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Brain Research

Research report

Effects of stroke severity and treatment duration in normobaric hyperoxia treatment of ischemic stroke

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ARTICLE INFO

Available online 26 January 2016

Keywords:
NBO
Ischemic penumbra
Cerebral ischemia
Reperfusion
MRI
Diffusion
Arterial spin labeling

ABSTRACT

In order to improve clinical trial design and translation of normobaric oxygen (NBO) treatment of ischemic stroke, NBO treatment parameters need to be better understood. This study investigated NBO treatment efficacy at two different stroke severities and two NBO treatment durations in rats. For the 60-min middle cerebral artery occlusion (MCAO), NBO treatment for 25 min and 150 min were studied. For the 90-min MCAO, NBO treatment for 55 min and 150 min were studied. Cerebral blood flow (CBF), apparent diffusion coefficients (ADC) and T2 MRI were acquired during occlusion prior to treatment, after reperfusion, and 48 h after MCAO. The effects of NBO treatment on lesion volumes, and CBF, ADC and T2 of ischemic core, perfusion–diffusion mismatch and normal tissue were analyzed longitudinally. The major findings were: i) NBO treatment was effective in both groups of stroke severities, salvaging similar percentage of initial abnormal ADC tissue, and ii) NBO treatments continued after reperfusion were more beneficial than NBO treatment during occlusion alone for both MCAO groups. These findings underscore the importance of the effects of NBO duration and stroke severity on treatment outcomes.

1. Introduction

Normobaric oxygen (NBO) treatment has the potential to improve brain tissue oxygenation and rescue hypoxic tissue following ischemic stroke (Shin et al., 2007). Many studies have shown that NBO treatment reduced histological infarct volume and improved behavioral function in experimental stroke (Henninger et al., 2007, 2009; Jin et al., 2013; Kim et al., 2005; Liu et al., 2012; Singhal et al., 2002a, 2002b, 2007; Sun et al., 2010, 2011, 2014). The mechanisms of NBO-mediated neuroprotection in stroke include improved tissue oxygenation (Shin et al., 2007), improved aerobic metabolism (Singhal et al., 2007), and reduced blood-brain barrier damage (Liu et al., 2009), reduced free radical damage (Yuan et al., 2010) and reduced peri-infarct depolarization (Shin et al., 2007). However, a few studies reported NBO treatment worsened

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http://dx.doi.org/10.1016/j.brainres.2016.01.030
0006-8993/

stroke outcomes, including increased infarct volume (Haelewyn et al., 2011) and white matter damage (Mickel et al., 1987, 1990). In a phase I clinical trial, NBO yielded transient improvements in MRI and clinical deficits. In the absence of arterial re-canalization, 8-h NBO treatment significantly improved relative cerebral blood flow (CBF) within the ischemic regions at 4 and 24 h. However, these improvements were reported to be transient (Singhal et al., 2005). Subsequent phase II clinical trial (NCT00414726) was terminated due to imbalance in deaths favoring control arm, although deaths were not attributed to treatment by the blinded external medical monitor. Future clinical trial in NBO treatment of stroke is likely. In order to better inform future NBO stroke trials, NBO treatment parameters need to be better understood. Some of these NBO treatment parameters include when to start treatment (early versus late treatment), during which ischemic phase to treat (during occlusion versus after reperfusion), how long to treat (several hours to days), and which patient groups will likely benefit (i.e., patients with mild versus severe stroke, and patients with versus without substantial perfusion–diffusion mismatch (Albers, 1999; Fisher, 2003; Kidwell et al., 2003; Warach, 2003)).

Amongst the NBO treatment studies in experimental ischemic stroke, only a few used MRI to monitor tissue fate longitudinally before and during treatment. Singhal et al. found that NBO treatment of permanent middle cerebral artery occlusion (MCAO) in rats minimized apparent diffusion coefficients (ADC) abnormalities during the acute phase and reduced histological infarct volume at 48 h, as compared to the air group (Singhal et al., 2002a). Henninger et al. found that NBO treatment in both permanent and transient MCAO models reduced ADC abnormalities and stopped the progression of perfusion–diffusion mismatch during occlusion. At 24 h, both NBO groups showed significantly smaller histologically defined lesion volumes compared to the air group (Henninger et al., 2007). Both of these studies investigated the NBO treatment only during occlusion and the effects of NBO treatment extending *after* reperfusion on tissue ADC, CBF and T2 are unknown.

