Dynamic spot sign predicts hematoma expansion in acute Intraparenchymatous Hemorrhage: a Perfusion CT study

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Dynamic spot sign predicts hematoma expansion in IPH.
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“The brain is the organ of destiny. It holds within its humming mechanisms, secrets that will determine the future of the human race.”

Wilder Penfield

To my family, they are the pillar that never fails.
ANKNOWLEDGMENTS

I would like to thank my methodological tutor, Teresa Puig, for her true involvement and support during all the process, always with a smile.

I would also like to emphasize and thank the great help and collaboration that has provided to me the Radiological Department of Josep Trueta Hospital and specially Dr. Josep Puig; it has been key to this research protocol elaboration.

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1. ABSTRACT

**BACKGROUND:** Hematoma expansion has been associated with mortality and poor clinical outcome in patients with Intraparenchymatous hemorrhage (IPH). The presence of contrast extravasation (spot sign) detected by CT angiography (CTA) has been considered a good predictive radiologic marker of the hematoma’s expansion and clinical outcome. Despite its good sensibility, a 20% of patients with negative spot sign undergo with posterior hematoma expansion. On the other hand, some studies showed the presence of hypoperfusion in perihematomal area and have tried to relate it to the perihematomal edema. Although there hasn’t been found a correlation between hypoperfusion and perihematomal edema, neither have hypoperfusion and hematoma expansion been studied and correlated with clinical severity and clinical outcome.

**PURPOSE:** The aim of this study is to know whether the perfusion CT increases the sensitivity detecting spot sign as well as to know whether the perihematomal hypoperfusion is associated with subsequent growth of the hematoma and its impact on the prognosis of patients.

**DESIGN:** The study will be an observational prospective cohort study with a duration of 3 years, performed in Josep Trueta Hospital in Girona, Spain.

**POPULATION:** The study population will be all the patients with diagnosis of acute spontaneous intracerebral hemorrhage with a proven initial NCCT scan realized on the emergency department admission and of <12 hours of evolution. A non-probabilistic consecutive sampling will be conducted expecting to gather a minimum sample of 155 patients. The two cohorts (positive and negative spot sign) will be followed in time to analyze hematoma expansion.

**METHODS:** Patients will be studied by a baseline cranial non-contrast CT, perfusion CT and CTA and a non-contrast CT at 24 and 72 hours. The CTA and PCT will assess the presence of spot sign and the difference between the baseline CT and the 24-hours and 72-hours CT will determine the hematoma expansion. Neurological deficit will be evaluated by NIH stroke scale on admission, at 24 hours, 72 hours, 7 days and 90 days after onset. Functional impairment will be assessed by m-Rankin Scale previous to onset and at 90 days.

**Key words:** Intracerebral hemorrhage  hematoma expansion  spot sign  perfusion CT  clinical outcome
2. ABREVIATIONS

AHT  Arterial Hypertension
aTTP  Activated Partial Thromboplastin Time
AVM  Arteriovenous Malformation
BBGG  Basal Ganglia
CBF  Cerebral Blood Flow
CBV  Cerebral Blood Volume
CPP  Cerebral Perfusion Pressure
CTA  Computerized Tomography Angiography
CVD  Cerebrovascular Disease
CVR  Cerebral Vascular Resistance
DM  Diabetes Mellitus
DND  Delayed Neurological Deterioration
eHE  Early Hematoma Expansion
END  Early Neurological Deterioration
ESR  Erythrocyte Sedimentation Rate (ESR)
GCS  Glasgow Coma Scale
HE  Hematoma Expansion
HLD  Hyperlipidemia
HLo  Hematoma Location
HU  Hounsfield Units
HVi  Baseline Hematoma Volume
ICH  Intracerebral Hemorrhage
ICP  Intracerebral Pressure
INR  International Normalized Ratio
IPH  Intraparenchymatous Hemorrhage
IVH  Intraventricular Hemorrhage
JTH  Josep Trueta Hospital
Dynamic spot sign predicts hematoma expansion in IPH.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>kVp</td>
<td>Kilovolts</td>
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<tr>
<td>mAs</td>
<td>MiliAmperes</td>
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<tr>
<td>MMCT</td>
<td>Multi-Modal Computerized Tomography</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>MTT</td>
<td>Mean Transit Time</td>
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<td>NCCT</td>
<td>No-Contrast Computerized Tomography</td>
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<td>NIHSS</td>
<td>National Institute of Health Stroke Scale</td>
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<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
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<tr>
<td>PCT</td>
<td>Perfusion Computerized Tomography</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
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<tr>
<td>PT</td>
<td>Prothrombin Time</td>
</tr>
<tr>
<td>SAH</td>
<td>Subarachnoid Hemorrhage</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SICH</td>
<td>Spontaneous Intracerebral Hemorrhage</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Science</td>
</tr>
<tr>
<td>TTP</td>
<td>Time To Peak</td>
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3. INTRODUCTION

Cerebrovascular disease (CVD) is a serious global health problem, it is consequence of blood circulation alteration causing a permanent or transitional brain capacities deficit. In Spain its incidence is 155 cases/100,000 population/year (1). CVD can be produced by two different mechanisms, in ischemic strokes the blood flow deficit is produced by a vessel obstruction, and in intracerebral hemorrhage (ICH) the blood flow deficit is caused by a vessel rupture, provoking a blood collection in the brain tissue (1,2). ICH includes subarachnoid hemorrhage (SAH) and Intraparenchymatous hemorrhage (IPH). SAH represents a 5-7% of strokes (1), the bleeding extends through the subarachnoid space and communicates with the ventricular systems. On the other hand, IPH’s bleeding is contained into the brain and it represents a 15% of strokes (2).

We can classify IPH in two groups by its cause, Primary IPHs are caused by the spontaneous rupture of cerebral vessels due to chronical damage by arterial hypertension (AHT) or. AHT is approximately the cause of the 60% of all IPH with no difference between age or sex groups. Chronic AHT modifies the vessel’s wall becoming irregular and weak and leading to their rupture and bleeding. Amyloid angiopathy is the first cause of IPH in elderly people, vessel’s deterioration cause the rupture of little meninges’ vessels; the hemorrhage observed in these patients tend to relapse, to be multiple and to be placed in periphery brain or cerebellum. (1,3).

Secondary IPHs are less frequent, it can be caused by many diseases as arteriovenous malformations (AVM) or aneurysm (3,4). (Table 1)

IPH is a devastating disease which implies serious complications and long lasting impairment. Its incidence reaches over 10-20 cases/100,000 population/year, affecting over 1 million people over the world. In Spain, the rate of incidence is similar, reaching 15 cases/100,000 population/year (2,4,5). IPH incidence has remained stable over the years even though the better control of some risk factors, as AHT (a careless control of AHT with antihypertensive medication is still the most crucial risk factor for IPH) (3). Age and gender also influences in IPH’s incidence, it’s been observed a higher incidence in elderly patients (probably because of the elevated prevalence of AHT, amyloid angiopathy and use of

| Table 1. Summary of Intraparenchymatous Hemorrhage causes. |
|------------------------------|-----------------------------|
| **INTRAPARENCHYMATOUS HEMORRHAGE CAUSES** |
| **Primary Causes** | **Secondary Causes** |
| Arterial Hypertension | Arteriovenous malformation |
| Amyloid angiopathy | Aneurysm |
| Cerebral tumors | Hematological diseases |
| Anticoagulant and fibrinolytic treatment | Vasculitis |
| Inflammatory or infectious artery diseases | Drugs (alcohol, cocaine, amphetamines, crack, cholinergic nasal spray?) |
antithrombotic drugs) and little increase in men’s incidence of IPH (6,7). In addition, alcohol and cocaine abuse increase IPH’s risk; an acute rise in the blood pressure damages little vessels, that can’t afford the increment, and produce the bleeding. Alcohol also affects indirectly the coagulation cascade by secondary liver disease and cocaine can, as well, produce vasculitis (3,4).

IPH’s importance remains in its great morbidity and mortality. IPH’s mortality rates varies from 35 to 50%. The 40% of patients die in the first month, (of these, the majority in the firsts hours) and the 15% die within 6 months of onset (of these, the great majority in the first 48 hours) (4). Also, certain disability remains in the 50% of the patients causing a great morbidity, just the 10% are independent the first month and the 20% at 6 months (2,4,6).

Despite these alarming numbers, the therapeutic options remain almost inexistent. The current main therapeutic strategy is based upon vital support, vital signs and neurological state control (blood pressure, temperature control, breathing support, glucose management, etc) and prevention and treatment of complications (thromboprofilaxis, seizures treatment, pneumonia prevention, serious cardiac events prevention and others) (2,4,8). The absence of specific treatment is in large part due to the lack of IPH’s pathophysiology knowledge after the vessel rupture.

The progress of the hematoma formation can be divided in several phases (Figure 1). The chronical damage in brain vessels produce their rupture. The bleeding creates an initial hematoma and produces the hydrostatic edema, this edema is due to the compensatory rising of blood pressure and the accumulation of osmotically active clot proteins (2). This hematoma damages the surrounding tissue through two main mechanisms: a) the hematoma’s mass effect produces a direct damage by compression and can, as well, cause brain herniation (hasten the evolution into decease) and b) the toxic effect is caused by the inflammatory and coagulation cascade, the clot generates hemoglobin breakdown products that, in addition to the inflammatory response per se in cells, lead to the neuronal and glial apoptosis (2,5).

