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EDITORIAL

Normobaric hyperoxygenation: a potential neuroprotective therapy for acute ischemic stroke?

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1. Introduction

Despite highly effective endovascular therapy (EVT), clinical outcome after acute ischemic stroke (AIS) remains poor, with significant long-term disability in half of patients following large vessel occlusion (LVO) [1].

Irreversible cerebral infarction in AIS does not happen at once but evolves over time; usually several hours. If blood flow is not reestablished soon after vessel occlusion, severely hypoperfused but still viable brain tissue – the penumbra – progresses to necrosis [2]. Sustaining the penumbra until reperfusion may widen time windows for effective recanalization and improve clinical outcome.

As brain damage in AIS is primarily mediated by tissue hypoxia, increasing penumbral oxygen supply seems a logical approach to achieve neuroprotection.

In animal models of transient middle cerebral artery (MCA) occlusion, normobaric hyperoxygenation (NBHO, i.e. respiration of near 100% oxygen at atmospheric pressure) led to increased not only penumbral oxygen levels but also blood flow and volume. NBHO reduced peri-infarct depolarization, led to a restitution of purine nucleotide levels, reduced lactate concentrations and preserved N-acetyl-aspartate levels within regions of ischemia, suggesting improvement of oxidative metabolism. NBHO reduced markers of apoptotic cell death and improved histological (selective neuronal loss, inflammation and blood–brain barrier function), neuroimaging and behavioral outcomes if initiated very early after vessel occlusion [3].

On the other hand, NBHO did not augment formation of reactive oxygen or nitrogen species or markers of oxidative stress after ischemia-reperfusion (such as hemeoxygenase-1, protein carbonyl, hydroethidine, or 8-hydroxy-20-deoxyguanine). Other indirect markers of oxidative stress such as matrix metalloproteinase 2 and 9 and caspase-8 were either unchanged or even decreased through NBHO [4].

In addition, experimental data suggests synergistic positive effects of NBHO and intravenous thrombolysis (IVT) without increasing the risk for hemorrhagic complications [5].

Hyperbaric oxygenation (i.e. inspiration of pure oxygen in a pressure chamber) enhanced these effects and even improved outcomes of experimental permanent vessel occlusion, but its application in the clinical setting is limited by technical hurdles and high cost [3].

2. Current clinical evidence

Only three human studies have evaluated the effects of NBHO in AIS.

In a randomized pilot study including 16 IVT-ineligible patients with AIS within 12 h of symptom onset, study subjects received either high-flow oxygen (45 L/min) for 8 h or medical air. NBHO increased penumbral blood volume and flow, providing reassurance that hyperoxia-induced vasoconstriction (known to occur in healthy brain tissue [6]) does not develop in ischemic regions. In the NBHO arm, the ischemic lesion volume (assessed using MR-diffusion) was significantly reduced during NBHO and clinical status was improved at 24 h. This benefit was not translated to later time points, supporting the argument that neuroprotective effects of NBHO may not be sustained without tissue reperfusion [7]. Another randomized controlled trial (RCT) conducted in India (N = 40) that used similar inclusion criteria but reduced flow rates of 10L/min over 12 h failed to show improved stroke outcomes [8]. A phase II-NBHO RCT evaluating 8 h of high-flow oxygen versus medical air delivered at 30–45 L/min via a simple face mask, starting within 9 h of stroke onset, was initiated in 2007 [NCT00414726]. This trial aimed to enroll 240 patients but was stopped by the safety committee after only 85 patients had been enrolled (43 NBHO, 42 Air) due to a higher mortality rate in the NBHO arm. Later blinded reevaluation did not indicate any link between mortality and NBHO and attributed the imbalance in deaths to early withdrawal of care due to massive infarcts or moribund admission status. Analysis of several prespecified safety end points did not show significant differences between groups. While the primary efficacy outcomes did not differ between the NBHO and standard treatment arm, a prespecified voxel-based MRI analysis showed that the apparent diffusion coefficient values within

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ischemic regions improved during NBHO, suggesting benefit. A number of experts have criticized the premature termination and called for a repeated trial [9].

Other trials often cited in the context of NBHO including an RCT conducted in Taiwan (N = 46), which found mild hyperoxygenation (FiO_2 of 0.4) to be associated with lower mortality and fewer complications in patients with large MCA infarctions [10] and two recent retrospective studies (N = 2643 and 554), which found no influence of hyperoxia on mortality and length of hospital stay in ventilated AIS patients [11,12], support a positive safety profile of hyperoxygenation.