In this study, we aimed to address two specific NBO treatment parameters mentioned above, namely: is NBO treatment more effective in mild or severe ischemic stroke, and is NBO treatment more effective given during occlusion only or extended beyond reperfusion? Serial multimodal MRI was used to study two different degrees of stroke severity (60-min and 90-min occlusion) in a rat MCAO model, and two NBO treatment durations (during occlusion only and extended after reperfusion) for each of the MCAO groups. In the 60-min MCAO group, 25-min and 150-min NBO treatments were studied. In the 90-min MCAO model, 55-min and 150-min NBO treatments were studied. NBO treatments started 35 min after MCAO following the initial pre-treatment MRI. CBF, ADC and T2 measurements were made prior to treatment, during occlusion, after reperfusion and 48 h after MCAO. The primary readout was lesion volume at 48 h and secondary readouts are quantitative CBF, ADC and T2 of the core, mismatch and normal tissue at different time points. *Our central hypotheses are that NBO treatment is effective in reducing infarct volume for both stroke severities, and NBO treatment extending after reperfusion is more beneficial in reducing infarct volume than NBO treatment during occlusion alone.*

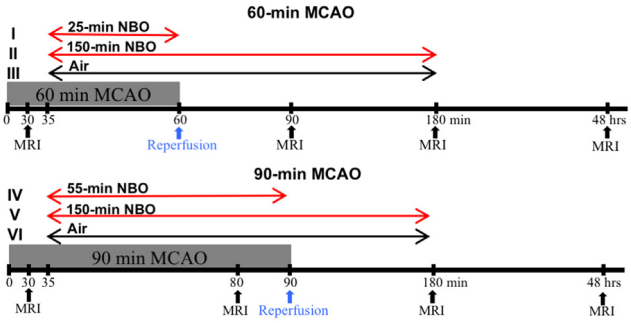

Fig. 1 – Experimental designs of NBO treatment groups for 60- and 90-min MCAO animals.

2. Results

The randomized, vehicle controlled and double-blinded experimental design is shown in Fig. 1. Respiration rate (58±3 bpm), heart rate (350–450 bpm), and arterial oxygen saturation (95±4%) by oximetry were within normal physiological ranges unless otherwise perturbed by NBO, consistent with stroke studies under similar experimental preparations from our laboratory (Shen et al., 2003, 2004b, 2005, 2014; Sicard et al., 2006a, 2006b; Tanaka et al., 2007).

In the contralesional homologous regions, CBF and ADC values were within normal physiological ranges and they were not statistically different amongst groups (data not shown), consistent with previous findings from our laboratory (Shen et al., 2003, 2004b, 2005, 2014; Sicard et al., 2006a, 2006b; Tanaka et al., 2007). Percent changes in ADC and CBF were thus analyzed with respect to the homologous regions in the contralesional hemisphere for comparison across time points.

3. NBO treatment following 60-min MCAO

The effects of NBO on lesion volume on MRI images are shown in Fig. 2A and B. At 30 min after MCAO, ADC and CBF lesion volumes prior to treatments were similar amongst the three groups. Perfusion deficit volumes were larger compared to ADC deficit volumes, confirming the presence of a perfusion-diffusion mismatch in all three groups. At 48 h after occlusion, T2-derived lesion volume was smallest in the 150-min NBO group followed by the 25-min NBO and the air group.

The group lesion volume data are shown in Fig. 2C. At 30 min, the CBF lesion volumes of the three groups were not significantly different from each other (343±44, 339±20, 285±40 mm^3, respectively, $P>0.05$) and all were significantly larger than the ADC lesion volumes ($P<0.05$), confirming the presence of a perfusion–diffusion mismatch in all three groups. All three groups started with similar abnormal ADC lesion volumes before NBO treatment. After reperfusion (90 min post occlusion), lesion volumes dropped significantly in all groups and remained reduced at 180 min. At 48 h,