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Strokes and traumatic spinal cord and brain injury

CEREBROVASCULAR ACCIDENT, STROKE UNIT, REHABILITATION, OPTICAL, DIFFUSE CORRELATION SPECTROSCOPY, CEREBRAL BLOOD FLOW, CEREBRAL SELF-REGULATION

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1. Summary of the project

Stroke remains a significant challenge for our healthcare system. Approximately 13,000 stroke patients are admitted annually to Catalan hospitals, representing one of the leading causes of death and disability in adults. In the last decades there have been notable advances in stroke care, mainly with the widespread use of reperfusion therapies and the organization of care in multidisciplinary stroke units that have led to a significant improvement in patients' functional outcome. However, up to 30% of patients still have severe disability in performing their daily activities after suffering a stroke.

There is growing awareness of the need to redefine and personalize the therapeutic strategies based on key physiological factors such as cerebral blood flow (CBF). CBF is a fundamental parameter for brain tissue viability and cerebral function. In acute stroke, decrease of CBF rapidly initiates a cascade of processes leading to impaired cerebrovascular autoregulation (CA) function and ischemic brain damage. The goal of most interventions in stroke is to maintain CBF homeostasis to diminish ischemic injury and prevent secondary complications. However, the impairment of CA may increase brain vulnerability to cerebral perfusion changes and affect the efficacy and safety of acute stroke care interventions. Therefore, the clinical application of CBF monitoring at the bedside could potentially improve the detection of conditions that increase the risk of secondary complications and help guide stroke therapy. Unfortunately, such a technology is still lacking in the daily clinical care.

Diffuse correlation spectroscopy (DCS) is an emerging optical technique for noninvasive monitoring of brain perfusion that utilizes the detection of temporal intensity fluctuations of light scattered by moving blood cells in the microvasculature of cerebral cortex. Previous research has shown that DCS can successfully track autoregulatory changes of CBF without the need for contrast agents in patients with acute brain injury, including acute stroke, and has been validated against other techniques such arterial spin labelling MRI or Xenon-CT. Time resolved spectroscopy (TRS) is another diffuse optical technique that can be hybridized with DCS and is capable of measuring tissue oxygen saturation (StO_2).

This is a transdisciplinary project that explores the translation of basic research in biomedical optical imaging into clinical practice in the setting of acute stroke care. The technological subproject aimed at introducing noninvasive physiological neuromonitoring for patients with acute stroke by assembling a compact, portable optical neuromonitor that can be deployed at the bedside and integrated in acute stroke care routine. This will give access to information on cerebral hemodynamic function that may provide new biomarkers relevant for the response to acute stroke interventions. Specifically, the clinical subproject explored the usefulness of integrating aspects of CBF regulation into neurorehabilitation planning. Out of bed early mobilization (EM) is a widely accessible and cost-effective rehabilitative intervention that is promoted as a best practice recommendation for acute stroke care. The rationale for EM after acute stroke is to prevent immobilization-related complications and promote motor control recovery. However, higher doses of physical activity at the early stages of stroke have been associated with a worse functional outcome and higher risk of mortality, increasing the uncertainty among clinicians about how early and at what intensity rehabilitation should be prescribed after stroke. It has been hypothesized that hemodynamic changes induced by upright positioning may be the main mechanisms underlying the potential harmful effect of early intensive rehabilitation after stroke. Therefore, our objective was to evaluate whether the effect of an early intensive EM program on motor recovery and neurological complications in patients with acute stroke is influenced by individual CBF autoregulation as measured by optical monitoring at the bedside. Our primary hypothesis was that the presence of impaired CA assessed with optical CBF monitoring at the time of first mobilization can identify patients who are less likely to benefit or could be harmed by intensive (higher dose) EM at the acute stage of stroke.

We designed a single center prospective, open, randomized, controlled trial with blinded outcome assessment in a tertiary stroke center. Inclusion criteria were age ≥18 years, clinical diagnosis of first or recurrent ischemic stroke or spontaneous intracerebral hemorrhage, admission to the Stroke Unit within 24 hours after known symptom onset, availability of transcranial optical monitoring during first mobilization, and written informed consent. Exclusion criteria were pre-stroke modified Rankin scale score >3, transient ischemic attacks, exclusively retinal stroke, unstable neurological or medical condition, and a suspected or confirmed lower limb fracture at the time of stroke preventing the implementation of the mobilization protocol. All patients included

in the study received first out-of-bed mobilization at 24±6 hours from symptoms onset under DCS monitoring of bilateral frontal CBF and systemic parameters (noninvasive continuous blood pressure, heart rate and end-tidal CO_2) to calculate indices of CA. Patients were subsequently allocated to receive an intensive EM program or usual rehabilitation care using a computer-generated blocked random allocation (1:1), with stratification by stroke severity and type of stroke. Standard care included out-of-bed mobilization at the discretion of the treating neurologist and nurses, as well as one daily session of physiotherapy and/or occupational therapy for 5 days a week. The intensive EM group received standard mobilization plus 2 or more additional daily sessions of out-of-bed mobilization focused on sitting, standing and walking activities of at least 20 minutes each provided by two trial therapists for 6 days a week during the first 14 days or until discharge if earlier. The frequency (number of sessions) and dose (minutes) of out-of-bed activity in both groups were recorded daily.

