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COMBINED USE OF HYPERBARIC OXYGEN AND STEM CELL THERAPY IN MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY - A CASE REPORT

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ABSTRACT Standard treatment of acute traumatic brain injury (TBI) consists of either conservative or removing the clot (surgery), restoring perfusion, supporting metabolic requirement and limiting inflammatory and oxidative damage. Many centres worldwide are researching newer modalities for better outcomes. As a result, the survival rate of patients with TBI has increased significantly. Hyperbaric oxygen (HBO) therapy has been shown to protect neurons from the damaging effect of hypotension and ischemia, improve neuronal aerobic metabolism, promote mobilisation of stem cells. In the regenerative medicine, hematopoietic stem cell transplantation is evolving as a promising treatment modality in various neurological disorders like multiple sclerosis, Parkinson's disease and stroke with varying clinical outcome. This case report of a 21 year old boy, suggests that hyperbaric oxygen in combination with stem cell therapy along with neuro-rehabilitation has a potential to reverse the damage after TBI leading to an improved quality of life in head injury patients.

KEYWORDS : Traumatic brain injury, hyperbaric oxygen therapy, stem cell therapy

Introduction

TBI is a significant public health problem worldwide. TBI patients require combination of several treatment modalities and care delivered by interdisciplinary team. HBO and stem cell treatments are prospective therapeutic options, which can enhance neurological recovery to some extent. Stem cells are able to renew themselves and have the ability to differentiate into distinctive mature cell types, leading to new tissue formation, repair, and regeneration. HBO is intermittent inhalation of 100% oxygen at greater than normal atmospheric pressure (1.5 atmospheric absolute) and this may be beneficial for TBI as a result of improvement in oxygenation of tissues.

Case report

A 21 years male from Ethiopia sustained severe traumatic head injury following assault and was unconscious at the scene with history of nasal bleed and vomiting. He was shifted to local teaching hospital where, he was intubated and ventilated in view of poor sensorium (GCS: E1 M2 V1). Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) of brain were done which revealed left fronto-temporal acute subdural hematoma along with multiple small haemorrhagic contusions suggestive of diffuse axonal injury (Figure 1). He underwent left fronto-temporal decompressive craniectomy and evacuation of subdural hematoma on the next day of trauma along with other supportive care. Tracheotomy was performed in view of prolonged ventilator support and better airway toileting. He was gradually weaned off ventilatory support. He was referred to our institution after 6 weeks of trauma. On arrival at our institution, he was on tracheotomy tube with Glasgow coma scale (GCS) of 5 (E1 M3 VT), pupils were bilaterally 3mm reacting and right sided hemiparesis. He was admitted to Neuro Intensive Care Unit. He required 2 to 4 litres of O2 to maintain saturation through tracheotomy tube. CT brain was done which revealed post-craniotomy status with post operative changes in left fronto-temporal region and dilatation of ventricles (Figure 2). He was managed by insertion of ventriculo-peritoneal shunt. He showed no improvement and was then planned for trial of hyperbaric oxygen therapy (HBOT) after taking attendants consent. HBOT at a pressure of 1.5 ATA for 90 minutes was started after 8 weeks of trauma. After initial 5 sittings, he was able to maintain saturation on room air. He received 40 sittings of HBOT. After completion of HBOT, his sensorium gradually improved (GCS: E4 M4 VT). Following HBO therapy, he was planned for a trial of stem cell therapy. After the approval of ethics committee he underwent stem cell transplantation after 15 weeks of trauma. Fifty millilitres of bone marrow was aspirated, processed and transfused intra-thecally. After a month of stem cell therapy (19 weeks following trauma), we noticed he was able to obey simple commands and could move his limbs spontaneously. He underwent cranioplasty after 20 weeks of trauma. He received intensive physical and cognitive rehabilitation with neuro-psychological and nutritional support. He showed significant improvement in cognitive as well as motor functions and his GCS improved to 11 (E4 M6 VT). Tracheotomy was decannulated when tracheal secretions were minimal and was discharged. He was followed up for over a period of 8 months. He is conscious, alert, dysphasic, accepts normal diet, plays simple ball games, continent and walks with minimal support.

Discussion

Traumatic brain injury (TBI) is an insult to the brain secondary to external mechanical forces possibly leading to permanent or temporary impairment of cognitive, physical and psychosocial functions with an associated diminished or altered state of consciousness[1]. It is estimated that nearly 1.5 to 2 million persons are injured and 1 million succumb to death every year in India. Road traffic injuries are the leading cause (60%) of TBIs followed by falls (20%-25%) and violence (10%)[2].

The biomechanics of TBI involve both linear and rotational forces. It is these rotational forces that lead to twisting and shearing injuries in the brain parenchyma, particularly in grey-white matter junction resulting in diffuse axonal injury (DAI). Pathologically, DAI encompasses a spectrum of abnormalities from primary mechanical breaking of the axonal cytoskeleton to transport interruption, swelling and proteolysis through secondary physiological changes. Depending on the severity and extent of injury, these changes can manifest acutely as immediate loss of consciousness or confusion and persist as coma and/or cognitive dysfunction[3].

Management of TBI patients depends on the severity and extent of injury. Patients with mild TBI with positive CT findings and moderate TBI are admitted to the Intensive Care Unit (ICU) and followed with serial neurological examinations. With severe TBI, ICP monitoring and maintaining cerebral perfusion pressure (CPP) forms the fundamental principle. These patients may or may not require surgery depending upon the clinico-radiological findings. Protocols to control ICP using sedation, hyperosmolar therapy in the form of Mannitol, hypertonic saline and hyperventilation have been extensively employed with variable results. High-dose barbiturate therapy, such as Pentobarbital, has the potential benefit of suppressing cerebral metabolism, thus decreasing oxygen demand have the added benefit of neuroprotection. Other supportive measures include hypothermia, infection control, hemodynamic management, glycemic control and prophylaxis for deep vein thrombosis. After brain injury, the brain

attempts to regenerate by resorting to a developmental-like state with increased neurogenesis, synaptogenesis, re-myelination, re-formation of the blood brain barrier and angiogenesis.

