Hyperbaric Oxygen Brain Injury Treatment Trial: A Multicenter Phase II Adaptive Clinical Trial

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Definition of Severe Traumatic Brain Injury

- Glasgow Coma Scale (GCS) score 3-8
- Intracranial hypertension 40-50%
- Multiple injuries 50%
- Surgical mass lesion 40-50%
- Mortality 30-35%
- Favorable outcome 40-45%

Need for a Trial

- Outcome from severe TBI has been flat lined for several decades
- No specific treatment despite multiple randomized clinical trials
- Medical and economic costs of severe TBI are large
- HBO_2 has significant potential as a treatment

Potential Mechanisms for HBO2 Efficacy

- Pre-clinical findings
  - Depressed mitochondrial function following injury is restored
  - ATP production is improved
  - Ischemia induced brain cell loss is attenuated
  - Neural apoptosis is reduced
  - Cognitive deficits are markedly attenuated
  - Intracranial hypertension is reduced

Potential Mechanisms for HBO2 Efficacy

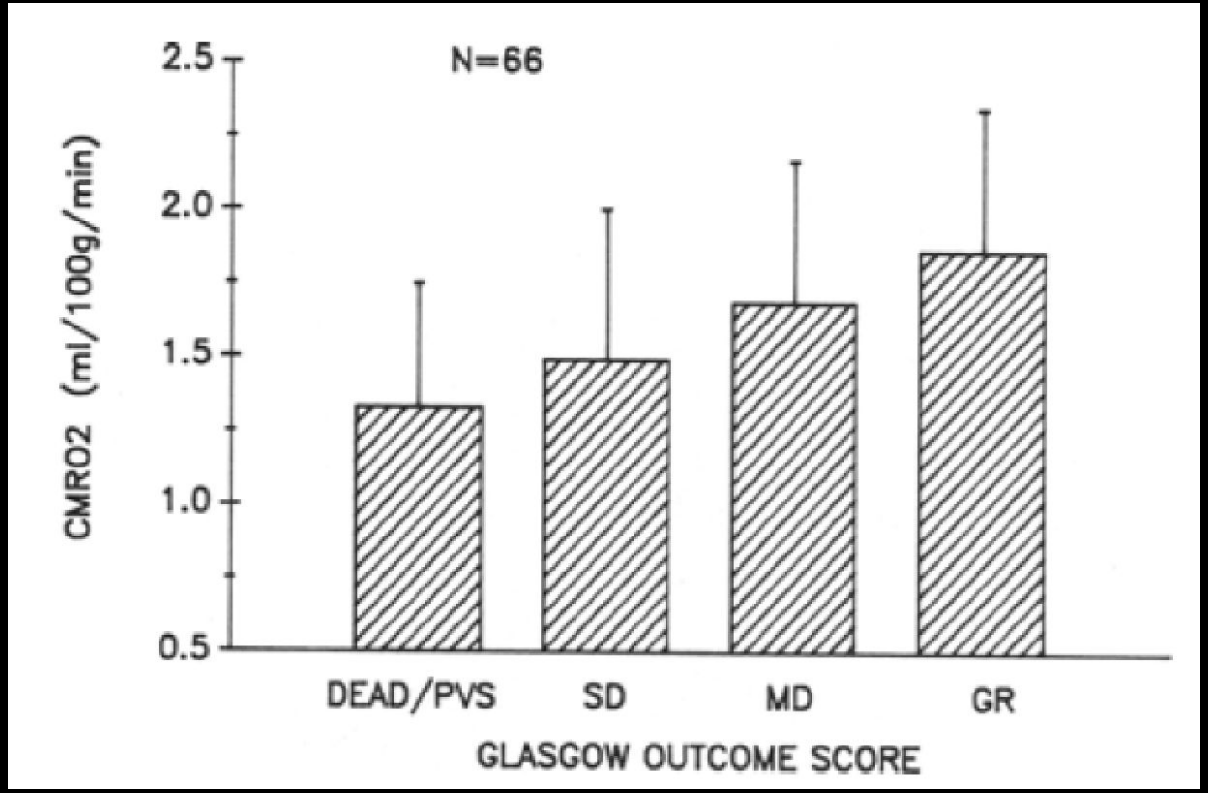
- Using surrogate markers several of the mechanisms demonstrated pre-clinically have been replicated in human severe TBI

