# Hyperbaric Oxygen Therapy in Improving Neurological and Functional Outcome of Persons with Severe Hypoxic Ischemic Encephalopathy

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## ABSTRACT

**Background**- The prevalence of severe Hypoxic Ischemic Encephalopathy (HIE) is increasing and their prognosis for meaningful recovery is poor. Adjunctive Hyperbaric Oxygen therapy (HBOT) has been used in patients with severe disorder of consciousness but studies to evaluate benefits are scarce. **Objective**- Evaluate the changes in level of consciousness, neurological status and functional status in patients with severe hypoxic ischemic encephalopathy (HIE) who underwent HBOT. **Methods**- This is a retrospective study involving 54 patients with severe HIE. Validated outcome scales (Coma Recovery Scale-Revised for level of consciousness, Glasgow Coma Scale for neurological status, and Glasgow Outcome Scale for functional status) prior to starting HBOT and at discharge were evaluated. Clinical Data, Duration of injury, Number of HBOT sessions and medical complications attributed to HBOT were analysed. Wilcoxon sign ranked test was used for statistical analysis. **Results**- Fifty two percent patients had change in level of consciousness with 13% achieving consciousness. Fifty percent patients had improvement in neurologic Status. 35% of patients showed functional improvement with 13% patients achieving independence for ADLs at discharge. Higher initial GOS score significantly increased the odds of having higher GCS and level of consciousness at discharge. Younger age, female gender, HBOT session started within a month of injury and higher GOS score significantly increased the odds of functional recovery at discharge. No major complications were attributed to HBOT. **Conclusions**- There is scope for improvement in consciousness, neurological status, and functional status after severe HIE. HBOT is safe and well tolerated by persons with severe HIE.

**KEYWORDS-** Hypoxic Brain Injury, Hypoxic Ischemic Encephalopathy, Disorder of Consciousness, Hyperbaric Oxygen therapy.

## INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is a severe type of brain injury that occurs when brain doesn't receive enough oxygen for a period of time resulting from insults such as cardiac arrest, drowning, asphyxiation. Based on prospective studies, the incidence of cardiac arrest is estimated to be 50-100 per 100,000 in the general population1. With improved techniques in resuscitation and artificial life support, greater

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numbers of patients survive with variable degrees of residual brain injury. Severe hypoxic-ischemic injury primarily affects the grey matter structures due to their high metabolic requirement for oxygen and glucose to supply large number of synapses. This makes grey matter more susceptible to hypoxic -ischemic injuries leading to significant neurologic disability, ranging from mild cognitive deficits to minimally conscious state (MCS) and vegetative state (VS) depending on the severity of damage2,3.

In severe hypoxic brain injury, patients initially present in a comatose condition which usually progresses to VS or MCS. It is challenging to predict the prognosis based on clinical findings at this time 4. In a large scale study of adults with post-hypoxic brain injury, 64% patients died, 9% remained comatose or in an unresponsive wakefulness syndrome (UWS) and 27% of patients regained consciousness 5. In a study by Heinz et al in 2015 with 93 patients , 82% of patients had disorder of consciousness (DOC) at admission and 75.3% of them had a poor outcome (Barthel Index <50)6. The primary goal of a rehabilitation program in severe brain injury is to promote arousal. There are currently no treatment guidelines for individuals with DOC but both pharmacologic as well as non-pharmacologic methods have been used in clinical practice7,8. Hyperbaric oxygen therapy (HBOT) is one of those methods, and has shown to inhibit apoptosis, suppress inflammation, protect the integrity of blood-brain barrier, and promote angiogenesis and neurogenesis9.

HBOT is defined as the inhalation of 100% oxygen under the pressure greater than 1 atmosphere absolute (ATA). Among neurological conditions, HBOT has been evaluated among patients of traumatic and non-traumatic injuries of the brain with varying results. Some research has shown that hyperbaric oxygen (HBO) can decrease the rate of mortality and disability caused by hypoxic-ischemic encephalopathy (HIE) in neonates10. In 2019, Sankaran et al in their study to assess the efficacy of hyperbaric oxygen therapy (HBOT) in patients with hypoxic ischemic encephalopathy (HIE) did a case control study with 25 patients and found a significant difference in CRS-R favouring the HBOT group11. Hyperbaric Oxygen therapy (HBOT) has been used along with conventional rehabilitation methods in some centres, but no large-scale studies are available at present. We undertook this study to evaluate the changes in level of consciousness, neurologic status, and functional status in patients with severe HIE who underwent HBOT at our centre.