At this point, the hemorrhage can stop and be reabsorbed following the natural process. But sometimes, the expansion of the hematoma is produced. We still don’t know what are the causes for this enlargement to happen. We do know, that hematoma expansion is the main cause of early neurologic deterioration (END) and a clear prognostic factor, ¼ of patients suffer a deterioration of consciousness the first 24 hours from onset more frequently with hematoma expansion (3,9). It’s been observed that this enlargement tends to appear between 1 and 6 hours from onset in the 30-40%, a 36% the first 24 hours and a 27% the first 48 hours) (2,9,10).
Some hours later, perihematomal edema evolves. The blood-brain barrier rupture changes the edema from hydrostatic to cytotoxic and vasogenic (3). Edema volume can increase from baseline up to 72 hours, it usually remains essentially constant for the first hour and then can underwent expansion and persist up to 5 days (11–13). The intensity of vasogenic edema is a response to the degradation hemoglobin products, it has been proved a correlation between these blood components’ concentration and the severity of the blood-brain barrier disruption (14); also, it’s has been observed that the blood-brain barrier rupture is related to the early hematoma expansion and to a poor clinical outcome (9,15).

Hematoma expansion and perihematomal edema have become the missing link to understand IPH; it is still not clear factors have the key role in its pathophysiology.

![Diagram](image)

**Figure 1.** Summary diagram of the phases and pathophysiological mechanism implied in Intraparenchymatous Hemorrhage.

As seen above, hematoma expansion and perihematomal edema are clear predictive factors for mortality and END (16–18). Other factors have been proven to be predictive of 30-day mortality too: age, baseline hematoma volume, intraventricular hemorrhage (IVH) and infratentorial location (17). 30-days mortality correlates with baseline hematoma volume and hematoma location (he most frequent locations are basal ganglia, 60%, and the worst locations are cerebellum and brain stem) (2,4,19–21); larger volumes usually present decreased level of consciousness (due to elevated intracranial pressure, ICP, and distortion of thalamic and brain-stem reticular activating system) (3). IVH has been defined as a powerful risk factor
of 30-days mortality, END and poor functional outcome at 3 months; IVH presented at 48h increases 2.6-fold the risk of END (9).

Hematoma expansion is observed in less than the 40% of IPH patient, but its correlation with END and poor functional outcome makes it a very relevant feature (22), also it can be modified and it makes it a potential treatment target (17,18).

Early hematoma growth has been related to the presence of multiple bleeding focus in the clot’s periphery, this active bleeding might be provoked by the rupture of vessels in the surrounding hematoma tissue, as a secondary process because of the mechanical shearing produced by the hematoma itself (20). The “spot sign” represents the visual presence of this continued bleeding, it appears in the images as an enhancement and it can be seen using different imaging techniques as Computerized Tomography Angiography (CTA), Magnetic Resonance Imaging (MRI) and Cerebral Arteriography (20) (Figure 2).

Figure 2. Patient with left IPH shows hematoma expansion 24 hours after onset. [Images loaned by Dr. Puig from Hospital Josep Trueta in Girona.]
A) Baseline NCCT image, the hematoma is placed in left basal ganglia. B) T2 MRI sequence from the same patient at baseline, the enhancement represents the contrast extravasation (spot sign). C) NCCT scan 24 hours after onset, there’s an evident growth of the hematoma. NCCT: non-contrast computerized tomography; MRI: magnetic resonance imaging.

Spot sign symbolizes contrast extravasation; the presence of contrast extravasation is related to hematoma expansion and is an independent predictor for mortality and functional outcome (17,20,23–26). In several
studies, spot sign has been identified in 25-35% of patients and in all of them the spot sign was associated with a posterior hematoma growth (20,23,24,27,28). It has been also related to larger hemorrhages, more severe clinical presentation (lower Glasgow Coma Scale, GCS and higher NIH Stroke Scale scores, NIHSS) and IVH expansion (24).

Nowadays the best technique to study and identify spot sign is CTA (Figure 3), it has a high sensitivity and specificity (near to 60% and 80%) detecting spot sign (10,25). CTA allows us to study the cerebrovascular system in a non-invasive way. Images are obtained after administering iodine intravenous contrast at a different timing depending on which vascular phase we want to see (arterial, capillary or venous phase). As CTA is not a continuous dynamic process, we can’t obtain continuous information of the cerebral vascular situation (10,25).

Moreover, approximately a 20% of patients with negative spot sign in CTA scan develop posterior hematoma enlargement (25,29), this means that there are a number of patient with high risk of mortality and END no detected at their arrival into the Hospital.

Du FZ, et al (25) proved in a meta-analysis that combined CTA procedures had higher sensitivity detecting spot sign (92%) and suggested the use of Multi-modal CT (MMCT) and faster to improve the sensitivity. The incorporation of MMCT would provide us the chance of study IPH in a dynamic way, this method can be completed quite quickly (5-10 minutes) and the additional radiation dose is affordable considering the great IPH’s mortality rate (30).
Sun s, et al (10) proved in their study that Perfusion Computerized Tomography (PCT) had higher sensitive, specificity, positive predictive value (PPV) and negative predictive value (NPV) predicting hematoma expansion than CTA (Table 2). These findings can’t be extrapolated and further investigation is needed, but it suggests that the amount of these imaging techniques could improve the sensitivity detecting spot sign and reduce the 20% no identified of patients with high risk of hematoma expansion.

Table 2. Comparative values of sensitivity, specificity, PPV value and NPV for CTA and PCT. The data has been extracted from 2 studies (10,25).

<table>
<thead>
<tr>
<th>Computerized Tomography Angiography</th>
<th>Perfusion Computerized Tomography</th>
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<tr>
<td>Sensitivity</td>
<td>70.0%</td>
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<tr>
<td></td>
<td>89.3%</td>
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<tr>
<td>Specificity</td>
<td>91.7%</td>
</tr>
<tr>
<td></td>
<td>94%</td>
</tr>
<tr>
<td>PPV</td>
<td>70.8%</td>
</tr>
<tr>
<td></td>
<td>83.3%</td>
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<tr>
<td>NPV</td>
<td>87.5%</td>
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<td>96.3%</td>
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CTA: computerized tomography angiography, PCT: perfusion computerized tomography, PPV: positive predictive value and NPV: negative predictive value.

This new MMCT modality includes NCCT, CTA and PCT. It has been successfully incorporated into acute stroke imaging protocols. MMCT has proved to be faster, reliable and effective detecting cerebrovascular disorders and vascular changes in ischemic strokes (29,31).

PCT scan is as a continuous imaging study, it permits to observe and evaluate progressive cerebrovascular changes. It operates with intravenous iodinate contrast, once the contrast enters the blood circulation PCT recruits contrast-enhanced images by dynamic acquisition of sequential and fast slices on a cine mode during rapid high-flow contrast administration (31). The acquisition lasts approximately 290 seconds and the result are multiple images from a specific cerebral axial slice. In such a way, the vascular situation of the brain is shown at different moments (“cine mode”), as if they were frames in a movie (dynamic). This characteristic allows PCT scan to detect contrast extravasation that, otherwise, CTA can’t detect because of its static imaging acquisition mode (29–32).

PCT may be able to detect spot signs that CTA may not detect because the highest contrast extravasation saturation can be delayed and appear after CTA procedure has ended. Also, as PCT just evaluates a single cerebral slice, if contrast extravasation appears at other levels of hemorrhage it won’t be detected neither. Because of all these limitations, we think that the combination of both techniques would surely increase sensitivity and specificity detecting spot sign.
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The vast knowledge about PCT has been achieved with ischemic strokes’ studies. In recent years, the management of ischemic stroke has changed because of a better knowledge of the physiopathology of vascular occlusions thanks to this technique. PCT operates detecting the changes in density-time curves in a determinate slice, this changes are proportional to the contrast-enhancement produced by the contrast concentration travelling at that moment through the arteriovenous system. (30,31)

All the obtained density data is converted to Hounsfield Units (HU) and then to pixels creating an image that we finally see in the screen (31). Using a deconvolution software, the main parameters’ data (Table 3) is converted into visual maps that summarize the cerebrovascular situation (Figure 4).

Table 3. Main analysis parameters in perfusion computerized tomography.