Potential Mechanisms for HBO_2 Efficacy

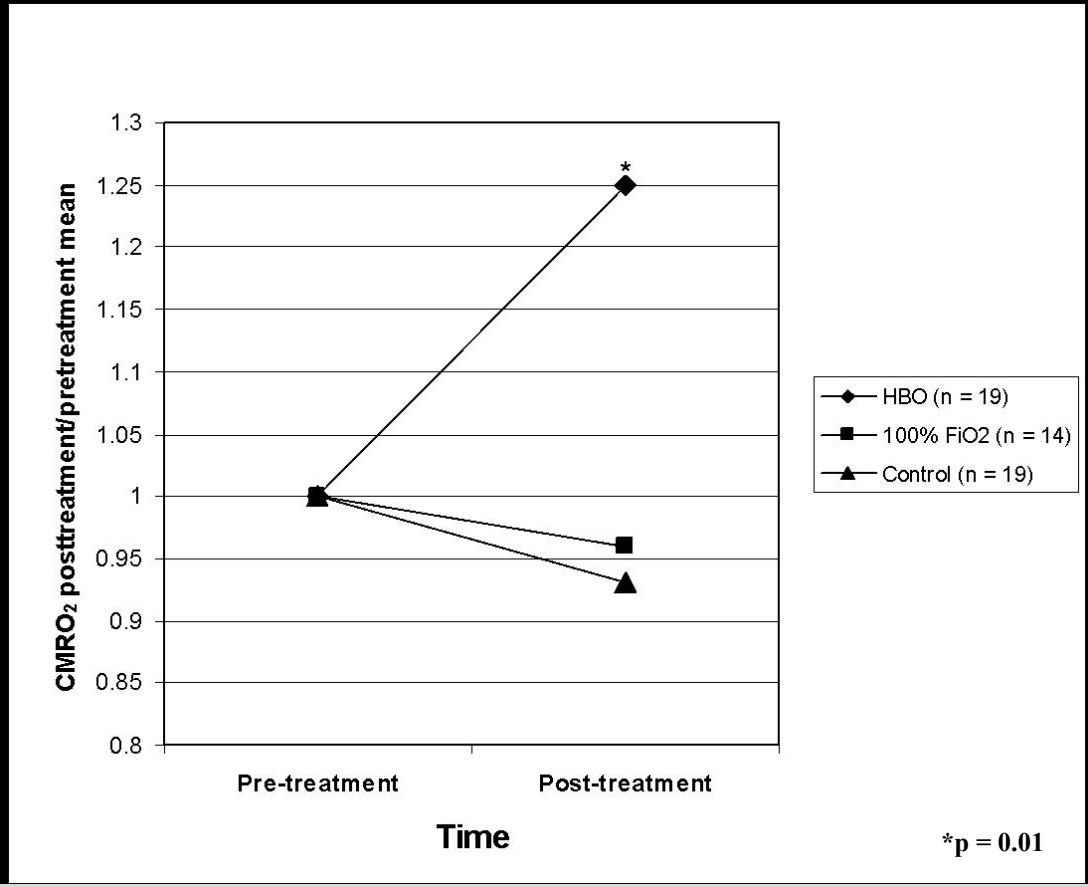
- In 186 $CMRO_2$ studies in 65 patients, Obrist found patients with GCS scores $\leq$ 8 had $CMRO_2$ levels below 1.6 which is less than half of normal (3.3 ml/100 gm/min)
- The lower the GCS, the lower the $CMRO_2$
- Reduced $CMRO_2$ independent of anatomic pathology