## METHODOLOGY

### Population

The retrospective study was conducted at the Neurorehab Unit of a tertiary care hospital. HBOT registry was searched for patients with severe HIE (VS or MCS) who underwent adjunctive HBOT during March 2017- Feb 2020. A total of 63 patients were found and their medical records were reviewed. 4 patients died during the hospital stay due to medical complications not related to HBOT and were excluded. 5 patients' medical records were not complete and were excluded from the study. A Total of 54 patients met the criterion and were included in the study. Perry TM Monoplace Chamber was used for providing HBOT under medical supervision. Hyperbaric oxygen at 2 ATA pressure was given for 60 minutes per session for 6 days a week for up to a total of 60 sessions maximum. Pre requisites for starting HBOT was a) Cardiopulmonary Stability b) Intracranial Pressure stability c) Disorder of consciousness d) Minimal suction requirement with at least 2 hours of suction free periods consistently e) No history of Asthma, COPD or other chronic lung diseases f) No history of ear diseases or tympanic perforation g) No history of uncontrolled seizures h) No active systemic infection i) No supplemental oxygen requirement in past 24 hours, and j) Able to maintain steady blood sugar values.

## VALIDATED OUTCOME SCALES

Level of Consciousness was assessed by Coma Recovery Scale-Revised (CRS-R), Neurological Status by Glasgow Coma Scale (GCS) and Functional Status by Glasgow Outcome Scale (GOS). Level of consciousness was classified into VS, MCS, or Conscious state as per evaluation of auditory, visual, motor, verbal, communication, and arousal functions on CRS-R Scale12. Neurological Status was classified as Mild injury, Moderate injury or Severe injury based on total

GCS score of 13-15, 9-12 and less than 9 respectively13. Glasgow Outcome Scale of 2&3 was considered as significant disability requiring assistance for daily living, and GOS 4&5 as patients who were independent for ADLs14. Improvement in level of consciousness was defined as change in level of consciousness from either VS to MCS or MCS to consciousness. Improvement in neurologic status was defined as change in status of brain injury from severe to moderate, or, moderate to mild as per total GCS. Improvement in functional status was defined as change in at least 1 level in GOS scale.

## PROCEDURE

Case records of the 54 patients were obtained from medical records department and analysed. Demographic data including age, gender, number of sessions of HBOT undertaken and duration of hypoxic injury at the time of starting HBOT was noted. The GCS, GOS and CRS-R scores before HBOT and at the time of discharge was noted. Any complications that occurred due to HBOT or that resulted in missing of HBOT sessions were noted.

To evaluate the role of age, gender, number of HBOT sessions and duration of brain Injury on outcome measures, patients were divided into

a) Less than or equal to 45 years and More than 45 years

b) Male or Female gender

c) HBOT started within a month of brain injury or more than 1 month

d) Patients who took less than 12 sessions and more than 12 sessions

## STATISTICAL ANALYSIS

Analyses were performed using SPSS software for Windows (version 25, 2007, IBM Corporation, Armonk, New York, United State). Data was presented as frequency (%) or Median (minimum-maximum). Wilcoxon sign ranked test was used to analyse the difference in values before and after intervention. Ordinal Regression analysis was used to compare the differences.