Two further prospective trials (N = 550 and 301) did not actually focus on hyperoxia as an acute treatment but aimed to prevent poststroke hypoxia and maintain normal oxygen saturation. These trials compared low-flow (2–3 L/min) oxygen supplementation to room air delivered from 24 to 72 h after ischemic or hemorrhagic stroke and provided inconclusive results [13,14]. The phase III Stroke Oxygen Study (N = 8000) with a similar objective [15] showed no benefit of – but also no safety issues with – low-flow supplemental oxygen (results presented at the 23rd European Stroke Conference 2014 in Nice, France).

Given the current controversial evidence regarding NBHO in AIS, what is the way forward?

3. The future of clinical NBHO trials in acute stroke

Despite several setbacks of oxygen therapy in the recent past, there are still good reasons to believe in the potential of NBHO in AIS. Two major limitations apply to all previous NBHO [7–9] and many failed neuroprotection-in-AIS trials [16]: inclusion of patients with advanced time windows after stroke onset and exclusion of patients eligible for recanalization therapies (i.e. IVT and EVT). The intention behind this approach was probably to help those stroke victims for whom there was no effective treatment available. However, this means that the two most important insights gained in preclinical research were dismissed and not translated into the design of the clinical trial: early start of treatment and transient ischemia.

We believe the time is ripe for a paradigm shift in trial design regarding neuroprotection in AIS in general, and more specifically with NBHO. In the age of EVT and advances in prehospital stroke care (e.g. stroke emergency mobiles (STEMO)), it is finally possible to translate the preclinical experience into the real world and replicate models of transient AIS in humans. In a recent editorial, Tymianski suggested the conduction of a neuroprotective trial including EVT-eligible patients in an early time window only [17].

We agree with Tymianski's view, but this concept can be taken further.

4. The two-step approach

We suggest a two-step approach including a phase II proof-of-concept RCT in a highly selected patient cohort as well as a surrogate end point and – if this first stage is completed successfully – a large confirmatory phase III RCT with standard clinical end points. The main advantage of this approach would be a feasible sample size in the phase II trial and thus the ability to conduct more but smaller trials testing more potential neuroprotectants leading, in turn, to a higher likelihood of overall success. Sample size calculation for the phase III trial can be derived from the proof-of-concept trial instead of relying on preclinical data only.

The following points, however, need to be considered:

4.1. Patient selection

Taking the aforementioned considerations into account, the optimal patient for inclusion in a contemporary phase II proof-of-concept trial for neuroprotection in stroke should present with a major stroke due to currently routinely EVT-accessible LVO (i.e. the terminal internal carotid artery or M1-segment of the MCA) early after symptom onset.

Neuroprotection – just like reperfusion – can only lead to tissue salvage if parts of the ischemic tissue are still viable. Currently, the best way to identify potentially salvageable tissue is via the imaging-based mismatch concept, which may estimate infarct core volumes and identify areas of viable tissue [18]. Core/penumbra-mismatch imaging has been successfully applied for patient selection in recent EVT trials, indicating that good collateral status in a patient with LVO predestines for this treatment. However, analysis of trial data also revealed limitations regarding prediction of treatment response [19]. Furthermore, the 'ghost core' [20] and DWI reversibility [7] have taught us that dogmatic imaging paradigms do not always reflect the whole truth.

Regarding neuroprotection adjunct to EVT, it may well be that the largest benefits from a neuroprotectant are achieved in patients with otherwise rapid progression of infarction, whilst 'slow progressors' with good collaterals may not benefit from any treatment adjunct to EVT. To answer the open question, whether neuroprotection makes a difference in the rapid progressors with a 'malignant' imaging profile, patients must undergo perfusion imaging prior to study treatment but should not be de-selected on its basis.

4.2. Endpoint selection

In stroke patients with currently routinely accessible LVO, a short-term (post-treatment) efficacy end point is preferable to the (current standard) three-month clinical efficacy end point for the following reason: In case of unsuccessful EVT, morbidity and mortality and withdrawal of care are frequent and the risk of altering the clinical course through decompressive surgery may be considerable – factors that may all have a higher impact on outcome than the actual study intervention. This and high drop-out rates between 24 and 48 h and even more so at three months after AIS may threaten the validity of a small trial. The long-term clinical outcomes would, however, remain useful to assess safety.