Obrist, J Neurosurg 61:241, 1984

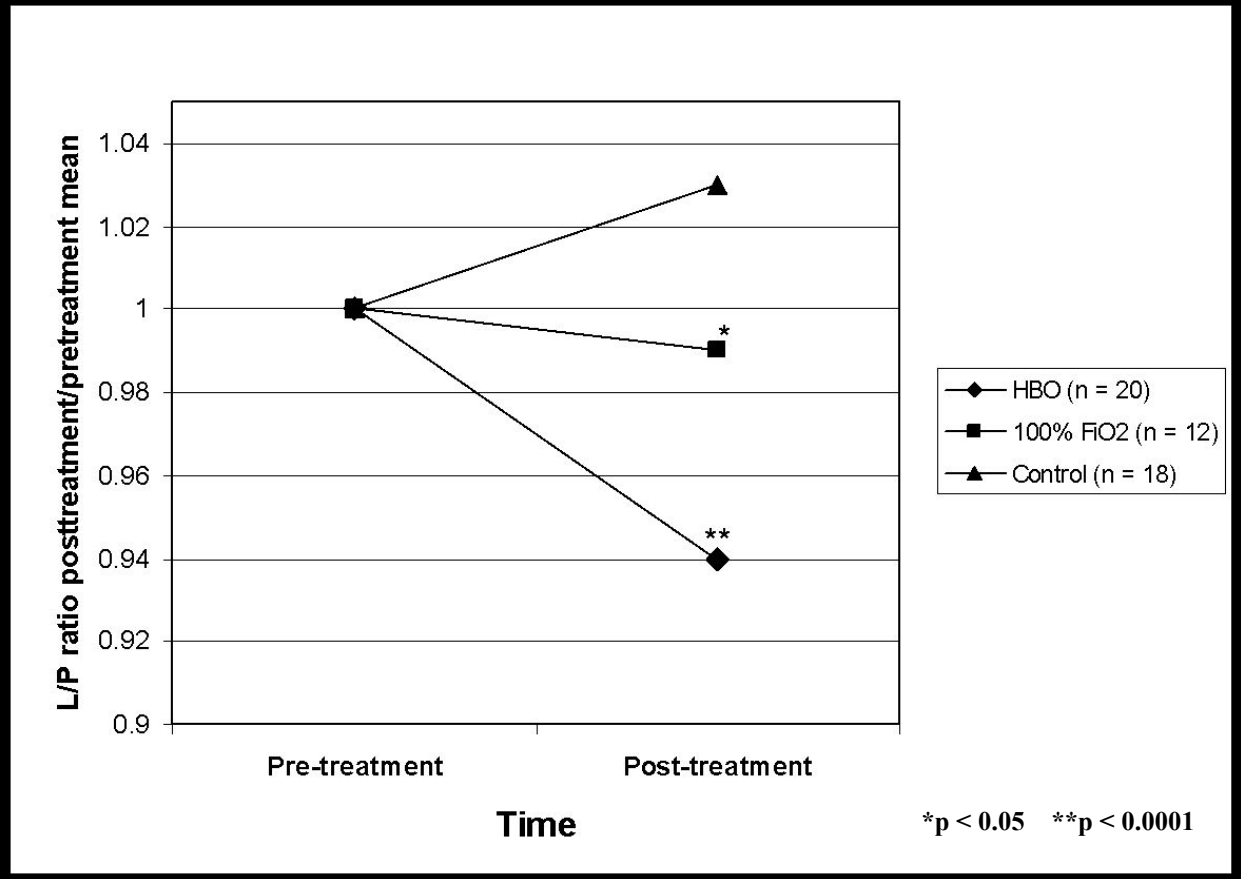
Low $CMRO_2$ is Associated with Poor Outcome



