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REVIEW

Normobaric hyperoxia therapy for traumatic brain injury and stroke: a review

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Abstract
Traumatic brain injury (TBI) and acute ischaemic stroke are major causes of mortality and morbidity and there is an urgent demand for new neuroprotective strategies following the translational failure of neuroprotective drug trials. Oxygen therapy—especially normobaric, may offer a simple and effective therapeutic strategy which we review in this paper. Firstly we review mechanisms underlying the therapeutic effects of hyperoxia (both normobaric and hyperbaric) including mitochondrial rescue, stabilisation of intracranial pressure, attenuation of cortical spreading depression and inducing favourable endothelial-leukocyte interactions, all effects of which are postulated to decrease secondary injury. Next we survey studies using hyperbaric oxygen therapy for TBI and stroke, which formed the basis for early studies on normobaric hyperoxia. Thirdly, we present clinical studies of the efficacy of normobaric hyperoxia on TBI and stroke, emphasising their safety, efficacy and practicality. Finally we consider safety concerns and side effects, particularly pulmonary pathology, respiratory failure and theoretical risks in paediatric patients. A neuroprotective role of normobaric hyperoxia is extremely promising and further studies are warranted.

Key words: *Traumatic brain injury, stroke, hyperoxia, neuro surgery.*

Introduction

Traumatic Brain Injury (TBI) is the cause of death for 50,000 people in the United States of America and results in non-lethal but severe disabilities in another 70,000 to 90,000 each year.[1] Around 1,000,000 hospital admissions each year in the European Union alone are due to TBI,[2] thereby making TBI a significant socioeconomic burden on Western Society.[3] Moreover, some believe that this is underestimated owing to underreporting of milder forms of TBI and its consequences.[4]

Likewise, each year more than 700,000 people in the United States of America have strokes, of whom 150,000 die—the country's third-leading cause of death.[5,6] Currently the only proven therapy for acute ischaemic stroke is early thrombolysis although several studies are ongoing including hypothermia, magnesium, caffeinol, statins and albumin.[7]

Moreover, as yet no neuroprotective agent for stroke or TBI has shown to improve outcome on a randomised control trial. Several clinical trials in the eighties failed to translate effectively on human patients despite optimal *in vivo* experimental results, most notably NMDA receptor antagonists.[8] The reasons for this are multifactorial and have been reviewed extensively.[9]

Hyperbaric oxygen therapy, defined as oxygen delivered at pressures above atmospheric pressure, has long been shown to increase the supply of oxygen to ischaemic foci.[10,11] However, applications are cumbersome and uneconomical.[12] Normobaric hyperoxia, defined as oxygen delivered at fractions of inspired oxygen (FIO2) between 40–100% (i.e., above the atmospheric concentration of 21%) but at atmospheric pressure, can achieve significant increases in brain tissue oxygen tension (PbtO2) with minimal costs and significantly reduced risks.[13]

However, there has been much debate as the relationship between oxygen tension and blood oxygen carrying capacity is complex and processes such as oxidative stress are mainly sensitive to oxygen tension whereas others pertaining to ischaemia are primarily sensitive to the rate of oxygen delivery. Under normal clinical situations (in the absence of pulmonary shunting and a normal transfer factor) and at atmospheric conditions haemoglobin is close to 100% saturated and increasing FIO2 from above 21% is unlikely to improve oxygen transportation to tissues seeing as only a very small fraction of oxygen ($<1\%$) that is transported is actually dissolved in plasma.

The pathophysiology of TBI remains controversial and whether or not secondary injury cascades in TBI are the result of stroke like damage is

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controversial[14–18] and an entirely independent neuroprotective mechanism remains possible, perhaps direct attenuation of secondary injury. On the other hand, mitochondrial dysfunction in stroke and TBI is well recognised[19] and this may be the substrate that hyperoxia seeks to improve.[12,20]

Mechanisms of action

Mitochondrial rescue

Progressive dysfunction of cerebral metabolism is a well recognised consequence in patients with TBI as well as animal models thereof.[16] Ensuing ionic flux in TBI increases glucose demand and promotes astrocytic glycogenolysis, consistent with the compartmentalisation theory.[21] Owing to the hypoxic conditions, the majority of this glucose is metabolised anaerobically and converted into lactate.[22] Neurons may not benefit much from this lactate because of mitochondrial dysfunction which is inherent to TBI pathophysiology.[15,23] Improving this depression of cerebral metabolism may be a legitimate treatment option.

Importantly, cerebral PbtO2 has been reported to be significantly decreased following TBI.[24] and increasing the availability of oxygen would be expected to increase background aerobic metabolism and is likely to protect against cell death. Another biochemical premise for this claim is that the enzyme kinetics of mitochondrial redox enzymes are enhanced when PbtO2 values are higher.[25,26] Taking all these into account, supplementary oxygen would be expected to increase the rate(s) of reaction for aerobic metabolism and therefore promote survival of neural tissue.[27,28]

Importantly, hyperoxia does not improve mitochondrial function unless administered quickly after the injury. The obvious reason for this is that the areas of brain under threat (''penumbra'') would have already infarcted before administration of hyperoxia, and the basic objective of preventing secondary damage would be lost. This may explain why in a clinical study Magnoni *et al.*, who administered hyperoxia more than 48 hours after post-injury, did not see any improvement in their patients.[29]

In addition, hyperoxia therapy must be sustained to have any therapeutic effect; otherwise the penumbra would revert as ischaemic conditions redevelop. This may explain why Diringer *et al.*, who administered hyperoxia for only 1 hour to patients with TBI failed to detect improved cerebral metabolic rate despite sophisticated techniques.[17]

Genetic clues

To classify the genetic basis of hyperbaric oxygen's neuroprotective basis in an animal model of subarachnoid haemorrhage, Ostrowski *et al.* showed that although post endovascular perforation the genes HIF-1α, VEGF and BNIP3 were expressed, the expression of HIF-1α in particular was attenuated by hyperbaric oxygen.[30] This is interesting since the downstream targets of HIF-1α include enzymes that promote anaerobic glycolysis, and therefore complements the clinical microdialysis data of Tolias *et al.*[13] Moreover, this confirms and strengthens the argument of mitochondrial rescue.

