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Strokes and traumatic spinal cord and brain injury

NEW PREDICTIVE BIOMARKERS OF OPTIMAL FUNCTIONAL RECOVERY AND OF GOOD RESPONSE TO ENDOVASCULAR TREATMENT OF ACUTE ISCHAEMIC STROKE. PROMISE STUDY (SOMATOSENSORY EVOKED POTENTIALS MONITORING DURING ACUTE ISCHEMIC STROKE) STUDY

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1. Project Summary

1) Objectives

Endovascular treatment in patients with acute ischemic stroke of a large vessel does not always lead to an optimal clinical and functional prognosis, despite a complete vascular recanalization. Several predictive factors of neurological prognosis after reperfusion treatment have been described based on clinical criteria (age, NIHSS scale score, systolic blood pressure, and hyperglycemia) and neuroimaging (extension of early signs of ischemia using the ASPECTS scale, site of arterial occlusion, perfusion parameters that identify the "core" as well as the ischemic penumbra tissue and the state of collateral circulation). Despite the incorporation of all these into the usual clinical algorithm for the diagnosis and treatment of reperfusion of acute ischemic stroke, the percentage of significant functional disability or death at three months of stroke ranges from 21-67%. For this reason, determining new biomarkers predicting which patients with acute ischemic stroke could respond satisfactorily to endovascular treatment could be useful in determining a priori which patients could be transferred directly to a comprehensive stroke center (CSC) or, even in the angiography ward to be treated with mechanical thrombectomy (MT) with respect to those in which such treatment could be futile. There is experimental and clinical evidence that somatosensory evoked potentials (SEPs) are indicators of cerebral blood flow. Therefore, our hypothesis is that a viable brain tissue neurophysiological biomarker, the N20 response of SEPs, could provide a substantial predictive value with respect to that provided by clinical and neuroimaging variables. This approach could optimize the selection of patients who would benefit from reperfusion treatment by MT beyond the currently accepted therapeutic windows.

Primary objective: To confirm that the N20 response of SEPs has a substantial predictive capacity for short-term functional prognosis in patients treated with MT, using the modified Rankin scale (mRS) at 7 days of ischemic stroke. The score on mRS at 7 days is considered to be highly correlated with the functional prognosis at 90 days (Dávalos A et al. Lancet Neurol 2017). Certified blind local assessors as a result of SEP registration will assess this primary goal in each patient through a structured interview.

Secondary goals: Assessment of the primary objective (functional independence measured with mRS) at 90 days. Assessment of severity and disability at 7 days and

90 days according to the distribution of mRS scores Assessment of the dramatic early response to treatment (decrease in NIHSS score equal to or greater than 8 points from baseline or NIHSS score of 0 or 2 at 24 hours Assessment of a 24-hour neurological improvement (defined as a decrease in the score on the NIHSS scale equal to or greater than 4 points with respect to the baseline. To investigate whether the N20 response is associated with the volume of tissue in ischemic penumbra I to the state of collateral circulation in the basal neuroimaging I and with the final volume of infarction in the control neuroimaging after reperfusion treatment (MT) using multimodal neuroimaging techniques such as multiparametric MRI or infusion CT (TC-CBF / CBV), which are implemented in routine clinical protocols. Regarding the safety variables, the frequency of mortality and symptomatic intracranial hemorrhage confirmed with neuroimaging and evaluated by blind researchers will be assessed, using the definition used in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) and definitions of European-Australasian Acute Stroke Study (ECASS II).

2) Brief summary of design, procedure and methods

The target population of this study is patients with acute ischemic stroke due to a large vessel occlusion of the anterior circulation (middle cerebral artery in its M1 or M2 segment, with or without significant occlusion or stenosis of the ipsilateral carotid artery). and with an optimal previous functional situation (mRS 0-2), which arrive at the research center (Germans Trias i Pujol University Hospital, HUGTiP) according to the usual channels of the Catalan ictus code (codi ictus) and which, being treated according to the standard protocols of the ESO clinical guidelines and ASA, receive a reperfusion treatment (MT). All patients included in the study or, failing that, their relatives will have signed a specific informed consent. Exclusion criteria are: ASPECTS score below 6 on CT or 4 on the brain MRI diffusion sequence. In addition, patients with a documented history of previous extensive stroke, neuromuscular disease, or tumors of the central nervous system that may interfere with the recording and analysis of the N20 response of SEPs will be excluded. SEPs are obtained by stimulating both median nerves in the carpus and with transcranial registration in both the ipsi- and contralateral cortex at the corner of the stroke. They will be recorded immediately before, continuously and until the end of the reperfusion treatment (MT). N20 responses generated in both the affected and contralateral cerebral hemisphere (control) will be measured qualitatively (presence / absence) and quantitatively (latency and amplitude expressed in ms and microV, respectively). It will be performed