Cerebral Metabolic Rate of Oxygen

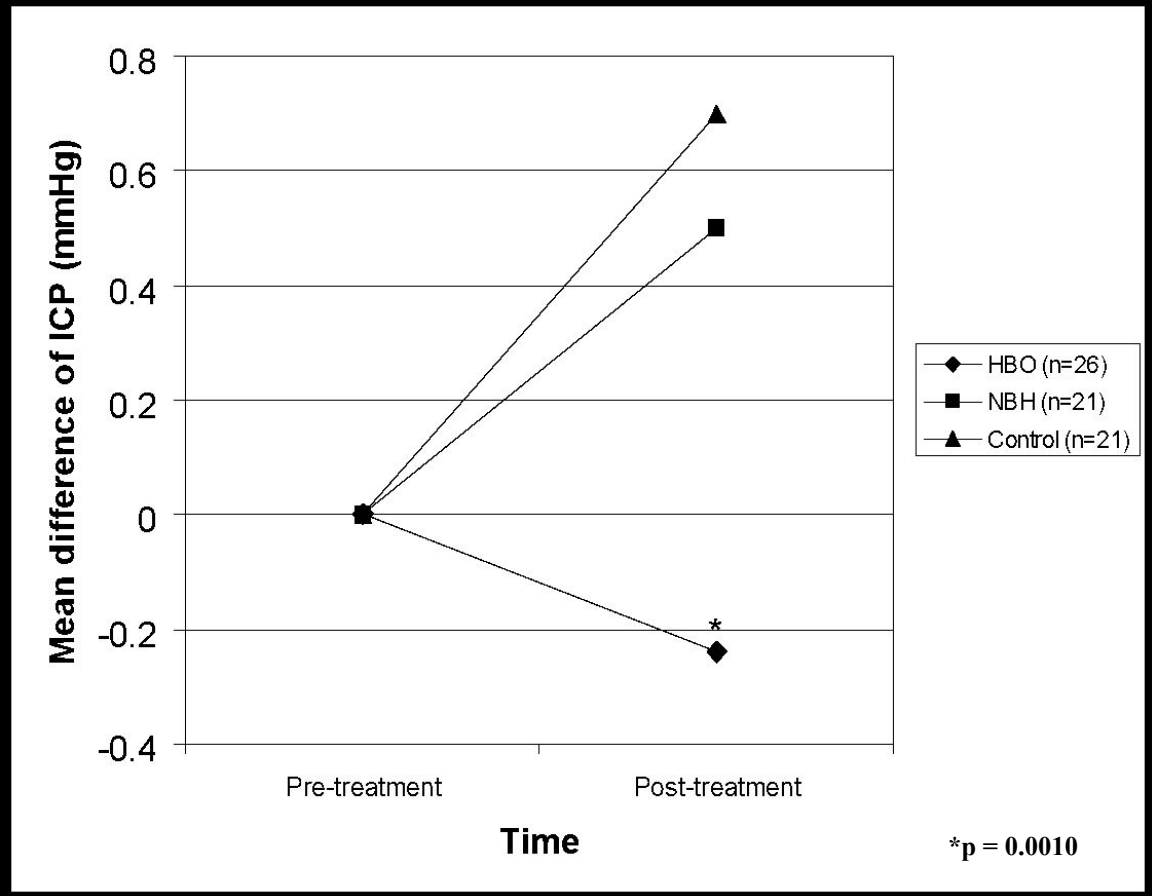


Lactate/Pyruvate Ratio



Rockswold, J Neurosurg 112:1080-1094, 2010

Mean Difference of ICP



Critical $PbtO_2$ Level

- There was significant improvement in $CMRO_2$ and L/P ratio when $PbtO_2$ levels were $\geq$ 200 mmHg as compared to < 200 mmHg
- This level was reached in only 51% of HBO_2 treatments at 1.5 ATA
- Lung function (P/F ratio) significantly effects $PbtO_2$ levels achieved
- The $PbtO_2$ achieved may be the critical factor in 6-month outcome, not the ATA utilized

Rockswold, J Neurotrauma 112:1080-1094, 2010

Inclusion Criteria

- Age 16-65 years
- Severe TBI, defined as a iGCS of 3 to 8 in the absence of paralytic medication
- For patients with a GCS of 7 or 8 or motor score = 5, Marshall CT score > 1
- For patients with an alcohol level > 200 mg/dl, Marshall CT score > 1
- For patients not requiring a craniotomy/craniectomy or any other major surgical procedure, the first HBO_2 treatment can be initiated within 8 hours of admission
- For patients requiring a craniotomy/craniectomy or major surgical procedure, the first HBO_2 treatment can be initiated within 14 hours of admission

Exclusion Criteria

Criteria	Metric	Rationale
First hyperbaric oxygen treatment cannot be initiated within 24 hours of injury	Time to first hyperbaric oxygen treatment	Subjects treated >24 hours are unlikely to benefit
GCS of 3 with mid-position and non-reactive pupils bilaterally (4mm) in the absence of paralytic medication	GCS	Avoid enrolling futile cases.
Penetrating head injury	Clinician exam	Avoid enrolling subjects with very poor prognosis
Pregnant	For women of childbearing age, pregnancy will be assessed either by urine or serum pregnancy test	The effect of hyperbaric oxygen treatment on unborn fetus is unknown
Preexisting neurologic disease (e.g. TBI or stroke or neurodegenerative disorder) with confounding residual neurologic deficits	History obtained from family and review of electronic medical record	Minimize the influence of prior neurologic injury on ascertaining TBI outcome
Prisoner or ward of state	Look for prison guards	Challenges to conducting follow-up assessments