<table>
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<th>Table 3. MAIN PARAMETERS IN PCT</th>
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<tr>
<td><strong>TTP</strong> is the <em>time to peak</em>, it corresponds to the time needed for a determinate spot to get the maximum contrast density (Hounsfield Unit, HU).</td>
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<tr>
<td><strong>MTT</strong> is the <em>mean transit time</em>, it corresponds to the difference between venous and arterial flow; the time that lasts a region to return to its typical density once all the contrast volume has passed.</td>
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<tr>
<td><strong>CBV</strong> is the <em>cerebral blood volume</em>, it indicates the volume of blood per unit of brain mass.</td>
</tr>
<tr>
<td><strong>CBF</strong> is the <em>cerebral blood flow</em>, it indicates the volume of blood per unit of brain mass.</td>
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PCT is an accessible technique that allows to study ischemic stroke and to screen patients who would benefit of thrombectomy or thrombolytic therapies. It has been lately introduced into clinical practice as a method to detect the presence and extension of brain areas salvable from ischemia (30,31). Infarction core behaves increasing MTT and reducing CBF and CBV, because of the disappearance of the physiologic auto-regulation that produces local diminished. Some areas still not infarcted, behave different by increasing MTT, decreasing CBF but presenting normal or elevated CBV; it is explained because of the physiologic attempt to re-perfuse the affected area by vasodilatation and supplying blood demand with collateral circulation (30–33). Using summary overlapped perfusion map (Figure 4), changes in MTT and CBV can be easily seen. It illustrates a mismatch between the real infarcted area is and the salvable tissue (called “penumbra”) (30).
Figure 4. Perfusion CT maps from a patient with ischemic stroke. [Images loaned by Dr. Puig from Josep Trueta Hospital].

NCCT scan show the acute phase of stroke, we can see an hyperdense MCA or “cord sign” (one of the early signs of ischemic strokes) in M1 portion. It is noticeable increased values in MTT map, slightly increased values in CBV map values and decreased values in CBF map. The summary map (4 PCT maps overlap) shows a large area of penumbra and no area with ischemic characteristics; the penumbra area correlates with the marked narrowing in the right MCA (M1 territory) seen in the NCCT scan. **NCCT**: non-contrast computerized tomography; **TTP**: time to peak; **MTT**: mean transit time; **CBV**: cerebral blood volume; **CBF**: cerebral blood flow; **MCA**: middle cerebral artery.

On the other hand, PCT technique has been applied to study IPH, specifically perihematomal edema area. It was hypothesized that there is a decrease cerebral blood perfusion in this area. Several studies proved that although there is a reduced perfusion, it remained below ischemia’s threshold values (21,34).

These findings contributed to consider the aggressive management of blood pressure as an important and secure treatment option. It’s been also studied the relationship between perihematomal hypoperfusion and edema enlargement, but it hasn’t been proved; as well as the relationship between edema enlargement and blood pressure values (35). Neither has blood-brain barrier alteration been related to perihematomal edema (36).

It has been proved, though, that even the CBF and CBV are reduced in perihematomal area (in comparison to contralateral tissue) there is no decrease in cerebral perfusion pressure (CPP) and an increase in the
cerebral vascular resistance (CVR). The elevated CVR is thought to presumably secondary to the compression of the micro-vasculature by the hematoma’s mass effect (37).

Although there are evidences that perihematomal hypoperfusion it’s unlikely to have an impact in perihematomal edema enlargement, there are no evidences that confirm or deny the correlation between hypoperfusion and hematoma expansion and/or its correlation with clinical severity and predictive of clinical outcome.

For these reasons, the aim of the study is to know whether the addition of PCT scan to the current diagnosis protocol (NCCT and CTA) in IPH patients, can improve the sensitivity and/or specificity of the spot sign detection as a predictive marker for hematoma expansion and poor clinical outcome. Also, it is the aim of this study, to evaluate whether perihematomal hypoperfusion causes hematoma expansion.

The following image is an experimental PCT study done in Josep Trueta Hospital done to a patient with IPH. This image has the purpose to show how a real performance of PCT scan, defended in this research protocol, would look like.

*Figure 5. Perfusion CT maps from patient with a deep right intracerebral hemorrhage, located in basal ganglia (lentiform nucleus).* [Images loaned by Dr. Puig and Dr. Silva from Hospital Josep Trueta in Girona.]

It is noticeable a global reduction in CBV and CBF values in the hematoma core and the perihematomal zone (edematous associated component. It is also observed preserved tissue in hematoma and perihematomal areas (white arrows). NCCT: non-contrast CT, CBV: cerebral blood-volume map, CBF: cerebral blood-flow map, MTT: mean transit time map, TTP: time to peak map.
4. JUSTIFICATION

First of all, IPH has to be considered a disease of major importance due to its great fatality rate, it is greater than 50% at 30-days (1,2). IPH is a medical emergency and we know that the savable interval is very little, the most of the patients deteriorate in the first few hours. Consequently, IPH needs to be diagnosed and treated in the less time possible (38,4). The elevated mobility and mortality generate worse prognosis than ischemic stroke, the most prevalent type of strokes. Despite IPH represents the 15% of all stroke patients, the therapeutic options remain almost inexistent (2,4,8). This problem is still unsolved partly because of the IPH’s complex pathophysiology and partly because of the lack of treatments’ evidence. A better understanding of the pathophysiology would provide new unexplored ways to treat IPH or confirm the current practice and, thus, diminish its mortality and morbidity.

We know that IPH has several phases, the chronical damage in little brain vessels produce their rupture, then the bleeding creates an initial hematoma and produces a hydrostatic edema surrounding it and once the hematoma is formed it can damages the surrounding tissue through its own mass effect and through toxic products of hemoglobin and other substances degradation (2,38,5). What we still don’t know is which elements are truly the cause of the posterior hematoma expansion at this point. Also, perihematomal edema and perihematomal hypoperfusion’s roles in hematoma expansion remain unclear.

We suspect that these features have an important role in IPH’s evolution and pathophysiology, and we also think that they might be predictive for hematoma expansion and clinical outcome. Hematoma expansion and perihematomal hypoperfusion have become the missing link to understand IPH.

We do know, that hematoma expansion is the main cause of early neurologic deterioration (END) and a clear prognostic factor (3,9) and this makes of it an important target. It has been observed that each 1ml of hematoma expansion rises a 5% the probability to be dead or to be dependent at 90-days and, alternatively, each reduction of 2-4ml provides a 10-20% reduction in the risk of dependency or death at 90 days (10,18). If we could detect hematoma expansion before it starts growing, we would be able to detect patients at high risk of developing END and worse clinical outcome. New in-development treatments (for instance recombinant activated clotting factor VII) could be tested in this subtype of patients and their potential risks would be then affordable, tipping the benefit-risk balance in their behalf.

In order to improve this hematoma expansion prediction, we think that a sure bet would be combine the present diagnosis imaging protocol (NCCT and CTA) with PCT, widely used to study ischemic stroke (10,25,29,31). The dynamic characteristic of PCT would detect the 20% of patients without a positive
Dynamic spot sign predicts hematoma expansion in IPH.

Spot sign in CTA scan and posterior hematoma expansion. It would supply this lack and provide information to study IPH’s pathophysiology (perfusion, blood volume, permeability…) at the same time (25,29–32).

Although MRI studies can supply more accurate information, multi-modal CT tests are more widely available, less time-consuming and provide similar information. The time-consuming factor is crucial, as we know, IPH patients tend to worse the first few hours (2,4,6,9,10) and, if confirmed, the chance to identify modifiable factors as soon as possible could be paramount to treatment, medical complications and clinical outcome.

In summary, the implementation of PCT imaging techniques (as part of MMCT) in IPH patients could increase the spot sign detection and better predict hematoma expansion and clinical outcome and open a new way to identify high risk patients. It might also help to understand IPH’s pathophysiology by studying perihematomal hypoperfusion and perihematomal edema, as well as, bring to light new treatment targets.
5. HYPOTHESES

First hypothesis: Spot sign detected by Perfusion Computerized Tomography (PCT) is a predictive marker for hematoma expansion and a predictive factor for poor clinical outcome at 90-days in Intraparenchymatous hemorrhage (IPH) patients.

Second hypothesis: PCT detected hypoperfused tissue surrounding hematoma causes early hematoma expansion in IPH patients.

6. OBJECTIVES

- To compare PCT’s and CTA’s sensitivity and specificity detecting spot sign, in patients with spontaneous intracerebral hemorrhage.
  - To know the incidence of spot sign detected with perfusion CT, in patients with spontaneous intracerebral hemorrhage.
  - To determine if contrast extravasation detection with PCT is able to predict mortality at 90-days and early neurologic deterioration (END).

- To determine the association between perihematomal hypoperfused tissue with hematoma expansion in patients with IPH, using CT perfusion technique combined with CT angiography.
  - To study, by PCT scan, the blood perfusion and blood volume characteristics of perihematomal tissue.
  - To determine the association between hypoperfused tissue and poor clinical outcome.
7. METHODS

7.1. STUDY DESIGN
This study design will be an observational prospective cohort study with a follow-up of 90 days for each patient, during 2 years. The total length of the study period will be 3 years and it will be performed in Josep Trueta Hospital (JTH).

7.2. SUBJECTS SELECTION
The study population will be all the patients older than 18 years, with diagnosis of acute spontaneous Intraparenchymatous hemorrhage with a proven initial NCCT scan performed at admission, in the Emergency Department of the JTH in Girona, between 2016 and 2018.

7.2.1. INCLUSION AND EXCLUSION CRITERIA

- **Eligibility criteria:**
  » Presence of supratentorial IPH in NCCT scan
  » NCCT carried out within 12 hours within onset.
  » Informed consent signed by the patient or a legal surrogate or close relatives.