The primary outcome was the change in the score on the Spanish version of the Postural Assessment Scale for Stroke (S-PASS) from baseline to the end of the intervention period. S-PASS evaluates the ability to maintain a position and balance during positional changes in bed, sitting and standing, showing a high predictive ability for activity of daily life function after stroke. S-PASS has 12 items, with total score ranging from 0 to 36 (highest score best). Other secondary outcome measures included change in S-PASS score at 90 days and functional outcome measure with the modified Rankin Scale (mRS) score at 90 days (a score of 2 or less indicates functional independence). Safety outcomes included deaths, neurological deterioration, defined as an increase in the NIHSS score in 4 or more points during the intervention period, stroke recurrence, falls and syncope or presyncope. All outcome measures were evaluated by independent outcome assessors blinded to treatment allocation or cerebral and systemic monitored parameters.

Sample size was initially calculated in 100 patients per group, considering a standard deviation of 12 for the PASS score, with a difference to be detected of 5 and a percentage of losses of 10%, with 80% power to detect a treatment effect.
Analyses were based on intention to treat. We performed regression models to compare the effect of the interventions on outcome end-points and explored potential interactions between intensity of rehabilitation and CBF-related parameters on the effect of early rehabilitation.

2. Results

Technological subproject

The final achievements of the project can be summarized as:

- New, one-of-a-kind optical platform that is the fastest and most comprehensive one available for neuromonitoring in clinical practice.
- New biomarkers relating cerebrovascular hemodynamics to neurological status and its evolution. In particular, we could characterize CA by an autoregulation index (DCSx), defined as the moving Pearson correlation coefficient between CBF and mean arterial blood pressure during first mobilization in the Stroke Unit.
- Rich data-set of in vivo data that will be utilized in further analyses and developments.
- Extension to side-studies on cerebral effects of wearing masks during COVID-19 pandemic, evaluation of healthy cerebral hemodynamics.

Clinical subproject

Patients admitted to the Stroke Unit from April 2019 to March 2020 and from June 2020 to July 2021 were screened for eligibility to participate in the trial. Recruitment rate was affected by COVID-19 pandemic-related hospital restriction to external personnel access and research activities in acute care settings. During the recruiting period, 106 patients were included in the study. Of them, 52 patients were randomly assigned to receive intensive EM and 54 patients to receive usual care. Both groups were comparable regarding demographic and baseline clinical characteristics. Mean age was 73.3±13.6 and median baseline NIHSS was 6 (IQR, 3-14), indicating an averaged mild to moderate severity of stroke. The type of stroke was ischemic in 89% patients and hemorrhagic in 11%.

The time to first mobilization was comparable in the intensive and the standard EM group (25.8 h and 25.7 h from symptoms onset, respectively, p=0.933). Optical monitoring could be deployed without delaying mobilization and without side effects. After first mobilization, the median length of the physical intervention was 7 (6-11) days in the intensive group and 8 days (7-11) in the standard group (p=0.441). The intensive EM group received three times more daily number of sessions and dose of out-of-bed mobilization compared to the usual care group (p<0.001).

Clinical response of EM according to the intensity of mobilization:
At entry, median S-PASS score showed mild to moderate balance dysfunction in both groups (median score of 31 in the standard group and 30 in the intensive group). A significant increase in S-PASS score was observed from baseline to the end of the intervention and at 90 days in both usual care ($p<0.002$ and $p<0.001$, respectively) and intensive EM group ($p<0.001$ both). However, the intensive EM showed a higher postural improvement (higher S-PASS increase) at the end of treatment, compared to the standard EM). In the linear regression analysis, we found a significant association between the amount of therapy (dose) and postural recovery, in favor of the intensive (higher dose) EM intervention. At 3 months, no significant differences on change in PASS score between groups was found. This suggest a favorable effect of intensive EM on achieving faster motor recovery.

In the analysis of secondary end points, there were no significant between-groups differences in the 90-day functional outcome or mortality. Similarly, no significant differences were found in the incidence of neurological complications, including neurological deterioration or recurrence. Regarding other adverse events during the intervention, a higher incidence of orthostatic intolerance symptoms was observed in the intensive EM group.

