics

The study will be carried out in accordance with the Helsinki and GCP declarations, as well as with local governing laws.

References

1. Davenport RJ, Tennis MS, Wellwood I, Warlow CP. Complications following acute stroke. Stroke 1996; 27: 415-420.
2. Kelly J, Rudd A, Lewis R, Hunt BJ. Venous thromboembolism after acute stroke. Stroke 2001; 32: 262-267.
3. Antiplatelets Trialist's Collaboration. Collaborative overview of randomized trials of antiplatelet therapy (III). Reduction in venous thrombosis and

pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. BMJ 1994; 308: 235-246.

4. Kamphuisen PW, Agnelli G. What is the optimal pharmacological prophylaxis for the prevention of deep venous thrombosis and pulmonary embolism in patients with acute ischemic stroke. Thromb Res 2006; May 2 (epub ahead of print).
5. Adams HP jr, Del Zoppo G, Alberts MJ et al. Guidelines for the early management of adults with ischemic stroke. Circulation 2007; 115: e478-e534.
6. Paciaroni M, Agnelli G, Venti M, Alberti A, Acciarresi M, Caso V. Efficacy and Safety of Anticoagulants in the prevention of venous thrombo-embolismin in patients with acute cerebral hemorrhage. A Meta-Analysis of Controlled Studies. J Thromb Haemost. 2011 Feb 16

Informed Consent Form

I, the underwritten …….

Born in …….. on ……

Express my desire to participate in the study entitled:

"PREvention of VENous Thromboembolism In Hemorrhagic Stroke patients.

Cod: **PREVENTIHS STUDY**

With regard to this study, I have been informed of the following:

1. The study has been approved by Regional Ethics Committee;
2. The objectives and the potential side effects have been clearly explained by the investigators of the study,
3. My consensus is valuntary;
4. I am aware that the results of the study can be or not my favour;
5. I have understood the possible side effects I could encounter. This has been clearly outlined in the accompanying leaflet, that I have read.
6. I consent to the investigators any data collected on my clinical course regarding the disease for the purpose of this study.
7. I comprehend that, although the results of the study are planned to be published, my name will never result.
8. I understand that I can drop out of the study and/or suspend the prescribed treatment at any moment, without the risk of compromising any future treatments.
9. For any issues that could be attributed to the prescribed treatment of the study, I can contact the following investigators: …….. at the telephone number……;
10. I consent/do not consent to inform my General Practitioner regarding my participation in this clinical trial.

Name and Surname of the patient (or of the legal representative):
printed ……..

Signature of the patient (or of the legal representative)
…… Date ……...

I, Dr. ……., have thoroughly explained the project of the research and the type of procedure to follow. After having accepted my explanations, the patient expressed without prejudice his/her consent to participate in the study.

Signature …….. Date ……..

Results

The study was prematurely stopped after the randomization of 73 patients due to the low recruitment rate and the consequent inability to close the study in the anticipated time frame. The study was carried out between May 1, 2016, and March 30, 2020: thirty-eight patients were randomized in the enoxaparin group and 35 in the control group.
The primary end point, any VTE at 10 days, was 15.8% (6/38 patients) in the enoxaparin group and 20.0% (7/35 patients) in the control group (ITT: adjusted RR 0.97 [95% CI 0.26–3.57]). The secondary end point, the prevalence of DVT (proximal and distal) and PE at 90 days was 18.4% (7/38 patients) in the enoxaparin group and 25.7% (9/35 patients) in the control group (ITT: RR 0.72 [95% CI 0.30–1.72]). Overall, 1/38 of the enoxaparin (2.6%) and 3/35 of the standard therapy (8.6%) patients had severe bleedings (ITT: RR 0.31 [95% CI 0.03–2.82]). Thirteen patients died during the 90-day study period: 7 in the enoxaparin group (18.4%) and 6 in the standard therapy group (17.1%) (ITT: RR 1.07 [95% CI 0.40–2.89]).

Full paper citation

Paciaroni M, Agnelli G, Alberti A, Becattini C, Guercini F, Martini G, Tassi R, Marotta G, Venti M, Acciarresi M, Mosconi MG, Marcheselli S, Fratticci L, D'Amore C, Ageno W, Versino M, De Lodovici ML, Carimati F, Pezzini A, Padovani A, Corea F, Scoditti U, Denti L, Tassinari T, Silvestrelli G, Ciccone A, Caso V. PREvention of VENous Thromboembolism in Hemorrhagic Stroke Patients – PREVENTIHS Study: A Randomized Controlled Trial and a Systematic Review and Meta-Analysis. Eur Neurol. 2020 Nov 13:1-10. doi: 10.1159/000511574. Epub ahead of print. PMID: 33190135.