- **Exclusion criteria:**
  » Patients older than 18 years.
  » Known secondary intracerebral hemorrhage cause: hemorrhage related to trauma, coagulopathy, underlying aneurysms or AVM, hemorrhagic transformation of brain infarction
  » Initial or subsequent intraventricular extension of the hemorrhage proven on CT scan.
  » Surgical hematoma evacuation performed after baseline NCCT.
  » Clinical or hemodynamic instability (the patients may be hemodynamic stable at least before enrolling the study, after complications will be accounted in the results of the study).
Dynamic spot sign predicts hematoma expansion in IPH.

» Patients with a severe neurological deterioration at admission (NIHSS >25) or known moderate-severe Dementia.

» Patients with an advanced or terminal illness (expectancy of life under 6 months).

» Accurate time from onset not available or unclear (if the time of symptoms onset is unknown, last time seen normal will be accepted).

» Evidence of pregnancy

» Known allergy or contraindication (as known renal failure) at time of admission, regarding intravenous iodinated contrast administration

7.2.2. SAMPLE AND SAMPLING

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 31 subjects are necessary in first group and 124 in the second to recognize as statistically significant a difference greater than or equal to 15 units. The common standard deviation is assumed to be 25. It has been anticipated a drop-out rate of 10%.

The incomes’ number of IPH patients in JTH is 130 patients/year, a 70% of these patients are admitted into the Hospital the first 12 hours from the symptoms onset. If we estimate that a 20% of patients will be excluded, we narrow the sample into approximately 73 patients/year. Since it is necessary a minimum sample of 155 patients to have statistical significant results in this research protocol, it is expected to last approximately 2 years.

A non-probabilistic consecutive sampling will be used in this study. The patients will be selected as they arrive at the Emergency Department of JTH in Girona (Spain). We will apply the protocol mentioned in the next “Data collection circuit” section. The whole project is expected to last 3 years entirely, the first 2 years will be expended recollecting the patients’ data and the last year will embrace the study analysis and the writing and publishing of the paper.

The facilities in JTH are fully equipped technologically and pursue the objectives in this study. The medical team is also highly qualified to attend IPH patients, both, nurses and physicians, have a long experience working in “Stroke Intensive Care Unit” (SICU).
7.3. VARIABLES

DEMOGRAPHIC VARIABLES:

- **Age**: it will be expressed as the number of years.
- **Gender**: it will be expressed as categories woman and man.

CLINICAL VARIABLES

- **Hemodynamic parameters**: will be collected at baseline: they will be expressed as the number of beats/minute for **heart rate**, **blood pressure** as the number of systolic and diastolic values, **temperature** as the centigrade degree number and **oxygen saturation** as the percentage in capillary blood.

- **Laboratory variables**: they will be expressed as mg/dl for **glucose**, as g/dl for **hemoglobin**, as number x10⁹/L for **platelet count**, as mm/h for **erythrocyte sedimentation rate** (ESR), as mg/dl for **serum creatinine**, as a whole number for **INR**, as seconds for **prothrombin time** (PT) and **activated partial thromboplastin time** (aTTP).

- **Toxic habits**: they will be expressed as Yes or No for **alcohol intake**, **smoking** and other drugs.

- **Medical history**: they will be expressed as Yes or No for **AHT**, **Diabetes mellitus** (DM), **hyperlipidemia** (HLD), personal or family history of **IPH** or known secondary cause, previous **ischemic stroke** and previous **vascular disease**.

- **Antiplatelet, anticoagulant and/or antihypertensive treatment**: will be considered as dichotomous variables and hey will be expressed as Yes or No.

- **Onset-to-baseline CT time**: it will be expressed as minutes.

RADIOLOGICAL VARIABLES

- **Hemorrhage location (HLo)**: it will be expressed as basal ganglia/thalamus, lobar hemorrhage, brainstem or cerebellum.

- **Baseline hematoma volume (HV)**: will be assessed by (AxByC)/2 equation with baseline NCCT data. It will be expressed as ml.
Radiological criteria for *spot sign* will be expressed as Positive or Negative.

*Hematoma expansion* (HE) will be primary defined as the difference between 2\textsuperscript{nd} or 3\textsuperscript{rd} NCCT and the baseline NCCT, in hematoma volume; it will be expressed as ml. We will also consider it as a percentage: \[
\frac{(2^{nd}/3^{rd} \text{NCCT HV} - \text{baseline NCCT HV}) \times 100}{\text{HV1}}
\] As there is no clear consensus in the bibliography, about what is the best form to define this variable, we have given the continue variable more importance, but we will also conduct a second analysis with the qualitative measure.

PCT study will be assessed by *TTP, MTT CBV and CBF parameters*. Theses parameters will be converted and represented by Permeability maps. They will be expressed minutes, minutes, ml/100g/min, and ml/100g, respectively.

We will consider *Hypoperfusion* when CBV values are 20-40ml/100g/min, if the values are between this reference they will be coded as “hypoperfusion” and if they are not, as “no hypoperfusion”.

*Presence of intraventricular hemorrhage* (IVH) will be assessed by the radiologist own criteria and codified as “present”, “no present” and “no appraisable”.

**CLINICAL OUTCOME VARIABLES:**

We will assess the clinical outcome from 3 points of view: 1) the neurologic evolution and deterioration of the patients during the whole process, 2) the functional outcome once at the hospital discharge and 3) the mortality during the process until the hospital discharge.

*Neurological deterioration* will be assessed by the *National Institute of Heath Stroke Score (NIHSS)*, it quantifies the severity of stroke symptoms (*For further information see “Annexes” section*). It will be expressed as <4 Mild, <16 Moderate, <25 Moderate-Severe and \(\geq\)25 Severe.

We will consider *early neurological deterioration* (END) an increase of \(\geq\)4 scores between baseline NIHSS scoring and 24 hours and *delayed neurological deterioration* (DND) an increase of \(\geq\)4 scores between 72 hours and 7 days from onset.

*Dependency degree or functional capacity* will be estimated by the *Modified Rankin Scales (mRS)*. (*For further information see “Annexes” section*). It will be expressed as Independent (0-2) and Dependent (3-5).

We will consider a “poor functional outcome” as a mRS scoring greater than 2 points at 90-days considering the previous punctuation.
• Mortality rate at 90-days will be estimated with the following equation:
  It will be expressed as the percentage of deaths during the study period.

\[
\frac{\text{Nº deaths during the study period}}{\text{Nº people enrolled in the study}} \times 100
\]

7.4. DATA COLLECTION

7.4.1. DATA COLLECTION CIRCUIT

1. All patients attending to JTH Emergency Department (ED) with the suspicion of IPH will be stabilized, a guided-neurologic exploration will be performed and the baseline data will be collected (by checking the patient’s medical history, questioning directly to the patient if he/she is conscious or interviewing the relatives): allergy, hemodynamic parameters, vascular risk factors, personal pathologic history of IPH or other relevant previous diseases, current treatment, current medical complications, pregnancy test if the patient is a woman and signed informed consent. Inclusion and exclusion criteria will be applied.

Also, baseline NIHSS will be performed and previous mRS will be obtained.

2. A blood sample will be extracted to all patients enrolled into the study at this point, the blood analysis will consist in: glucose, hemogram, hemoglobin, platelet count, ESR, serum creatinine, INR and activated partial thromboplastin time (aTTP).

3. Then, a NCCT scan will be performed (before 12 hours from onset) to rule out other possible diagnosis, confirm the diagnosis of IPH and classify the hemorrhage by the location of the hematoma.

4. If IPH is confirmed by the NCCT scan, we will proceed to complete the MMCT procedure (PCT and CTA). The radiation dose varies significantly with every parameter that we apply for the imaging acquisition. The selection of these parameters depends on the maximum radiation dose and the quality of the image obtained; as less kilovolts (kVp) used, more miliAmperes (mAs) are needed (more radiation dose) to obtain a high-quality image. The balance between kVp and mAs is key to apply the minimum needed radiation dose to obtain high-definition images. For PCT scan we will apply the parameters used in Ischemic Stroke’s Protocol in JTH: 100 kVp and 100 mAs.

Right after performing PCT scan, we will continue with CTA protocol. This procedure will contribute to the study the cerebrovascular system (it can diagnose secondary causes) and to detect the presence of “spot sign”, if exists.
JTH’s protocol is presented as a summary in Table 3. All parameters and technical specifications are detailed following the chronological order that will be applied to the patients.

Table 3. Summary of MMCT imaging acquisition protocol from Josep Trueta Hospital.