## RESULTS

In our study, 68.5% of the participants were males and 31.5% were females. The mean age was 47.2 years with 48% patients less than or equal to 45 years of age. HBOT was started within 30 days in 44% of patients. Twenty-eight percent of patients underwent less than 12 sessions with an average of 26.3 sessions per person. (Table 1)

Before starting HBOT, 74% of patients were in VS and 26% were in MCS. At discharge, 55% of vegetative state patients showed improvement in consciousness with 1 patient achieving consciousness (1.8%). Fifty-four percent of patients remained in MCS and 13 % of patients achieved consciousness (able to have a functional communication or functional object use). (Table 2)

Before starting HBOT, 77% of patients had severe brain injury (as per GCS) while others had moderate brain injury. At discharge, only 35% patients remained in severe brain injury but 52% patients had moderate injury. Thirteen percent of patients had only mild injury at discharge. (Table 3)

Before starting HBOT, all the patients had a GOS score of 2 or 3, implying complete dependence for activities. At discharge, 13% of patients showed functional improvements achieving independence for ADLs (GOS 4 & 5). (Table 4)

A higher GOS prior to starting HBOT significantly increased the odds of having higher GCS and DOC at discharge. Younger age, female gender and HBOT session started within 1 month of brain injury significantly increased the odds of having higher GOS at time of discharge.

Ordinal Regression for level of consciousness showed that an increase in pre-GOS was associated with an increase in odds of having higher level of consciousness at discharge (odds ratio = 219.802) ($p<0.001$). Age, gender, time at which HBOT was started, and number of sessions did not influence the odds of having higher DOC at end line ($p>0.05$). Ordinal Regression Analysis for GCS showed that an increase in pre-GOS was associated with an increase in odds of having higher post-GCS (odds ratio = 55.498) ($p<0.001$). Age, gender, duration of brain injury and number of sessions did not influence the odds of having higher GCS at end

line (p>0.05). Ordinal Regression for GOS showed that the odds of less than or equal to 45 years being in higher grade of GOS was 6.175 times that of age more than 45 years (p<0.05), the odds of females being in higher grade of GOS was 4.417 times that of males (p<0.05) and the odds of HBOT session started within 30 days beings in higher GOS was 3.769 times that of when HBOT session started after the first month of injury (p<0.05).Number of sessions did not influence the odds of having higher GOS at end line (pp>0.05). An increase in initial GOS was associated with an increase in odds of having higher GCS at discharge (odds ratio = 77.298) (p=0.001).

## DISCUSSION

The findings of this study shows that there is scope for improvements in level of consciousness, neurological status and functional status in patients with severe HIE. A similar study with 113 patients, who underwent rehabilitation but not HBOT had 6% patients achieving favourable functional outcome (GOS 4,5) 15. Current literature suggests that only about 10% of HIE survivors achieved a good neurological outcome at 90 days. A recent European study indicated that only 5% of cardiac arrest survivors achieved full neurological recovery at 30 days 16. Thirteen percent of our patients achieved favourable outcome which is higher than what is previously reported in severe HIE. One of the reasons for better outcomes could be the selection bias, as only patients who were medically stable to undergo HBOT were selected in this study. Also, patients with up to 1-year post HIE were chosen in this study unlike most other studies whose cut off were usually 1 month to 6 months.

| ***Variable*** | **Frequency (n=54)** |
|---|---|
| *Males [N (%)]* | 37 (68.5%) |
| *Females [N (%)]* | 17 (31.5%) |
| *Age (years) (Mean±SD)* | 47.2 ±16.1 |
| *Age ≤45 years [N (%)]* | 26 (48.1%) |
| *Age ≥46 years [N (%)]* | 28 (51.9%) |
| *Duration of injury when HBOT started (days)(Mean±SD)* | 74±86 |
| *HBOT started ≤30 days [N (%)]* | 24 (44.4%) |
| *HBOT started ≥31 days [N (%)]* | 30 (55.6%) |
| *Number of HBOT sessions (Mean±SD)* | 27±19 |
| *Number of HBOT sessions ≤12 [N (%)]* | 15 (27.8%) |
| *Number of HBOT sessions ≥13 [N (%)]* | 39 (72.2%) |

**Table 1. Basic characteristics of study participants**

| | **Pre-HBOT sessions** | | **Post-HBOT Session** | | p value |
|---|---|---|---|---|---|
| | Freq. | **%** | Freq. | **%** | |
| **Vegetative State** | 40 | **74.1** | 18 | **33.3** | ***0.001**** |
| **MCS** | 14 | **25.9** | 29 | **53.7** | |
| **Conscious** | - | **-** | 7 | **13** | |

**Table 2. Level of Consciousness before and after receiving HBOT**

This study is important because it has a larger sample size and includes only patients with severe disorder of consciousness (VS and MCS). Validated outcome measures were chosen to assess the change in consciousness (CRS-R), neurologic status (GCS) and Functional status (GOS) before and after the HBOT program. Also, all patients received HBOT along with similar multidisciplinary rehabilitation programs including physical therapy, occupational therapy, and swallow therapy.