We know that, neural stem cells exist in the normal adult brain in the subventricular zone in the lateral ventricles and the subgranular zone in the dentate gyrus of the hippocampus. Following an ischemic or traumatic injury, endogenous neural stem cells proliferate, migrate to the site of injury and differentiate into neurons and glia[4].

One exciting discovery by Sanchez-Ramos JR5 is that bone marrow-derived cells (BMSCs), either hematopoietic or mesenchymal stem cells, may be able to give rise to neural and glial cells when transplanted into the adult CNS. When transplanted into naive adult rat CNS, these cells migrate throughout the brain and loose their immune reactivity for mesenchymal markers and express neuronal and glial markers at 12 and 45 days post-transplantation.

Mahmood et al[6,7] in their study on rats have observed that systemic administration of stem cells at 24 hours post-injury was associated with an increased number of bromodeoxyuridine-positive cells into the subventricular zone, hippocampus and pericontusional area at 2 weeks post-injury. It is suggestive of an increased neurogenesis possibly mediated by the trophic factors released by the transplanted cells.

In acute traumatic brain injury, hypoxia and hypotension are independently associated with increased mortality and morbidity. Thus secondary ischemia and oxygen deficiency are thought to be important mechanisms of cell death in traumatic brain injury[8]. This observation forms part of the rationale for the use of hyperbaric oxygen therapy, which increases blood flow to the damaged areas of the brain, as documented by serial Single Photon Emission Computed Tomography (SPECT) scans and other techniques[9].

In 2014, Heyboer et al[10] have shown that HBO therapy mobilizes bone marrow derived-stem cells by a free radical mediated mechanism, involving nitric oxide. HBO also assists stem cells by inducing placental growth factors (PGF) in marrow stromal cells. PGF is a key molecule in angiogenesis, which is the growth of new blood vessels from existing ones, and vasculogenesis, which is the spontaneous formation of new blood vessels. At 2.0 ATA, post-treatment values of CD34+ and CD45-dim leukocytes were 2-fold greater than pre-treatment values. There was also a 2-fold increase in intracellular content of hypoxic inducible factors -1, -2, -3 thioredoxin-1 which help in neurogenesis and poly-ADP-ribose polymerase in all post-versus pre-treatment samples.

Wang at al[11] have shown that in HBO therapy (2 ATA, once daily for 7 days within 3 hours of the brain damage) can promote endogenous neural stem cells to migrate to the cortex and differentiate into mature neurons in neonatal rats with hypoxic ischemic brain damage. Lee et al[12,] in 2013 have shown that mobilization of bone marrow stem cells to an ischemic area has increased in prolonged HBO treatments i.e. 3 weeks compared to 2 days, suggesting that the duration of therapy is crucial for promoting homing and neurogenesis.

Conclusion

Researchers around the world have enough evidence to support the hypothesis that both hyperbaric oxygen and stem cell therapy act synergistically to provide better results in traumatic brain injury patients. Both HBOT and stem cell therapy combination are considered to be at the forefront of regenerative medicine. Future research focusing on cellular transplantation in TBI will likely benefit from more extensive collaborations between experts in the fields of Neurotrauma and stem cell biology.

Conflict of interest – Nil
Financial disclosure – Nil
Approval taken from Ethical committee

Legends:

Figure 1. T2 weighted MRI axial section showing left fronto-temporal acute subdural and multiple intracerebral contusions.

Figure 2. Plain CT head axial section showing left fronto-temporal decompressive craniectomy status with gliotic changes and dilated ventricles.

Abbreviations:

TBI – Traumatic brain injury
HBO – Hyperbaric oxygen
CT - Computed Tomography
GCS - Glasgow coma scale
ICU – Intensive care unit
EVD - External Ventricular Drain
ATA – Atmospheric absolute
DAI - Diffuse axonal injury
ICP – Intracranial pressure
CPP – Cerebral perfusion pressure
PECT - Single Photon Emission Computed Tomography
CNS - Central nervous system
BMSC - Bone marrow-derived cells
MSC – Marrow stromal cells
PGF - placental growth factors

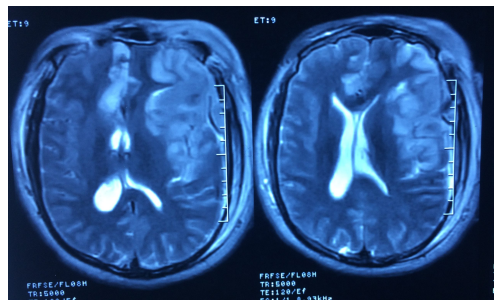

Figure 1. T2 weighted MRI axial section showing left fronto-temporal acute subdural and multiple intracerebral contusions.

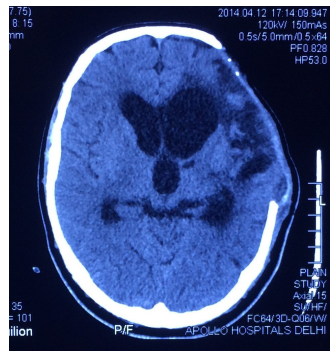

Figure 2. Plain CT head axial section showing left fronto-temporal decompressive craniectomy status with gliotic changes and dilated ventricles.

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