TENDER for PROOF
Sub-Centers for Clinical Trial

Penumbral Rescue by Normobaric O=O Administration
in Patients With Ischaemic Stroke and Target Mismatch ProFile:
A Phase II Proof-of-Concept Trial

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PROOF has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733379

Summary of the PROOF Project

Ischaemic stroke (IS) is one of the most common causes of death and the most common cause of chronic disability in the western world, most significantly affecting the ageing populations of high-income countries. It is caused by an occlusion of arteries that supply blood to the brain. Disruption of blood and oxygen supply to the brain leads to neuronal death in the ischaemic core within minutes. The hypoperfused-hypooxygenated tissue surrounding the ischaemic core, the penumbra, is at high risk for infarction over time but still salvageable. Intravenous thrombolysis (IVT) and mechanical thrombectomy (TBY) facilitate early vessel recanalization and thus survival of penumbral tissue. However, as viable penumbra fades rapidly, the therapeutic time window is narrow and many eligible patients do not reach specialized stroke centres early enough. Neuroprotective "bridging" strategies, sustaining the penumbra until reperfusion, may widen the therapeutic window, making recanalization treatments accessible to more patients and improve overall IS outcomes.

As ischaemic cell death is primarily mediated by hypoxia, increasing oxygen supply to the penumbra seems THE logical approach for neuroprotection in stroke. In human beings normobaric hyperoxygenation (NBHO) is easily achieved through inhalation humidified oxygen at high flow rates (i.e. ≥40L/min) leading to an inspiratory oxygen fraction (FiO2) of near 100%.

In animal models of IS, NBHO significantly increased penumbral oxygen pressure and attenuated brain injury (~35 to 50% infarct volume reduction) when it was initiated early after onset of ischaemia and vessel occlusion was transient (≤3 hours). When vessel-recanalization occurred later (≥4 hours) or ischemia was permanent, infarct volumes were either not reduced by NBHO, or only marginal effects were observed when NBHO was prolonged from three to six hours.

In clinical trials, low-flow oxygen supplementation and oxygen therapy at an FiO2 of 0.4, which are both not to be confused with NBHO, did not improve outcomes in IS patients.

Trials evaluating NBHO did not adapt insights gained in preclinical studies as initiation of oxygen therapy was delayed (therapeutic windows of 9 hours after stroke onset or more) and patients eligible for IVT and TBY were excluded, which made penumbral rescue through early initiation of NBHO and rapid and effective recanalisation unlikely. Furthermore, Padma et al. chose an oxygen flow rate of 10L/min, which is too low to achieve sufficient hyperoxygenation.

Nevertheless, in some of the patients studied by Singhal et al., NBHO could stabilise the penumbra during oxygen therapy. However, this effect was not promoted to later time points; most likely due to lack of early reperfusion ("nothing can hold its breath forever"). Based on the aforementioned preclinical data, patients with early and successful recanalisation are destined to benefit from NBHO treatment (neuroprotective "bridging").

Hypothesis: NBHO in addition to standard treatment reduces infarct growth from baseline to 24 hours compared to standard treatment alone if it is initiated prior to recanalisation and within 3 hours after onset of anterior circulation IS.

To achieve a positive proof-of-concept, NBHO treatment will be studied in patients with proximal vessel occlusion and small infarct core on admission. These patients are likely to receive recanalisation therapy (i.e. IVT and/or TBY) and thus, PROOF will be able to replicate the positive results from experimental models of NBHO in transient cerebral ischaemia.

Study design: Prospective, multicentre (up to 34 sites) adaptive phase IIb, parallel-group, randomized (1:1), standard treatment-controlled, open-label, clinical trial with blinded endpoint assessment (PROBE design).

Intervention (N=90-230): NBHO – inhalation of near 100% humidified oxygen (i.e. high-flow oxygen ≥40 L/min via non-rebreather face mask or – in case of TBY-related intubation/mechanical ventilation FiO2 1.0) – started within 3 hours after certain onset of IS and within 20 minutes after end of diagnostic imaging and applied (1) until the end of early and successful TBY (defined by TICI 2b/3 at the end of TBY procedure) or (2) for 4 hours if no or only insufficient reperfusion (defined by TICI 0 to 2a) is achieved during TBY procedure or in case TBY is not attempted.

Control group (N=90-230): Standard low-flow oxygen supplementation if SpO2 <95% according to guidelines of the European Stroke Organisation (ESO). In case of TBY-related intubation/mechanical ventilation, an initial FiO2 of 0.3 will be chosen and adapted if SpO2 <95%.
Follow-up per patient: 90 days
Main inclusion criteria: We include patients (18-80 years old) suffering IS of the anterior cerebral circulation, present to one of the study sites and may receive NBHO-treatment after baseline imaging including CT- or MR-perfusion within 3 hours of certain symptom onset (i.e. either witnessed or last seen well); patients must have at least moderate to severe stroke corresponding to an National Institutes of Health Stroke Scale (NIHSS) score of ≥6 and angiographic evidence of an occlusion of the terminal internal carotid artery or the middle cerebral artery.
Main exclusion criteria: We will explicitly exclude patients with large cerebral infarction at baseline imaging corresponding to an Alberta Stroke Program Early CT Score (ASPECTS) of <7 (CT) / <6 (MRI), patients with high-grade extracranial carotid artery stenosis, relevant pre-stroke disability corresponding to a modified Rankin Scale (mRS) score of ≥2 and patients with relevant acute/chronic respiratory disease.
Primary endpoint: Infarct growth from baseline to 24 hours (absolute difference of infarct core volume on imaging at 22 to 36 hours to infarct core volume at baseline)
Key Secondary Endpoint: NIHSS at 24 hours
Safety Endpoints: Death, any/respiratory serious adverse events until day 5/discharge and day 90, incidence of any/symptomatic intracranial bleeding and/or brain oedema
Further Clinical Efficacy Endpoints: mRS, quality of life and neurocognition at day 90, NIHSS at day 5/discharge and day 90

Set of Requirements

Infrastructural Basis
> 500 admissions of stroke patients per year
> 50 interventional thrombectomies in stroke patients per year
Experience with clinical studies in the field of acute stroke
Established study team including investigators with good clinical practice (GCP) certificate
Certified NIHSS- as well as mRS-raters
Written fixed therapeutic stroke protocol including standardized imaging (acute phase and follow-up) and peri-interventional management (general anaesthesia or conscious sedation)
Readiness of the colleagues of the anesthesia at the centre for ventilation with FiO2 of 1.0 over 4 hours if necessary

Imaging Basis
Non-contrast CT- or MR imaging as well as angiography and perfusion is performed as standard method of stroke imaging
The total thickness of the layer stack for CT perfusion is at least 8 cm
The temporal resolution of CT perfusion is less than 2 seconds
MRI (DWI, FLAIR, TOF-MRA, T2*w/FLAIR) within 22-36h as control imaging is feasible at the centre