Relationship between CBF autoregulation, intensity of EM and outcome:
Changes in frontal CBF in both ipsilesional and contralateral hemispheres, systemic hemodynamic (BP, HR) and respiratory ($EtCO_2$) parameters across positional changes in all patients were analyzed. Overall median frontal CBF decreased significantly in both the ipsilesional and contralateral hemisphere when patients were progressively mobilized from supine to 30°, sitting and standing. Median ipsilateral rCBF decrease was 10.2% from supine to sitting and 17.8% from supine to standing. No association was found between postural CBF parameters and baseline clinical variables. In particular, CBF parameters during first mobilization were not related to stroke severity, etiology or presence of large vessel high grade stenosis or occlusion. Postural CBF changes and DCSx values were comparable in both treatment groups.

When exploring the potential clinical value of all optically monitored parameters, using logistic regression analysis we found that ipsilesional DCSx during first mobilization was significantly associated with the incidence of neurological deterioration (n=9) during

admission (p=0.039). Moreover, there was a significant interaction between dose of therapy and DCSx (p=0.021), suggesting that higher doses of therapy in patients with higher DCSx values (worse CA) is associated with a higher risk of neurological deterioration, whereas the amount of dose did not affect outcome in patients with low DCSx values (better CA).

In conclusion, a more intensive (higher dose) EM program was associated with a faster recovery of postural function compared to standard mobilization in patients with acute stroke. However, a higher risk of neurological deterioration was found in patients with worse CA function who received higher amount of EM during the first week from stroke onset.

3. Relevance and potential future implications

Our project gives support to the clinical usefulness of continuously measuring cerebral hemodynamic changes in patients with acute stroke in the setting of Stroke Unit care using novel bedside optical neuromonitoring systems at the bedside.

We demonstrated the feasibility of tracking cerebral physiologic changes in real time during a therapeutic intervention and provided new insights into the evaluation of the benefit/risk of therapy in the acute stage of stroke. In particular, we improved our understanding about the cerebrovascular changes induced by early physical activity on the acute injured brain and provided a biological rationale for choice of the most appropriate intensity of rehabilitation at the acute stage of stroke. This could be potentially applied to other acute stroke therapies, such as reperfusion therapy or blood pressure management. The integration of this information in the stroke care process may help to make treatment decisions on the basis of brain physiology and monitor the efficacy of interventions in real time, which may potentially increase its benefit and improve patients' outcome. This is a step forward in the integration of physiological-based stroke management in clinical practice.

In summary, we propose a new approach towards personalized health-care in stroke care based on patient-specific assessment of the cerebral physiology by bringing optical neuromonitor to routine clinical use.

4. References generated by the study

Gregori-Pla C. et al. Microvascular cerebral blood flow fluctuations in association with apneas and hypopneas in acute ischemic stroke. Neurophotonics. 2019 Apr;6(2):025004

Gregori-Pla C, et al. Early microvascular cerebral blood flow response to head-of-bed elevation is related to outcome in acute ischemic stroke. J Neurol. 2019 Apr;266(4):990-997.

Delgado-Mederos R. et al. Cerebrovascular and systemic hemodynamic response to early out-of-bed mobilization in acute stroke patients. European Stroke Conference 2021. European Stroke Journal 2021 Vol. 6(1S) 187

Bosch De Basea-Gomez A. et al. Early assessment of exercise capacity with the six minutes walk test in patients with acute mild stroke. European Stroke Conference 2021. European Stroke Journal 2021 Vol. 6(1S) 188

Navarro-Román M. et al. Early clinical evaluation of postural control and risk of falls in patients with mild stroke. European Stroke Conference 2021. European Stroke Journal 2021 Vol. 6(1S) 188

Fischer J. et al. Does wearing a non-medical face mask cause changes in cerebral hemodynamics? European Conferences on Biomedical Optics (ECBO), volume ETu1C.4, Munich, Germany, 2021. SPIE/OSA.

Kobayashi L. et al. Hybrid diffuse optics for bedside measurements of cerebral hemodynamics in a large cohort of stroke patients. European Conferences on Biomedical Optics (ECBO), volume ETu3A.2, Munich, Germany, 2021. SPIE/OSA.

Kobayashi L. et al Novel biomarkers for the prognosis of neurological deterioration - towards individualized post stroke physiotherapy regiments. Society of fNIRS 2021 (fNIRS). Society of fNIRS, 2021.

Kobayashi L. et al. New biomarkers derived from hybrid diffuse optical techniques: a first step to personalized treatment in the stroke unit. SPIE, SPIE, 2022

Fischer J. et al. Non-invasive assessment of cerebral autoregulation in ischemic and hemorrhagic stroke patients. SPIE, SPIE, 2022.

Gregori-Pla C. et al. Blood flow response to orthostatic challenge identifies signatures of the failure of static cerebral autoregulation in patients with cerebrovascular disease. BMC Neurol. 2021 Apr 9;21(1):154.

Fischer JB. et al. Cerebral and systemic physiological effects of wearing face masks in young adults. Proc Natl Acad Sci U S A. 2021 Oct 12;118(41):e2109111118.