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>NCCT head</strong>:</td>
<td>3 mm axial slices from skull to vertex, excluding eye orbits from scanning range if possible, 120kVp, 300 mAs. Estimated radiation dose: 48mGy.</td>
</tr>
<tr>
<td>2. <strong>Dynamic PCT</strong>:</td>
<td>50ml (Tomeron® 300mg I/ml) iodinate contrast followed by 21ml of saline with a 5ml/sec injection rate through 18-20G IV access, applying 5 seconds of delay before imaging acquisition and 290 seconds of scan duration. 100 kVp, 100 mAs and in a cine scan mode (10mm slices) will be used. Estimated radiation dose: 245 mGy.</td>
</tr>
<tr>
<td>3. <strong>CTA</strong>:</td>
<td>80 ml (Tomeron® 300mg I/ml) iodinate contrast followed by 21ml of saline with a 5ml/sec injection rate and through 18-20G IV access. A bolus tracker technique will be used to apply a personalized delay. The procedure will cover from the top of aortic arch to vertex. 120 kV, 250 mAs will be used with a 0.45 mm thickness of slices. Estimated radiation dose: 16.5 mGy.</td>
</tr>
</tbody>
</table>

All procedures will be presented in a 512x512 matrix. The total duration of the MMCT is approximately 15 minutes. The total estimated radiation dose is 309.5 mGy.

**NCCT**: non-contrast computerized tomography, **PCT**: perfusion computerized tomography, **CTA**: computerized tomography angiography, **kV**: kilovolt (electric potential), **mAs**: miliAmpere per second (electric intensity), **IV**: intravenous, **G**: gauge, **MMCT**: multi-modal CT.

\* The total duration is divided in 57 seconds (25 cycles 1 cycle/2 seconds) and 233 seconds (6 cycles, 1 cycle/29 seconds to obtain Permeability maps).

\# Bolus tracker methodology is the one used in JTH for CTA scans. A locator is placed outside the body area, the CTA study initiates when the technician see the maximum enhancement in the artery system of the patient being studied in that moment. The absence of a limited time (seconds) of delay permits to adapt the scan to the patient’s characteristics.

\+ The mGy references are estimations for a human adult male obtained in a simulation performed in JTH’s Radiology department.

4. Once the MMCT protocol is performed, all the patients will be admitted in “Stroke Intensive Care Unit” (SICU).

A closely monitoring of clinical variables will be conducted. We will assess neurologic deterioration with NIHSS at baseline, 24 hours, 48 hours, 7 days and 90 days after onset. Although we know that END occurs in 20-40% of patients and tends to appear the first 48 hours after onset, we think that its relationship
with poor prognosis makes it an important factor to be considered at different points in the evolution timeline. Hence, we will be able to quantify not just the END but DND, if it appears, and to determine the correlation with hematoma expansion (9).

Also, clinical outcome will be evaluated with mRS, comparing the previous mRS score with the mRS score at 90-days. If patients are no longer in the SICU at this point (under medical criteria), the mRS evaluation will be conducted by phone.

5. Radiological variables will be measured twice during the whole period of the study. A complete MMCT procedure will be performed at admission (we will study spot sign presence and perfusion characteristics) and we will execute a NCCT at 24 and 72 hours to control and compare the volume of the hematoma.

<table>
<thead>
<tr>
<th>Symptoms onset</th>
<th>Patient admission</th>
<th>Baseline clinical and laboratory data collection</th>
<th>NIHSS and previous mRS</th>
<th>NCCT + IPH confirmation</th>
<th>Complete 1st MM-CT</th>
<th>NIHSS</th>
<th>2nd NCCT</th>
<th>NIHSS</th>
<th>3rd NCCT</th>
<th>NIHSS</th>
<th>NIHSS and mRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;12h)</td>
<td>(24h)</td>
<td>(48h)</td>
<td>(72h)</td>
<td>(7d)</td>
<td>(90d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 6. Protocol’s timeline. NIHSS: NIH stroke scale; mRS: modified Rankin Scale; NCCT: no-contrast CT; IPH: intraparenchymatous hemorrhage; MM-CT: multi-modal CT.
7.4.2. IMAGING ACQUISITION

Baseline imaging acquisition will be performed in the acute moment and follow-up imaging acquisition will be performed at 24 ± 3 hours after the onset. The images will be acquired by a 3-years experienced technician and will be supervised by the Radiologist 1.

The Radiologist 1 will inform and give a diagnostic orientation based on the baseline NCCT. If IPH is confirmed they will continue with PCT and CTA.

The variables calculated with NCCT scan information (baseline and 24 ours-from onset) will be: *Hematoma volume* will be calculated in accordance to AxBxC/2 equation on the baseline CT images. A for the maximal longitudinal diameter, B for the transverse maximal diameter, perpendicular to A, and C equivalent to the number of slices containing the hematoma. (slices’ thickness = 3mm).

*Hematoma expansion* (HE) will be defined as the difference between 2nd/3rd and the baseline NCCTs in hematoma volume. We will consider significant hematoma expansion when the increase is ≥33% in the HVi for small IPH (HVi <20ml) and ≥10% for larger IPH (HVi ≥20ml) or an absolute growth greater than 6 ml; between 2nd and baseline NCCTs (24,26).

All PCT scans will be assessed with a deconvolution-based algorithm by using an imaging workstation supplied with a commercial dedicated software (Extended Brilliance workstation 4.5, Phillips Healthcare). The result obtained with the algorithm will be transformed and presented in 5 different PCT maps: *TTP (T_{max}) and MTT (seconds), CBV (ml/min), CBF (ml/min/100g) and Overlap map.*

CBV (ml/100mg/min) will be calculated from the area under the time attenuation curve. MTT (seconds) will be computed by using a deconvolution operation. CBF (ml/min) will be calculated according to the central volume principle: CBF = CBV/MTT.

We will consider the following values as reference to interpret the maps:
MTT: high time for values ≤5 seconds and low time for values >5 seconds; CBV: ischemia for values <10ml/100g/min, penumbra for values 10-20ml/100g/min and oligoemia for values 20-40ml/100g/min; CBF: low volume for values <25ml/100g and high volume for values ≥25ml/100g (39).
All the PCT data will be expressed as mean and 95% CI values.

CTA scan will be examined looking for the *spot sign*, if present, it will be considered as at least 1 focus of contrast enhancement within the hematoma, with high density values (>120 HU), discontinuous from normal or abnormal vasculature surrounding the hemorrhage, and any size and morphology.
8. STATISTICAL ANALYSES

**Independent variable**

- For the first hypothesis, the independent variable is “spot sign”. It will be presented as a dichotomous variable.
- For the second hypothesis, the independent variable is “hypoperfusion in perihematomal tissue”.

**Dependent variables**

- Hematoma expansion: this variable will be expressed in absolute values (ml) and relative values (%).
- Clinical outcome at 90-days

**Co-variables**

- Age
- Gender
- Hemodynamic parameters heart rate, blood pressure, temperature and oxygen saturation.
- Laboratory variables: glucose, hemoglobin, platelet count, ESR, serum creatinine, INR, PT and aTTP.
- Toxic habits: alcohol intake, smoking and other drugs.
- Medical history: AHT, DM, HLD, personal or family history of IPH or known secondary cause, previous ischemic stroke and previous vascular disease.
- Antiplatelet, anticoagulant and/or antihypertensive treatment.
- Onset-to-baseline CT time.
- Hemorrhage location.
- Baseline hematoma volume.
- Presence of IVH.
- PCT parameters: TTP, MTT, CVB and CBF.
- NIHSS scoring: at baseline, 24h, 72h, 7 d and 90 d.
- mRS scoring: previous and at 90 d.
- Mortality rate at 90 d.

The data will be analyzed using Statistical Package of the Social Science (SPSS) 22.0.0.0. © software. Imaging data will be analyzed by 2 radiologist experts blinded to patients’ identity, onset-to-baseline CT time, clinical and laboratory data. Each scan will be analyzed separately (baseline NCCT, PCT, CTA and 24-hours NCCT). Inter-observer reliability for the detection of the radiological variables between the 2 radiologists will be calculated by using the Cohen Kappa statistic with separated analyses for each criterion.
In all analyses, probability values $p \leq 0.05$ will be considered statistically significant and $p \leq 0.001$ will be considered as highly significant. Confidence intervals (CI) will be expressed as 95%.

8.1. UNIVARIATE ANALYSES.
The 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. All continuous radiological parameters (TTP, MTT, CBF and CBV), NIHSS and mRS will be also presented as quartiles.

Sensitivity, specificity, PPV and NPV predicting hematoma expansion will be calculated for spot sign detected by PCT and CTA, respectively. The kappa statistic will be used to quantify the agreement between PCT or CTA enhancement signs, for the expansion of the hematoma.

8.2. BIVARIATE ANALYSES
Comparisons between groups will be carried out with t-Student test for dichotomous and normal distributed continuous variables or Mann-Whitney test if continue variable are non-normally distributed. To compare two categorical variables, we will use $\chi^2$ test.
In a second analysis, we will also use $\chi^2$ test to observed frequencies and determine differences between groups, for categorical and continue variable. Also, to compare PCT’s and CTA ‘s sensitivity, specificity, PPV and NPV.

