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HBOT IN ACUTE STROKE

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ABSTRACT

Objectives: Are there objective clinical benefits in providing Hyperbaric Oxygen therapy to patients with Ischemic Stroke? Do these correlate to radiological changes.

Design: Observational study (prospective cases matched to retrospective controls)

Setting: tertiary level neuro-rehabilitation unit

Participants: 26 patients (10 cases, 16 controls)

Duration: 2014- 2017

Intervention: Included patients were matched for age, gender, comorbidities, National Institute of Health Sciences Stroke Scale. Ten cases with ischemic strokes received 10 sessions of Hyperbaric Oxygen at 2ATA for one hour, one week from stroke. They were matched with sixteen contemporary controls and outcome measures were compared using students t-test.

Main Outcome Measures: Karnofsky Performance Score (KPS), change in Hounsfield units (HU) from the initial to post treatment, Computerized Tomography, and overall outcome at six months.

Results: There was a significant difference (p-value <0.05) in KPS and HU favoring the cases. All ten cases survived and progressed to rehabilitation. Two resumed employment. Of the sixteen controls, four expired during their inpatient course, twelve initiated rehabilitation, and none returned to work.

Conclusions: Hyperbaric Oxygen therapy given to patients with acute Ischemic strokes can lead to better outcomes and 6 months, and the changes can be appreciated in CT scans.

KEYWORDS :

Introduction

One in six people worldwide will have a stroke during their lifetime.[1] Though stroke incidence has decreased in developed nations, it has increased in developing countries.[2] The pathogenesis of ongoing damage post event involves excitotoxicity, acid toxicity, ionic imbalance, oxidative and nitrosative stress, inflammation and apoptosis[3]. Oxidative stress contributes to cerebral ischemia-reperfusion injury by excessive production of free radicals which trigger necrosis and apoptosis. Concomitant edema severity strongly correlates with neurologic impairments.[4]

Post acute stroke reperfusing the brain parenchyma is critical. Hyperbaric Oxygen therapy (HBOT) reduces stroke related brain tissue hypoxia[5]. It effects this by supersaturating the plasma with oxygen[6]. Hyperoxia reduces cerebral edema (thereby intracranial pressure), decreases lipid peroxidation (reduced apoptosis), inhibits of leucocyte activation (decreased inflammation)[7], and protects the ischemic penumbra from reperfusion injury[8]. All of this reduces secondary brain injury, leading to less morbidity and mortality[9].

While there is meta-analysis level support for its use in human TBI[9], despite 51 animal randomized control trials (RCT) and a meta-analysis showing significant benefits[10], some human RCTs do not support the use of HBOT in stroke. The reason for this discrepancy lies in the methodology of these studies. One study didn't differentiate stroke by mechanism, size, or location. Its primary measure was a 100 point neurological exam. Patients were taken 6 hours after entry into the study with subsequent dives every 8 hours, for a total of 15 dives. Many treatment group patients declined for unspecified reasons. The secondary measure of outcome was quantification of the volume of hypodensity due to infarction, as seen on a computed tomogram (CT scan) performed 4 months after onset. Considering mechanism of action this is a bit late to note changes effected by it. A treatment pressure of 1.5ATA was used, which is now known to be suboptimal, instead of 2 ATA.[10] Co-morbidities, and decompressive hemicraniectomy were not considered.[11] A different pilot study used a single treatment 24 hours from onset. Changes in NIHSS from baseline to a follow-up at four months showed the controls had better outcomes. Unfortunately again they didn't differentiate stroke by mechanism size, or location[12]. Despite the mentioned fallacies, being RCTs they are incorporated into meta-analyses that then lead to the current lack of recommendation for HBOT in Acute Ischemic Stroke. We propose that more specific measurements would be: a radiological correlate that reflects normalization of brain parenchyma, overall recovery, and outcomes. These remain to be shown with HBOT pertaining to acute ischemic stroke.

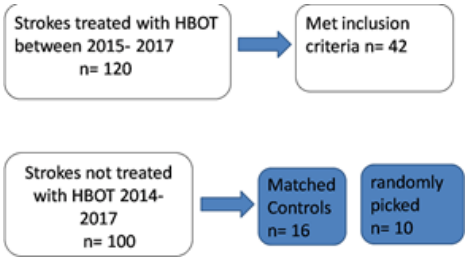
Computed tomography of brain is the primary measure for exigency evaluation of acute stroke as it is easily available, fast, low cost and accurate in differentiating hemorrhage from infarction. CT yielded Hounsfield units (HU) correlate to stages of infarct evolution. Hounsfield units of 30- 45 correlate to normal brain parenchyma, 10-20 to ischemia, and to > 20 for reperfusion.

We did this study to validate the benefits of HBOT in our patients, confirm if CT was an appropriate measure of change and see if the functional outcomes correlated with radiological changes. There is no existing literature to this effect.

Methodology

We did an observational study with prospective cases matched to contemporary controls (see figure 1). Institute Ethics Board approval was sought and received, and informed consent was taken. No grant funding was utilized. Patients were included if they met the following criteria: Ischemic stroke, first stroke, minimum size of 3 cm. They were excluded if they had: co-morbidities other than Diabetes Mellitus type 2, Hypertension, Coronary Artery Disease. To ensure we had comparable groups at baseline matching for: age, gender, co-morbidities, National Institute of Health Stroke Scale (NIHSSS) and localization to Middle Cerebral Artery distribution or not, was done. Being an observational study the local institutional review board was not approached but written informed consent was sought. Intervention consisted of 10 treatments at 2 Absolute Atmosphere (ATA) in a multiplace chamber. The following outcome measures were collected: Karnofsky Performance Score, change in Hounsfield units per CT from the initial to post treatment Computerized Tomography, and 6 month outcomes. No patients experienced adverse effects related to the intervention.

