



SPOTRIAS Project 1

Oxygen Therapy in Acute Stroke

Overview

Stroke is the third leading cause of death and the leading cause of disability in the United States. Ischemic stroke is caused by a blockage of blood flow to one or more brain arteries, usually due to a blood clot. As a result there is a reduced supply of oxygen and other nutrients leading to permanent brain damage. At present the clot-busting drug intravenous tissue plasminogen activator, t-PA, is the only acute stroke treatment approved by the Food and Drug Administration. Unfortunately less than 5 percent of individuals with stroke actually receive t-PA because it has to be administered within 3 hours of stroke onset to be safe and effective. Therefore, it is important to develop new therapies for stroke and strategies that can safely extend the time window for delivering clot-busting drugs.

Normobaric oxygen therapy (NBO)-high-flow oxygen delivered via a facemask-shows promise as a simple, widely accessible, low-cost therapy that can prevent stroke-related brain damage and extend the time window for administering clot-busting drugs.

Purpose

The primary goal of this trial is to compare the safety and therapeutic efficacy of NBO-started within 9 hours of symptom onset-to standard medical treatment. This trial will also determine the potential of NBO in extending the therapeutic time window for administering such drugs as t-PA.

Enrollment

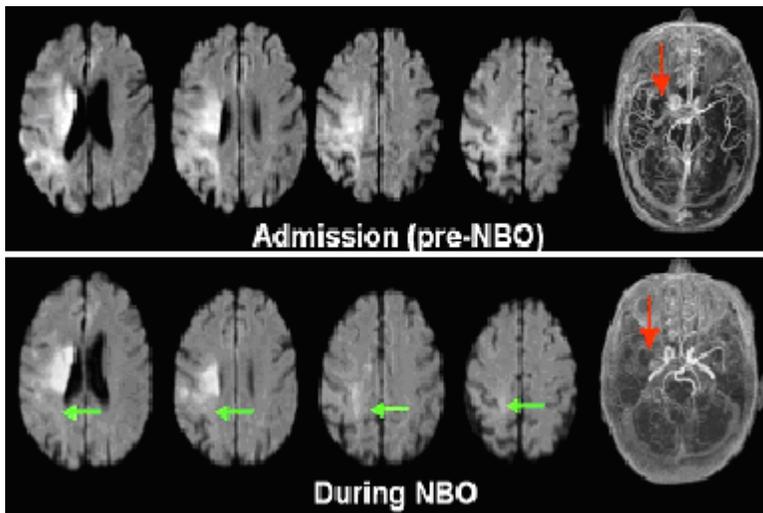
A total of 240 individuals with acute ischemic stroke will be enrolled at the Massachusetts General and Brigham and Women's Hospitals in Boston.

Procedures

Participants will be randomly selected to receive either room air or oxygen therapy administered for 8 hours. Neurological function scores and neuroimaging (magnetic resonance imaging, MRI, or computed tomography, CT, scans) will be obtained before, during, and after therapy, until 90 days.

Outcome Measures

The primary clinical outcome measure is a between-group comparison of the change in NIHSS scores from baseline to 4 hours (during therapy). The primary neuroimaging outcome measure is a between-group comparison of the change in MRI ischemic lesion volumes from baseline to 4 hours (during therapy).



Example. Brain MRI findings in a patient with stroke treated with normobaric oxygen therapy (NBO). Top, MRI obtained on admission shows a large ischemic lesion (arrows), and arterial occlusion (arrows). Bottom, MRI obtained during NBO therapy shows that the ischemic lesion has reduced in size. The artery remains occluded. The patient's neurological examination improved after NBO therapy was started.

Inclusion & Exclusion Criteria

Inclusion Criteria

1. Age greater than or equal to 18 years.
2. Acute ischemic stroke in whom treatment can potentially be started within 9 hours after symptom onset. If the symptom onset time is unknown, the time of onset will be defined as the time that is midway between the time when the subject was last seen neurologically intact, and when found to have a neurological deficit.
3. NIHSS score 4 or greater.

Exclusion Criteria

1. Patients being actively considered for intravenous or intra-arterial thrombolysis will be excluded until the Safety Monitoring Committee approves of their inclusion (anticipated in years 2 through 5).
2. Patients likely to have acute stroke intervention such as carotid endarterectomy or stent or angioplasty, hemicraniectomy, induced hypothermia therapy, etc.
3. Rapidly improving neurological deficits (transient ischemic attack).
4. Known history of severe chronic obstructive pulmonary disease (FEV1 less than 1.0 or oxygen dependent).
5. More than 3 L/min oxygen required to maintain peripheral SaO₂ > 92%.
6. NYHA class III heart failure.
7. Endotracheal intubation prior to enrollment or impending need for artificial ventilation.
8. Coma (NIHSS item 1a score of 3).
9. Suspected seizure at or after onset of stroke, or a known active seizure disorder.
10. Blood glucose below 50 mg/dL or greater than 250 mg/dL prior to enrollment.
11. Concurrent severe non-stroke medical illness requiring admission to a non-neurological ICU
12. Expected survival less than 90 days.
13. Any condition that might limit neurological assessment or follow-up in the opinion of the investigator.
14. Pre-menopausal women with a positive pregnancy blood test performed at admission.
15. Inability to obtain consent from the patient or legally authorized representative.
16. Active participation in another intervention study (e.g. investigational drug trial).
17. Proven alternate etiology for stroke-like symptoms (e.g. initial brain imaging shows primary intracerebral hemorrhage, subarachnoid hemorrhage, brain tumor, demyelinating disease, etc).

References

1. Singhal AB, Benner T, Roccatagliata L, Koroshetz WJ, Schaefer PW, Lo EH, Buonanno FS, Gonzalez RG, Sorensen AG.
A pilot study of normobaric oxygen therapy in acute ischemic stroke.
Stroke. 2005 Apr;36(4):797-802. Epub 2005 Mar 10.
PMID: 15761201 [PubMed - indexed for MEDLINE]

2. Kim HY, Singhal AB, Lo EH.
Normobaric hyperoxia extends the reperfusion window in focal cerebral ischemia.
Ann Neurol. 2005 Apr;57(4):571-5.
PMID: 15786465 [PubMed - indexed for MEDLINE]
3. Singhal AB, Dijkhuizen RM, Rosen BR, Lo EH.
Normobaric hyperoxia reduces MRI diffusion abnormalities and infarct size in experimental stroke.
Neurology. 2002 Mar 26;58(6):945-52.
PMID: 11914413 [PubMed - indexed for MEDLINE]
4. Liu S, Liu W, Ding W, Miyake M, Rosenberg GA, Liu KJ.
Electron paramagnetic resonance-guided normobaric hyperoxia treatment protects the brain by maintaining penumbral oxygenation in a rat model of transient focal cerebral ischemia.
J Cereb Blood Flow Metab. 2006 Oct;26(10):1274-84. Epub 2006 Jan 18.
PMID: 16421507 [PubMed - indexed for MEDLINE]
5. Flynn EP, Auer RN.
Eubalic hyperoxemia and experimental cerebral infarction. Ann Neurol. 2002 Nov;52(5):566-72.
PMID: 12402253 [PubMed - indexed for MEDLINE]