8.3. MULTIVARIATE ANALYSES
To analyze the degree of relationship between candidate predictor variables (spot sign, hematoma volume, hematoma expansion and hypoperfusion) and clinical outcome (NIHSS rates, previous and final mRS rates and mortality rate) we will use multiple regression. Probability values $p \leq 0.05$ will be considered statistically significant predictors.
Logistic regression analyses will be performed to analyze the association between hematoma expansion and potential confounders (age, gender, medical history, alcohol intake, smoking, anticoagulant treatment, antihypertensive treatment, blood pressure, NIHSS, onset-to-baseline CT time, hematoma location, intraventricular extension, baseline hematoma volume and baseline perihematomal volume). Probability values $p \leq 0.05$ will be considered as confounders variables.
9. WORK SCHEDULE

9.1. SCHEDULE

PHASE 0 (August 2016 – December 2016)
- Study protocol development (August 2016 – November 2016): The whole team will conduct the bibliographic research, identify the variables of interest and define the hypothesis and the objectives of the study.
- Coordinating meetings: The whole team will have several meetings during the study period with the aim of coordinate and solve the problems that can appear during the whole process. The proposed dates are:
  - 1st meeting (January 2017): This meeting will coordinate the several phases of the study and present the schedule.
  - 2nd meeting (November 2017): check-up meeting
  - 3rd meeting (June 2018): check-up meeting
  - 4th meeting (April 2019): the objective is to discuss the results and coordinate the writing of the study
  - 5th meeting (October 2019): this will be the latest meeting to solve last-minute problems before publishing.
* These are just provisional dates that can be modified adding or changing the months as the investigators decide.
- Presentation and approval of the Clinical Research Ethics Committee (December 2016)

FIRST PHASE (January 2017 – December 2018):
- Patients’ inclusion and clinical evaluation:
This will be executed during hospitalization of the patients and the 3-months follow-up after their hospital discharge. The responsible staff will be Investigators 1 and 2. This part will last the 1st and 2nd year, until the last patient is included into the study.
- Laboratory samples recollection:
This assignment will consist of the blood samples’ collection; the baseline samples will be obtained in the Emergency Department of JTH during the admission process when the patients arrive. The follow-up samples will be recollected in the SICU during the hospital stay. The person in charge will be the Nurse participating in the study, except for the baseline samples which will be extracted by the Emergency Department staff at that moment.
The analysis of the samples will be executed by the Hospital’s laboratory technicians and will be stocked in the Laboratory storage. This part will last the 1st and 2nd years, until the last patient is included into the study.

- Radiological procedures’ execution:
The radiological procedures will be performed in Josep Truet Hospital by a trained and 3-year-experienced in neuro-radiological techniques technician with the supervision of Radiologist 1. The facilities used will be the Radiology Department of JTH, they belong to the “Institut de Diagnòstic per la Imatge”, a subcontracted company placed inside the Hospital. They will follow the procedures’ protocol explained before (See “Table 3”). This part will last the 1st and 2nd year, until the last patient is included into the study.

- Database implementation:
The database implementation will be performed by Investigators 1 as the information is obtained. The clinical and laboratory information will be entered the database as the patients engage in the study. The neuro-radiological images will be analyzed by the 2 radiologist experts, blinded to the clinical data. At the end of the 1st phase (December 2018) a review of all the data will be checked by Investigator 1 (to detect gap information or errors). SPSS 22.0.0. 0 ® software will be the informatic program used to store the information and analyze it at next phase.

SECOND PHASE (January 2019 – April 2019):
- Data analysis:
Once all the data (demographic, clinical, laboratory’s and radiological) is gathered and entered in SPSS 22.0.0. 0 ® software, an expert statistic and external from the study staff, will analyze it.

THIRD PHASE (April 2019 – January 2020):
- Results interpretation and study writing (April 2019 – December 2019):
The results will be interpreted by the Investigators. The study will be written by Investigator 1 and 2.

FOURTH PHASE (December 2019 – January 2020):
- Results publication and disclosure of the paper:
We will try to publish our study in Stroke AHA Journal as well as other suitable journals. The preliminary results of the study will be presented in the next European Academy of Neurology after publishing the results. We also attempt to assist to other Neurology congress, if possible.
Dynamic spot sign predicts hematoma expansion in IPH.

Table 5. Study’s timetable. Investigator 1: principal investigator; Investigator 2 and 3: co-investigators; J: January; F: February; Mch: March; Apr: April; My: May; Jn: June; J: July; A: August; S: September; O: October; N: November and D: December.

<table>
<thead>
<tr>
<th>ASSIGNMENT</th>
<th>RESPONSIBLE STAFF</th>
<th>CALENDAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHASE 0</strong></td>
<td>Whole team</td>
<td>2016</td>
</tr>
<tr>
<td>Study protocol development</td>
<td></td>
<td></td>
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<tr>
<td>Presentation and approval of the Clinical Research Ethics Committee</td>
<td></td>
<td></td>
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<tr>
<td>Coordinating meetings</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PHASE 1</strong></td>
<td>Investigator 1 and Investigator 2</td>
<td>2017</td>
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<tr>
<td>DATA GATHERING AND DATABASE CREATION</td>
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<tr>
<td>1. Patients’ inclusion</td>
<td></td>
<td></td>
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<tr>
<td>2. Patients’ clinical evaluation</td>
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<td></td>
</tr>
<tr>
<td>3. Laboratory samples recollection</td>
<td>Nurse</td>
<td>2017</td>
</tr>
<tr>
<td>4. Radiological procedures’ execution and Imaging processing.</td>
<td>Radiology technician Radiologist 1 and 2</td>
<td>2017</td>
</tr>
<tr>
<td>5. Database implementation</td>
<td>Investigator 1 and 3</td>
<td>2017</td>
</tr>
<tr>
<td><strong>PHASE 2</strong></td>
<td>Statistician</td>
<td>2017</td>
</tr>
<tr>
<td>DATA ANALYSIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical and laboratory data analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PHASE 3</strong></td>
<td>Investigator 1 and Investigator 2</td>
<td>2017</td>
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<tr>
<td>RESULTS INTERPRETATATION AND STUDY WRITING</td>
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<tr>
<td><strong>PHASE 4</strong></td>
<td>Whole team</td>
<td>2017</td>
</tr>
<tr>
<td>PUBLICATON AND DISCLOSURE OF THE PAPER</td>
<td></td>
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</tbody>
</table>
9.2. BUDGET

The budget encompasses all the possible expenses that will be needed to accomplish this study. Some of the procedures are already performed in the Hospital protocols, as some of the required staff already works in the Hospital and the procedures are included in their daily duties. These common tasks are counted as zero expenses.

<table>
<thead>
<tr>
<th>BUDGET</th>
<th>COSTS</th>
</tr>
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<tbody>
<tr>
<td><strong>Staff costs:</strong></td>
<td></td>
</tr>
<tr>
<td>Statistician expert:</td>
<td>600 €</td>
</tr>
<tr>
<td>50€/h x 3h/day x 2 days/week x 3 weeks</td>
<td>0€</td>
</tr>
<tr>
<td>Other staff members:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal Staff costs:</strong></td>
<td>600 €</td>
</tr>
<tr>
<td><strong>Execution expenses:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>- Goods and services costs:</strong></td>
<td></td>
</tr>
<tr>
<td>High definition CT special studies execution (CTA, PCT):</td>
<td>31.000 €</td>
</tr>
<tr>
<td>1 study 200 € x 155 patients</td>
<td></td>
</tr>
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<td>Post-process MM-CT execution:</td>
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<tr>
<td>1 study 100 € x 155 patients</td>
<td></td>
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<tr>
<td><strong>Subtotal Goods and services costs:</strong></td>
<td>46.500 €</td>
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<tr>
<td><strong>- Travel and subsistence costs:</strong></td>
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<tr>
<td>European Academy of Neurology (2019)</td>
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<tr>
<td>Inscription</td>
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<td>Transport</td>
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<td>Accommodation</td>
<td>170 €</td>
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<td>Subsistence costs</td>
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<td><strong>Subtotal Travel and subsistence costs:</strong></td>
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<td><strong>Publishing expenses:</strong></td>
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<td>European Academy of Neurology (2019)</td>
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<td>Submission fee: 35 € / Abstract</td>
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<tr>
<td>Publication in Stroke AHA Journal:</td>
<td>$ 700 (642 €)</td>
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<tr>
<td>$70/printed page x 10 pages (limit 4500 words)</td>
<td>$ 425 (390 €)</td>
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<tr>
<td>Supplement: $425 / exceeding 1.000 words</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal Publishing expenses:</strong></td>
<td>1.160 €</td>
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<tr>
<td><strong>Total:</strong></td>
<td>49.290 €</td>
</tr>
<tr>
<td><strong>Total + 21% Indirect Costs:</strong></td>
<td>59.641 €</td>
</tr>
</tbody>
</table>
10. ETHICAL ASPECTS

The research protocol has been conducted according to human’s rights and ethical principles for Medical Research involving human subjects, outlined in the word Medical Association’s Declaration of Helsinki, last time reviewed in October 2013 (Fortaleza, Brazil).

The research protocol will be presented to the appropriate ethics committee, “Comisión de Ética para la Investigación Médica (CEIC), in Josep Trueta Hospital, Girona, Spain. Once the authorization of the committee is obtained, it will be presented to the Josep Trueta Hospital direction management for approval.