Figure 1



Patient allocation

Hyperbaric Oxygen therapy (HBOT)

After confirming infarction and localization, axial cuts in which the infarct was properly visualized were selected. The region of interest (ROI) was placed within the infarct to get a HU value at each stage of revascularization. These were evaluated and graded according to the variation seen in the readings. Improvement in the infarct areas was evidenced by hypointensity changing to hyperintensity. Serial CT scans were done in the first and third week from the event. In acute ischemic stroke the HU attenuation is directly proportional to the degree of edema. The color changed from gray to black corresponding to acute to chronic change. Revascularization was seen as a shift toward hyperdensity and as HU values >20.

Statistical significance was calculated using Chi square for baseline data, and student's t-test for the outcome variables.

Results

At baseline the two groups were comparable for: age, gender, co-morbidities, location and NIHSS (see table 1). Regarding outcome variables, at baseline Hounsfield units were similar for cases and controls. There was a significant difference (p-value <.05) in KPS and Hounsfield units favoring the cases after treatment (see table 2 and figure 2 respectively). At six months follow-up all ten cases survived and progressed through rehabilitation. Two later resumed employment. Of the sixteen controls, four expired during their inpatient course, twelve initiated rehabilitation, and none returned to work (see figure 3). No patients experienced adverse effects related to HBOT.

Table 1: Baseline details

	Case (10)	Control (16)
Age	58.2± 7.7	56.4± 5.5
Gender (M/ F)	4/6	7/9
Comorbidities	Nil- 4	Nil- 5
	DM II- 2	DM II- 3
	HTN- 5	HTN- 8
	CAD- 2	CAD- 3
NIHSS	15.8± 5.2	16.1± 5.0
MCA/ non-MCA	8/ 2	11/ 5

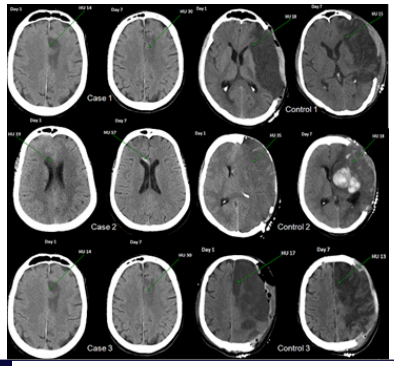
Legend- Diabetes Mellitus type 2 (DM II), Hypertension (HTN), Coronary Artery Disease (CAD)

Table 2: Outcome measures

	Case	Control	p value
Pre treatment Hounsfield units	19.2± 1.4	21.75± 5.1	0.98
Pre treatment Hounsfield units	31.9± 4.7	22.25± 5.6	0.05
KPS	65.45± 5.3	38.75± 27.7	0.05

Legend- Karnofsky Performance Scale (KPS)

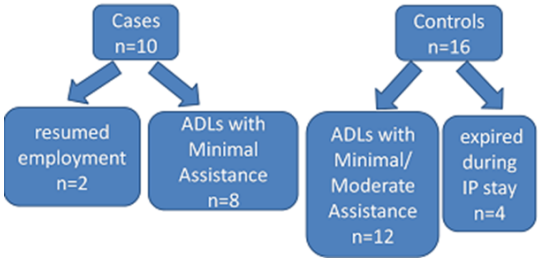
Figure 2



CT changes Cases vs Controls

Serial CTs showing evolution of infarct in three cases and controls with HU values

Figure 3



Six month outcomes

Discussion

Though there is conflicting evidence about HBOT in acute stroke our study shows CT can be used to show changes effected by this intervention and these correlate to outcomes. Imaging can be done on a weekly basis, or at the initiation and cessation of treatment. A minimum of 10 consecutive treatments is required to appreciate clinical and radiological changes, which will start typically after the fifth dive. The appropriate baseline measures for comparing groups is location, size, age, gender, co-morbidities, and NIHSS. Functional scales combined with an unbiased measure of change like radiology as outcome measures validate outcomes. We used the KPS as our review is retrospective, but finer scales like Functional Independence Measure, Disability Rating Scale, Orgogozo or Trouillas scales are better. Though neuroplasticity occurs, the functions of lost eloquent cortex are not easily replaced. The goal of using HBOT then is to lighten the ischemic burden, reduce edema, diminish excitotoxicity, and thereby facilitate recovery of consciousness post-stroke leading to less nosocomial morbidity.

Though some of our controls expired during their stay, the best were on par with the worst cases at six months follow-up. We attribute this to better overall recovery hence more participation on returning home.
Further studies should look at time to recovery of consciousness, consider incidence of concomitant nosocomial infections, and utilize modalities like MRI / CT perfusion studies.

Conclusion

Based on the results the following conclusions can be drawn: HBOT does reduce post stroke edema, is associated with better outcomes at six months, and the radiological changes correlate to the functional changes.

Limitations

Being a retrospective review the limitations to this study include: low sample size, and selection bias. We reduced bias this by randomly picking cases from our pool of 120 treated patients and matching them at baseline to the controls.

Disclosures: none

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