Treatment Arms

	Arm	
1.	Control (1.0 ATA)	0
2.	1.5 ATA	260
3.	2 ATA	416
4.	NBH (100% FiO2 at 1.0 ATA)	540
5.	2.5 ATA	592
6.	1.5 ATA+NBH	620
7.	2 ATA+NBH	776
8.	2.5 ATA+NBH	952

Treatments given BID x 5 days

Objectives

- Objective 1
  - Signal of efficacy: To determine, in subjects with severe TBI, whether there is a > 50% probability of hyperoxia treatment demonstrating improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial

- Objective 2
  - Dose selection: To select, in subjects with severe TBI, the combination of treatment parameters (pressure +/- intervening normobaric hyperoxia) that is most likely to demonstrate improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial

Primary Endpoint

- The treatment groups will be compared with respect to the proportion of subjects with favorable outcome at 6 months post randomization utilizing the injury severity adjusted GOS-E

Secondary Endpoints

- To analyze the level and duration of intracranial hypertension (> 22 mmHg) in HBO_2-treated versus control groups
- To analyze the therapeutic intensity level scores for controlling intracranial pressure in HBO_2-treated subjects compared to controls
- At sites utilizing Licox brain tissue partial pressure of oxygen (PO_2) monitoring, analyze the level and duration of brain tissue hypoxia (brain tissue PO_2 < 20 mmHg) in HBO_2-treated groups versus control
- To compare the type and rate of serious adverse events (SAEs) between hyperoxia treatment arms and control
- Peak $PbtO_2$ levels during HBO_2 treatments will be correlated with outcome at 6 months

Enrolling Sites

- Hennepin County Medical Center / University of Minnesota
- University of Maryland
- University of Nebraska
- Duke University Medical Center
- University of Iowa
- Ohio State University
- University of California - San Diego
- University of Alabama - Birmingham
- Detroit Receiving
- Hamilton General Hospital - Canada
- Honor Health / Osborn Medical Center - Scottsdale
- Advocate Lutheran General Hospital / University of Illinois
- Baylor University Medical Center
- Spectrum Health / Michigan State University
- Medical College of Wisconsin
- University of Kentucky

Generalization of HCMC Experience

- Investigators meeting/training sessions in Minneapolis February 15-16, 2018
- Simulation training video completed
- Simulation video required at each site before enrollment
- Sites selected for expertise in critical care hyperbaric medicine and severe TBI management
- Adaptation of monoplace chambers for HOBIT Trial

Oxygen Toxicity

- Previous clinical investigations utilizing
  - Microdialysate glycerol
  - CSF F2-isoprostanes
  - Bronchial alveolar lavage cytokines IL-8 and IL-6
  - PEEP levels > 10 cm H_2O
  - FiO_2 levels > 50%
  - Chest x-rays
  - Incidence of seizures
- Demonstrated no increased incidence in any parameter in HBO_2 treated patients compared to standard treatment

Oxygen Toxicity Monitoring in HOBIT

- 40-50% of severe TBI patients develop severe atelectasis, ventilator acquired pneumonia, pulmonary contusions, adult respiratory distress syndrome, or a combination of these conditions

Oxygen Toxicity

- The lung is particularly susceptible to damage by hyperoxia because of the large surface area exposed to oxygen in the lungs
- The challenge will be to distinguish natural history of oxygen toxicity

Oxygen Toxicity Monitoring in HOBIT

- No patient will undergo HBO_2 treatment with a P/F ratio < 200 or if a PEEP > 10 cm of H_2O is required to achieve a P/T ratio $\geq$ 200
- Specific attention to adverse events related to HBO_2 treatment, e.g., pulmonary dysfunction
- The incidence of pulmonary dysfunction will be compared across treatment groups *vs* controls

Conclusions

- This is a challenging trial involving critically injured patients and a complex intervention
- It will require diligence and attention to be successful
- We have a great team who can accomplish this