Written Informed Consent (IC) (see “Annexes” section) will be obtained from each patient or legal surrogate in situations where the patients were unable to do so. The patients enrolled in the study will find all the information about the purpose of the study, the potential risks and benefits of the study, how the investigation will be conducted and their rights as participants in the IC; all the information will be also thoroughly explained by the investigators. The patient information won’t be used without previous consent and it will be necessary sign it before taking any action.

The investigators guarantee that the research protocol and the Informed Consent has been written as dictated by the following state laws:

- “Ley orgánica 15/1999, de 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”.
- “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”.

The patients’ data will be stocked up and maintained confidential in a secured system, just accessible for the investigators. Anonymization will be applied to every data introduced in the system.

The protocol will also be presented to the “Agencia Española del Medicamento y Productos Sanitarios” (AEMPS) to obtain its authorization.

The investigators declare that all the imaging equipment has its European Certificate of Conformity. As PCT scan is not considered a specific indication for IPH diagnoses, it would be obligatory to contract a liability insurance for the patients participating in the study, unless the Hospital’s civil liability insurance covers it.

The authors declare that they have no conflict of interest.
11. STUDY LIMITATIONS

- As IPH can be diagnosed just after the clinical symptoms, it is necessary to use a non-probabilistic consecutive sampling method. Although, clinically, ischemic stroke and IPH symptoms are very alike, the baseline NCCT allows us to differentiate one diagnosis from the other and gather a proper sample. Sampling biases are unlikely to exist because the selection of patients will be carried out before the event (hematoma expansion) happens. Besides possible sampling biases, the patient’s continuity may be low because the study’s duration is no long (90 days each patient). The dropout rate we expect is very low, most of casualties due to deceases.

- The sample size of this study could be considered small, but it is reasonable for our Hospital’s patients’ income. If larger sample was needed, we could consider to engage other Hospitals into the study and design a multi-center study.

- In order to avoid systematic errors and information biases, all the CT machines used in this study fulfill the highest criteria for quality and the scales have been validated and are widely applied over the world.

- There is no clear consensus about the cut-off point for significant hematoma expansion, the limit values vary among the studies. Due to this controversy, measurements are presented in absolute (ml) and relative (%) volumes. The reference values used for this study are the most widespread values we found in our bibliography research (10,17,18,20,23–26,29). As there is no evidence, the cut-off in our study could have been settled over the real threshold of significant hematoma expansion’s and, thus, a percentage of patients with real hematoma enlargement would be omitted. We recommend to update and change the threshold values if new evidences appear in order to obtain realistic results.

- In order to reduce the imaging protocol’s dose radiation, some technical parameters have been modified in the PCT scan. Diminished kVp and mAs values permit to low the radiation dose; the slices’ thickness increase contributes reducing the radiation dose too, but it may also reduce the definition of the images and the sensitivity for spot sign detection. Latest studies proved that even a greater reduction of these parameters in PCT technique is affordable to obtain a proper image (40). Thus, the parameters used in this protocol try to balance radiation dose and image quality.
In this study, we assume that the growth items are linear in time, but we should consider the possibility that they are not necessarily. If this is right, we could discount a group of patients with later enlargement or a negative detection. In further studies, we could consider the possibility of extending the imaging evaluation, take into consideration the extra dose radiation risks and the increase of the budget too.

Considering that the participating patients in this study will come just from Girona’s Hospital, our results could be difficult to generalize and they would be only representative for this region (Girona province) or to a population with similar demographic characteristics.
12. REFERENCES


Dynamic spot sign predicts hematoma expansion in IPH.
**STUDY INFORMATION SHEET**

| Dynamic spot sign predicts hematoma expansion in Intraparenchymatous Hemorrhage: a Perfusion CT study. |
|---|---|
| NOMBRE DEL RESPONSABLE: | NOMBRE DEL PARTICIPANTE: |
| CARGO: | APELLIDO 1: |
| CENTRO: | APELLIDO 2: |
| UNIDAD: | DNI: |
| TEÉFONO DE CONTACTO: | NHC: |
|  | TEÉFONO DE CONTACTO: |
|  | E-MAIL DE CONTACTO: |

La información que se transmita a las personas participantes en esta investigación cumple los requisitos que se contemplan en la legislación española en el ámbito de la investigación biomédica y la protección de datos de carácter personal: Ley Orgánica 15/1999, de Protección de Datos de Carácter Personal; Ley 41/2002 básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica y Ley 14/2007 de investigación biomédica.

Este documento sirve para que usted, o quien lo represente, conozca las implicaciones de participar en el estudio y dé su consentimiento para participar en él, autorizando la realización de las pruebas necesarias el tiempo que requiera el estudio.

Usted puede retirar este consentimiento cuando lo desee. Firmarlo no le obliga a hacerse ninguna de las intervenciones. De su rechazo no se derivará ninguna consecuencia adversa respecto a la calidad del resto de atención recibida.

Antes de firmar, es importante que **lea despacio y con atención** la información siguiente.

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**FINALIDAD DE LA INVESTIGACIÓN**

Usted ha sido diagnosticado de Hemorragia Intracerebral. La Hemorragia Intracerebral consiste en la acumulación de sangre en el tejido cerebral producida por la rotura de un vaso sanguíneo, produciéndose así un hematoma interno. La Hemorragia Intracerebral es una enfermedad con una alta mortalidad y alta tasa de secuelas neurológicas. Se ha observado, que en las primeras 6 horas hay un alto riesgo de que este vaso sanguíneo vuelva a sangrar y provoque un aumento del hematoma. El crecimiento de la hemorragia conlleva el empeoramiento de la situación, provocando mayor compresión del tejido cerebral y un empeoramiento de los síntomas.

Actualmente disponemos de varios estudios de imagen que nos ayudan a ver, en ciertos casos, si hay un primer indicio de resangrado en pacientes con Hemorragia Intracerebral. Estas técnicas, Tomografía Computarizada y la Angiografía Tomografía Computarizada, son exploraciones radiológicas.
Aunque estas dos técnicas han permitido el avance en el diagnóstico y el manejo de los pacientes con Hemorragia Intracerebral, aún no conseguimos detectar todos aquellos pacientes con resangrado activo y que están en riesgo de empeorar. La adición de otra técnica, Tomografía Computarizada en perfusión, nos ayudará a detectar con mayor sensibilidad aquellos pacientes en riesgo, así como estudiar de forma más precisa los mecanismos de esta enfermedad y su mejor comprensión.

Si usted quiere participar en este estudio debe haber sido diagnosticado de Hemorragia Intracerebral. Su participación será de 90 días, durante los cuales será tratado igual que el resto de pacientes con Hemorragia Intracerebral (ingreso en el Hospital, monitorización de constantes vitales, análisis sanguíneo, atención y valoración por neurólogos especialistas) y se añadirán diversas pruebas radiológicas. Se le practicará una Tomografía Computarizada Simple para confirmar su diagnóstico, seguidamente se le administrará contraste yodado y se procederá a realizar la Tomografía Computarizada en Perfusion y, posteriormente, se volverá a administrar contraste yodado y se realizará la Angiografía Tomografía Computarizada. Todo este conjunto de pruebas no tendrá una duración mayor a 10-15 minutos. A las 24 horas se realizará otra Tomografía Computarizada Simple. Durante su estancia en el Hospital será atendido por el servicio de enfermería y valorado por los neurólogos, que controlarán su evolución hasta darlo de alta. Si en algún momento hay un empeoramiento clínico, se realizará otra Tomografía Computarizada Simple de forma urgente para detectar cualquier la causa, así como otras pruebas que sean necesarias. Usted será dado de alta según el criterio médico del neurólogo que lo asista. La investigación finalizará a los 90 días desde su ingreso en el Hospital, si usted es dado de alta antes de que finalice ese periodo y se necesita recoger datos, se contactará con usted por vía telefónica para que nos los pueda proporcionar.

Usted no podrá participar en el estudio si:
- Es menor de 18 años
- Han pasado más de 12 horas desde el inicio de los síntomas.
- Ha sufrido un trauma en los últimos 3 meses, si tiene una malformación arteriovenosa cerebral o ha sufrido un ictus isquémico en los últimos 6 meses.
- Tiene un tumor o algún tipo de Demencia
- Tiene una enfermedad renal.
- Está embarazada

RIEGOS E INCONVENIENTES PARA EL PARTICIPANTE
Los riesgos que derivan de este estudio son los riesgos de las técnicas radiológicas utilizadas.
La Tomografía Computarizada es una exploración radiológica con finalidades diagnósticas. Se realiza en una sala especial de rayos X y es llevada a término por personal especializado.
Se trata de una prueba muy poco molesta, los únicos inconvenientes son los propios de la exposición a radiaciones (rayos X), fundamentalmente una ligera elevación del riesgo a sufrir un cáncer en el futuro. En el estudio se realizarán varias exploraciones con lo que este riesgo se incrementa, pero se usan medidas especiales para reducir al máximo la dosis de radiación administrada necesaria en cada exploración. El riesgo a sufrir cáncer sigue siendo muy bajo en comparación con la incidencia normal del cáncer en la población.