More than half of the patients in vegetative state (52%) had change in level of consciousness, half of the patients (50%) had improvement in neurologic status while more than a third of them (35%)

showed at least some functional improvement. Changes in patient's abilities like visual tracking, movements towards auditory stimulus and semi-purposeful motor movements in patients who otherwise did not make functional recovery provided was also perceived as significant progress by caregivers. The effect of these non-functional changes on caregivers are understated and needs to be taken into consideration in rehabilitation.

| | **Pre-HBOT sessions** | | **Post-HBOT Session** | | p value |
|---|---|---|---|---|---|
| | **Freq.** | **%** | **Freq.** | **%** | |
| **Severe Injury (GCS<=8)** | 42 | **77** | 19 | **35.2** | ***0.001**** |
| **Moderate Injury (GCS 9-12)** | 12 | **23** | 28 | **51.9** | |
| **Mild Injury (GCS 13-15)** | - | **-** | 7 | **13** | |

**Table 3. Neurological Status before and after receiving HBOT**

| | **Pre-HBOT sessions** | | **Post-HBOT Session** | | p value |
|---|---|---|---|---|---|
| | Freq. | **%** | Freq. | **%** | |
| **GOS 2** | 48 | **88.9** | 32 | **59.3** | ***0.001**** |
| **GOS 3** | 6 | **11** | 15 | **27.7** | |
| **GOS 4** | - | **-** | 5 | **9.2** | |
| **GOS 5** | - | **-** | 2 | **3.7** | |

**Table 4. Functional Status before and after receiving HBOT**

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Our results further suggest that GOS might also serve as a prognostic variable in neurological early rehabilitation. A higher GOS before HBOT significantly increased the odds of having better level of consciousness and neurologic status at discharge. The results are comparable to the outcomes demonstrated in other studies using HBOT for DOC in severe brain injuries. Wang et al in their meta-analysis of HBOT in TBI found a higher post-treatment GCS score in the HBOT group in addition to greater improvement in GOS and lower mortality, as compared to the control group17. Bennett et al in their Cochrane review found that use of HBOT in TBI resulted in a statistically significant decrease in the proportion of people with an unfavourable outcome one month after treatment using the GOS18.

In neurological rehabilitation outcome studies, age emerges as an important and independent prognostic factor (e.g. in stroke outcome). We found that patient less than 45 years of age and female gender had better chances of functional recovery than those above 45 years and males ($p<0.05$). We did not find any relation between outcome and number of HBOT sessions taken, but HBOT when started within 30 days had better functional outcome ($p<0.05$).

Four patients were excluded from the study as they had succumbed to various medical complications not related to HBOT. While the risk for seizures is of significant importance in this patient population due to extensive brain damage and oxygen toxicity, we did not have this complication in any of our patients. HBOT was well tolerated in patients with severe neurological status when complemented with adequate medical management.

The study has its limitations being a retrospective study with no control group. The number of HBOT sessions varied significantly based on patient's length of stay and affordability. Outcome measures were not assessed at a particular timeframe post hypoxic brain damage but prior to HBOT commencement and at the time of discharge which was variable among patients. Patients also received simultaneous rehabilitation measures which can also be a confounder. There is clearly a need for further research using larger number of patients in a randomized control trial.

## CONCLUSION

Patients with severe hypoxic brain injury has potential for recovery of consciousness, functional and neurological status with HBOT. Functional status(GOS score) at time of admission had predictive value on neurologic status and level on consciousness at discharge. Younger age, female gender, and early HBOT had significant effect on

functional outcome. Large scale randomized control studies are required.

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