immediately before the reperfusion treatment (MT), during this and until its completion and transfer of the patient to the Acute or Semicritical Stroke Unit. A 24-hour follow-up SEPs study will be repeated in those patients who are still on HUGTiP. SEPs are registered by researchers collaborating on the project. From 8 am to 3 pm by the doctors of the Neuromuscular Diseases Unit of the HUGTiP, from 3 pm to 8 pm, by the staff contracted with the funds granted by the *La Marató de TV3 Foundation* and from 8 pm to 8 am as well as during the weekends, by collaborating researchers contracted with the funds of the *La Marató TV3 Foundation* grant that will establish localized duty shifts. In this way, 24-hour coverage is guaranteed for the registration of SEPs in order to minimize the loss of candidate patients for inclusion in the study and ensure the recruitment of the required sample. The analysis of the N20 responses of the SEPs is carried out in a deferred manner and is carried out by a blind researcher in the clinical and neuroimaging data of the patients. In all patients included, standard demographic characteristics, medical history, laboratory test results, and stroke severity were assessed by scoring on the NIHSS scale measured at the time of admission. The variables of different time flows from the onset of the stroke to the different diagnostic and therapeutic interventions during the acute phase of the stroke are also recorded. The basal neuroimaging may be indiscriminately computed tomography of the skull without contrast (NCCT) together with an angio-CT (CTA), a multiparametric MRI, or a CT-perfusion (CTP) if the MR is not available. At the 24-hour stroke, a follow-up NCCT is performed to assess the volume of the infarction or to determine if an intracranial hemorrhage or malignant edema has occurred. A CTA or angio-MRI is performed to confirm if revascularization persists within 24 hours of the stroke. All images are anonymized and stored in DICOM format. Researchers who are blind to the clinical prognosis and to the result of monitoring the N20 response of SEPs perform a visual analysis of the qualitative variables and a quantitative analysis of the post-process variables: first-pass permeability and perfusion maps. Post-processing analysis of broadcast sequences (DWI) and perfusion will be performed using the Olea Sphere platform. In addition, the RAPID software (ischemia view, Redwood City, CA) will be used to calculate the volume of the ischemic lesion on the RM-DWI or on the CTP-rCBF maps or by the automatic evaluation of the ASPECTS score on the NCCT. and the RM-DWI. Patients' functional status will be assessed using the mRS scale at 24 hours, 7 days or at hospital discharge and 3 months after stroke. All clinical, neuroimaging, and neurophysiological variables collected are recorded in a Case Report Form (CRF)

specifically designed for this study. All CRFs will be reviewed by a blind researcher for deferred inclusion and entered into a database anonymously.

Statistical analysis will be performed on the total number of patients monitored by an independent collaborating researcher. First, the sensitivity and specificity (and their 95% CI) of the pre-MT N20 response to predict functional independence at 7 days of acute ischemic stroke or at the time of hospital discharge will be analyzed. An estimated sample size of 228 patients. The adjusted predictive value of the N20 response as a functional biomarker of independence after a MT will be analyzed as a binary logistic regression and its predictive value in the full range of disability (shift analysis) by ordinal logistic regression. Different regression models will be constructed with other pre- and intrahospital clinical predictors, including clinical and neuroimaging variables. This analysis will provide the independent predictive value of the N20 response as a potential biomarker for the indication of reperfusion treatment. The binary predictive effect of the N20 response will also be analyzed as a function of the time from onset of symptoms to revascularization. Secondary analysis will include the unadjusted association of the N20 response with clinical and neuroimaging prognostic variables (determining whether the N20 response of SEPs may be a neurophysiological marker of ischemic penumbra and collateral circulation status) and safety variables.

2. Results

The N20 response has a substantial ability to predict functional prognosis in patients with acute ischemic stroke who are treated with mechanical thrombectomy (MT), measured both before and at the end of the procedure. Its sensitivity to functional recovery is 93%, while its absence has a predictive value over functional dependence of 93%. The predictive ability of N20 pre-MT is greater than that of the clinical variables used according to current clinical practice guidelines, alone or in combination. The predictive model that includes pre-hospital accessible clinical variables along with N20 offers predictive capacity equivalent to those containing variables that require a hospital environment and specialized healthcare personnel (NIHSS and ASPECTS). The N20 pre-MT response has a higher predictive capacity for good functional prognosis after MT than the imaging variables used in daily clinical practice (single CT and multimodal neuroimaging).