Drop-outs may be avoided by substituting the three-month clinical outcome with an early NIHSS (e.g. at 24 h after AIS). This score, however, neither adequately reflects stroke size [21] nor the attenuation of infarct growth by the neuroprotectant. Additionally, clinical scores determined early after major stroke/EVT may be confounded by the effect of peri-

interventional sedation and early complications (e.g. aspiration pneumonia).

Consequently, the ideal early surrogate end point must be imaging-based. Infarct volume alone at an early posttreatment time point (e.g. 24 h after AIS) may not be a good surrogate in a small trial due to inevitable heterogeneity. Infarct growth from baseline to an early posttreatment time point corrects for inter-individual variation and reflects the true neuroprotective effect on tissue at risk. It is known that perfusion imaging may not accurately predict infarct core volume in an individual patient [22]. However, it may be precise enough to predict or evaluate treatment effects in a group of study patients [23].

We need to keep in mind that in future, due to technical advances in EVT and accessibility of more distal MCA-branches, clinical outcome assessment (e.g. the modified Rankin Scale at 90 days) may be preferable in a trial including these patients as the drop-out risk is considerably lower. Given a higher infarct surface-to-volume ratio, beneficial effects of a neuroprotective agent might even be more pronounced in patients with M2 to M4 occlusions.

4.3. Design of the confirmatory trial

In a second step, a larger phase III trial may be undertaken. Due to prerequisites for substance approval, it must be driven by a clinical end point. Ideally, treatment start should be moved into the pre-hospital phase to increase neuroprotective effects, which will inevitably lead to inclusion of a more unselected patient group. The treatment effect will mainly be supported by the subgroup of patients with true and transient ischemia and diluted by a potentially large number of patients unlikely to benefit (e.g. stroke mimics) and higher drop-out rates, which will have to be taken into account when determining the sample size.

The assumed safety profile determines the treatment starting point: if the neuroprotective agent is safe in all patients, it may be administered prior to imaging. If it causes harm in ICH, treatment can only be started afterwards (e.g. in a STEMO). If stroke mimics need to be excluded, vessel or perfusion imaging is necessary.

Efficacy in non-transient AIS is important for cost-effectiveness considerations – but negligible with inexpensive treatments like NBHO. Expensive and inefficacious neuroprotectants will be sorted out by negative phase II trials.

5. The PROOF trial

PROOF (Penumbral Rescue by Normobaric O = O Administration in Patients With Acute Ischaemic Stroke and Target Mismatch ProFile; EudraCT 2017-001355-31) is a project funded within the Horizon 2020 program of the European Commission, which was launched in early 2017. It involves the conduction of an international multi-center, randomized phase II proof-of-concept RCT studying NBHO as an adjunct to standard AIS treatment, aiming to enroll up to 460 patients with an acute and routinely EVT-accessible anterior circulation LVO and a small infarct core within three hours of symptom onset. Study treatment consists of high-flow (≥40 L/min) oxygen via a sealed non-rebreather reservoir facemask (or FiO_2 of 1.0 during mechanical ventilation) to be delivered from diagnosis of AIS until the end of EVT, but no longer than four hours to avoid respiratory adverse events. Controls will receive standard oxygen supplementation only when required. The primary efficacy end point is ischemic core growth from baseline to 24 h.

6. Conclusion

Clinical neuroprotection research is facing major challenges. EVT may reopen the door for successful clinical trials. PROOF is the first RCTs to incorporate two cornerstones of experimentally effective neuroprotection, namely early initiation and fast reperfusion. Oxygen may prove to be a powerful neuroprotective – particularly if given very early. Given its low cost and if shown to be efficient, NBHO could impact stroke care worldwide.

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Declaration of interest

SP is the coordinating investigator of the PROOF trial. JCB is the national co-coordinator for the French centres of the PROOF trial. ABS is on the scientific advisory board for the PROOF trial, is the deputy principal investigator of the New England Regional Coordinating Center for the for the NINDS Stroke Trials Network (NIH U10-NS086729) and is on the scientific advisory board for the Biogen sponsored ACTION-II clinical trial. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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