**Riesgos sobre la administración de Contraste yodado**

Las pruebas de imagen que son necesarias para completar el estudio en la investigación requieren la utilización de contrastes yodados para su realización, para poder estudiar de forma adecuada su patología.

- El contraste yodado es una sustancia líquida (fármaco) que se inyecta por vena con el fin de obtener una mejor calidad de imagen y más información diagnóstica. Esta sustancia es generalmente bien tolerada, pero en algunos casos puede provocar reacciones alérgicas como cualquier otro fármaco. Éstas, pese a ser leves la mayoría de las veces, pueden llegar a ser excepcionalmente muy graves. No existen pruebas previas para detectar si usted es alérgico al yodo. No existen reacciones cruzadas (si usted es alérgico a otros medicamentos, no implica que tenga mayor riesgo de tener alergia al contraste yodado). Es de marcada importancia que alerte al personal sanitario que le atienda si alguna vez ha sufrido una reacción alérgica después de la administración de contraste yodado.

- La administración de contrastes yodados puede, en ocasiones, alterar el funcionamiento de los riñones cuando éstos ya están dañados previamente. Esta alteración suele ser poco importante, especialmente si se toman medidas necesarias y que se explicarán antes de la inyección del fármaco. Por ellos, es muy importante que informe al personal sanitario que le atienda si sufre algún tipo de insuficiencia renal.

**USO DE LAS IMÁGENES PARA INVESTIGACIÓN**

Las imágenes diagnósticas que se realizarán durante las técnicas de Tomografía Computarizada se usarán en este estudio para la investigación científica y para realizar estudios que pueden resultar en beneficio para usted.

- Posibles inconvenientes: posibilidad de ser contactado con posterioridad a fin de recabar nuevos datos u obtener nuevas muestras, para lo que se podrá solicitar nueva información sobre el modo de hacerlo.
El paciente siempre cuenta con la potestad de negarse a participar en posteriores requerimientos.

- Extensión y duración de los procedimientos.

**DERECHOS DEL PARTICIPANTE EN RELACIÓN CON LA INVESTIGACIÓN**

1. Derecho a la revocación del consentimiento y sus efectos, incluida la posibilidad de la destrucción o de la anonimización de las muestras e información radiológica y de que tales efectos no se extenderán a los datos resultantes de las investigaciones que ya se hayan llevado a cabo. Se deberá especificar el modo en que el participante puede ejercer el derecho de retracto y a quién debe dirigirse para ejercerlo.

2. Posibilidad de contactar con los investigadores en caso de aparición de efectos adversos imprevistos.

3. Derecho a revocar el consentimiento en cualquier momento, sin perjuicio de su tratamiento médico.

4. Derecho a decidir el destino de sus muestras y datos personales en caso de decidir retirarse del estudio.

5. Derecho a que se vuelva a pedir su consentimiento si se desea utilizar la muestra en estudios posteriores.

6. Seguro u otras medidas que existan para asegurar una compensación adecuada en el caso que el sujeto sufra algún daño.

7. Garantía de confidencialidad de la información obtenida, indicando la existencia del fichero, la finalidad de la recogida de los datos y destinatarios de la información, del carácter obligatorio o facultativo de las respuestas, de la posibilidad y donde ejercer los derechos de acceso, rectificación, cancelación y oposición, de la identidad y dirección del responsable del fichero, el modo en que se manejarán las bases de datos y la identidad de las personas que tendrán acceso a los datos de carácter personal del sujeto fuente.

8. Advertencia sobre la posibilidad de que se obtenga información relativa a su salud, derivada de los análisis que se realicen sobre sus muestras biológicas o sobre sus imágenes radiológicas, así como sobre su facultad de tomar una posición en relación con su comunicación.
CONSENTIMIENTO INFORMADO

El consentimiento sobre la utilización de imágenes /muestra biológica se otorgará, bien en el acto de obtención de las imágenes muestra o bien con posterioridad, de forma específica para esta investigación concreta.

El consentimiento específico podrá prever el empleo de las imágenes/muestras para otras líneas de investigación relacionadas con la inicialmente propuesta. Si no fuera este el caso, se solicitará al sujeto fuente que otorgue, si lo estima procedente, un nuevo consentimiento.

El consentimiento podrá ser revocado, totalmente o para determinados fines, en cualquier momento. Cuando la revocación se refiera a cualquier uso de la muestra, se procederá a su inmediata destrucción, sin perjuicio de la conservación de los datos resultantes de las investigaciones que se hubiesen realizado con carácter previo.

Datos del estudio para el que se otorga el consentimiento

| INVESTIGADOR PRINCIPAL: |
| TITULO PROYECTO: |

Datos del participante/paciente

| NOMBRE Y APELLIDOS: |

Persona que proporciona la información y la hoja de consentimiento

1. Declaro que he leído y la Hoja de Información al Participante sobre el estudio citado.

2. Se me ha entregado una copia de la Hoja de Información al Participante y una copia de este Consentimiento Informado, fechado y firmado. Se me han explicado las características y el objetivo del estudio, así como los posibles beneficios y riesgos del mismo.

3. He contado con el tiempo y la oportunidad para realizar preguntas y plantear las dudas que poseía. Todas las preguntas fueron respondidas a mi entera satisfacción.

4. Se me ha asegurado que se mantendrá la confidencialidad de mis datos.

5. El consentimiento lo otorgo de manera voluntaria y sé que soy libre de retirarme del estudio en cualquier momento del mismo, por cualquier razón y sin que tenga ningún efecto sobre mi tratamiento médico futuro.
DOY □ MY doy □
Mi consentimiento para la participación en el estudio de investigación.

DOY □ NO DOY □
Mi consentimiento para la anonimización de mis muestras.

DOY □ NO DOY □
Mi autorización para la realización de las técnicas de Tomografía Computarizada antes mencionadas, así como la administración de contrastes yodados.

DOY □ NO DOY □
Mi consentimiento para la manipulación y el uso de las imágenes radiológicas derivadas de los procedimientos y la información obtenida de mis muestras biológicas (táchese lo que no proceda) por los autores de esta investigación con fines docentes o de difusión del conocimiento científico.

DOY □ NO DOY □
Mi consentimiento para que se realicen las actuaciones oportunas, incluyendo modificaciones en la forma de realizar la intervención, para evitar los peligros o daños potenciales para la vida o la salud, que pudieran surgir en el curso de la intervención.

Firmo por duplicado, quedándome con una copia.

Antes de firmar este documento, compruebe que el contenido que va a firmar es correcto.

Fecha: ________________________________
Firma del participante/paciente/representante legal:

Fecha: ________________________________
Firma del Investigador o la persona que proporciona la información y la hoja de consentimiento:

X ________________________________

Hago constar que he explicado las características y el objetivo del estudio y sus riesgos y beneficios potenciales a la persona cuyo nombre aparece escrito más arriba.
MODIFIED RANKIN SCALE (mRS)

The mRS is one of the most commonly functional outcome tool used in medical practice and research in stroke. The scale was originally introduced in 1957 by Dr. John Rankin in Glasgow. The version currently used and accepted is the scale modified by C. Warlow in 1980.

MRS is an easy and quick instrument to use, it has been proven to be valid and clinically relevant for the assessment of stroke patients. The scale assesses, globally, the physical disability or dependency degree of stroke patients, it evaluates the functional capacity rather than the performance of specific tasks.

The scale consists of 6 grades, from 0 to 5; with 0 corresponding to no symptoms and 5 corresponding to severe disability.

In this protocol, mRS will be used to assess the previous and the final functional state of all the patients and define the clinical outcome variable alongside other variables.

References

NATIONAL INSTITUTE OF HEALTH STROKS SCALE (NIHSS)

The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS was originally designed as a research tool (1989), but now the scale is widely spread and used internationally as a clinical tool. Nowadays, NIHSS is the most used scale to assess neurologic functions in stroke patients.

The scale is designed to be a rapid (less than 10 minutes to complete), simple, valid, and reliable tool for daily care in medical practice. It can be administered by any well-trained physicians, nurse or therapist. In our protocol, it will be administered by the neurologists who take part in the study.

The scale allows the physician to explore neurologically the patient by its 15 items. Levels of consciousness, language, negligence, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss can be evaluated with this scale. A trained observer rates the patient’s ability to answer every question and to perform several activities. It is noticeable that the evaluation of acute cerebral infarction depends upon the ability of the observer to assess accurately the patient.

Each item is scored 3 to 5 grades; 0 grade is for normal. The obtained punctuation classifies the patient’s neurologic severity: 0 = no deficit, 1 = minimal deficit, 2-5 = mild deficit, 6-15 = moderated deficit, 15-20 = moderate-severe deficit, and >20 = severe deficit. An increase of 4 or more scores compared to the baseline NIHSS scoring is indicative of significant neurologic worsening.

NIHSS has a strong ability to detect easily a worsening or improvement of the neurologic state, it is valid to predict short and long term outcome of stroke patients in addition to inform of the current neurologic status.

In this protocol, NIHSS will be used as the tool to assess accurately the neurologic state of all patients during the whole study and define the final clinical outcome alongside with other variables.

References