3. Relevance and possible future implications

The results obtained from this study made it possible to carry out a series of activities aimed at initiating a process of transferring scientific knowledge with the aim of developing a product that has a positive impact on the prognosis and quality of life of affected patients. for an acute ischemic stroke. Funding has been obtained through competitive research projects: -Caja Impulse Validate Program of the La Caixa Foundation (September 2019) -Sapiens Scholarship from the Talents Program of the Germans Trias i Pujol Hospital and the La Pedrera Foundation (November 2019) - Headstarts Program (EIT Health) (June 2020) -Ship2B Foundation Acceleration and Investment Program -SME-H2020 call October 2020 with the obtaining of the Seal of Excellence certificate. With this specific training, mentoring and financial support, the technical development of a medical device has begun in line with the intellectual and regulatory property strategy with reference partners such as Tecnalia, Hoffman Eitle and Tecnomed, respectively. A business model and plan has been developed to determine the strategy for the device to reach the market and be implemented in the usual clinical algorithm for acute ischemic stroke given the positive results provided by the PROMISE research project. A panel with international stroke opinion leaders has also been organized to assess the results and their potential application and a cost-effectiveness study with the aim of quantifying the impact that the incorporation of the medical device would have on patients. with acute ischemic stroke and the health system. As a result of these activities and in order to carry them out, the spin-off of the Germans Trias i Pujol Health Sciences Research Institute Time is Brain, SL has been set up on 9 September. July 2020. We currently have a team of 7 collaborators. One of the PROMISE project researchers has become the CEO of the spin-off and has hired 3 team members: Dr. Gisela Ruiz Vega as CTO (full-time) and Raül Zurita and Oriol Vernis (part-time). During Q2 2021, a seed round was successfully launched and completed with the aim of completing the development of the functional prototype of the BraiN20® medical device and proceeding with its clinical validation. Two competitive funding projects have also been obtained: -Caixa Research Consolidate (September 2021) -NEOTEC (CDTI) (December 2021) The main contribution of the project is to show that the N20 response of somatosensory evoked potentials (PES) has a predictive capacity of the functional prognosis of patients with acute ischemic stroke higher than the diagnostic methods currently used (clinical scales, CT and / or MRI). However, the combination of N20 with prehospital clinical variables has a

predictive capacity equivalent to that of in-hospital diagnostic tools and even those used in high-tech centers. Therefore, based on the results obtained, we have generated evidence to drive the incorporation of the N20 response into the current diagnostic algorithm for acute ischemic stroke. We are adding a new biomarker that offers a totally innovative approach to that provided by current diagnostic methods. The creation of the spin-off Time is Brain, SL aims to develop a medical device, BraiN20® that allows an automatic and continuous recording of this response accessible to any type of health personnel. It is a fast, online, non-invasive, easy-to-use method for diagnosing stroke, even in a low-cost, pre-hospital setting. According to the results of the PROMISE study and health economics, its incorporation would increase diagnostic accuracy by 30%, reduce the time to access the treatment of mechanical thrombectomy by 60 to 100 minutes and allow continuous monitoring of brain viability. during the procedure, guiding the responsible doctor and detecting complications early.

4. Generated Scientific Bibliography

PhD: Intraoperative neurophysiological monitoring during the endovascular treatment of acute ischemic stroke. IOMIS study

Alicia Martinez, Giuseppe Lucente, Andrea Arbex, Alba Ramos, Miriam Almendrote, Monica Millan, Natalia Perez de la Ossa, Meritxell Gomis, Laura Dorado, Maria Hernández-Pérez, Carlos Castaño, Sebastian Remollo Friedemann. Alicia Garrido, Nicolau Guanyablens, Elena López-Cancio Martínez, Jaume Coll-Canti, Antonio Dávalos. Somatosensory Evoked Potentials Monitoring In Acute Ischemic Stroke (Promise) Study: A Biomarker Of Functional Recovery Prior To Mechanical Thrombectomy (clinicaltrials.gov: NCT04099615). International Stroke Conference. (New Orleans, February 2022) Patents WO2018149973-Prediction of the outcome of endovascular treatment in Acute Ischemic Stroke patients. Priority date 17 February 2017. National phases: EU, US and Canada. EP22382090-Prediction of the outcome of endovascular treatment in Acute Ischemic Stroke patients. February 2, 2022