Stabilisation of intracranial pressure

The role of intracranial pressure (ICP) itself in the management of TBI is not fully elucidated and several studies have shown optimistic reductions in intracranial pressure without any effects on the long-term outcome. However, reduction of ICP is still the centre of modern management of TBI.

There is paucity of animal data pertaining to the effect of normobaric hyperoxia on ICP, although the clinical study of Tolias *et al.* demonstrated significant reduction in the ICP of patients with severe TBI who were given 100% oxygen compared with historical controls.[13] Furthermore, this effect correlated well with improvement on the Glasgow Coma Scale (GCS). This improvement may be attributable to decreased cytotoxic oedema formation as a result of increased PbtO2, as has been demonstrated on an animal model.[31]

On the other hand, the effects of hyperbaric oxygen on ICP and outcome are controversial. Several studies have shown that hyperbaric oxygen causes a gradual increase in ICP with time.[32] A possible reason for this would be cerebral vasoconstriction[33–35] although some studies suggest that other factors may also be in play.[36,37] Rockswold *et al.* also generally noted gradual linear increases in intracranial pressure with hyperbaric oxygen.[38] Strangely, patients who started at a low baseline ICP showed increases upon treatment and vice versa—patients with high baseline ICP decreased upon treatment, consistent with two other published reports.[36,39] Interestingly, they attribute increased pressure in the hyperbaric chamber to increased pressure in paranasal sinuses and heat, which may eventually have overridden any benefit on ICP. Notwithstanding, it remains possible that despite increased ICP they averted oedema and ischaemia probably due to blood-brain barrier (aka cerebral vascular endothelium) stabilising properties of hyperbaric oxygen as shown in two animal studies.[40,41]

Endothelial-neutrophil interactions

Another possible explanation of oxygen therapy's beneficial effects pertains to endothelial-neutrophil interactions that are believed to partly underlie the pathophysiology of ischaemia/reperfusion injury as shown on animal studies.[42] Although these experiments have not been performed using normobaric hyperoxia, we infer a similar effect.

Leukocyte infiltration into ischaemic tissue, which would accelerate tissue death, has been decreased by hyperbaric oxygen in a rat model of ischaemic stroke.[43] Buras and Reenstra suggest that hyperbaric oxygen suppresses neutrophil-endothelial adhesion, thereby reducing ischaemia/reperfusion injury in particular.[44] Hypoxia and hypoglycaemia contributing to stroke up-regulate the inflammatory intercellular adhesion molecule ICAM-1, which is believed to play a protagonist role in stroke and subarachnoid haemorrhage, and hyperbaric oxygen induces endothelial nitric oxide synthase (eNOS) to successfully down-regulate ICAM-1.[45] Interestingly, there is also evidence for similar neutrophil-endothelial interactions during permanent focal cerebral ischaemia,[46] and it remains to be seen if on oxygen exposure improves late phase cerebral ischaemia. Such factors may explain the results of Beynon *et al.* who showed delayed hyperbaric oxygen to be more efficacious than early prolonged normobaric hyperoxia in middle cerebral artery occlusion models of cerebral ischaemia in rats.[47]

Cortical spreading depression

Cortical spreading depression is a self-propagating wave of nearly complete depolarisation of a sizable population of brain cells associated with massive redistribution of ions between intracellular and extracellular compartments.[48] Peri-infarct depolarisations are cortical spreading depression-like phenomena, albeit hypoxic, that play a key role in the propagation of secondary injury in stroke and TBI.[19,49] Their suppression in intensive care may be a promising method of salvaging penumbral tissue after stroke and TBI.[50]

While cortical spreading depression is not associated with neuronal death in the normal brain under physiological conditions,[51] it is known to be a contributor to ischaemic brain damage.[52] An exciting recent study showed for the first time that increasing oxygen availability by an infusion of hyperoxic synthetic cerebrospinal fluid shortens the duration of cortical spreading depression and improves local redox chemistry, as shown by two-photon microscopic NADH (Nicotinamide Adenine Dinucleotide) imaging and oxygen sensor microelectrodes in live mouse cortex.[53] In other words, cytotoxic oedema is the result of insufficient energy to re-establish ionic gradients that are lost during spreading depression.[54] Indeed, on a mouse middle cerebral artery occlusion model of focal ischaemia, normobaric hyperoxia was found to decrease peri-infarct depolarisations while increasing cerebral blood flow and oxygenation.[55] Taken together, logical explanation is that hyperoxia prevents cortical spreading depression post-stroke from becoming hypoxic spreading depression, thereby salvaging penumbral tissue.

Incidentally, oxygen therapy is the only NICE approved therapy for cluster headache, whose pathophysiology is believed to be neurovascular and involving spreading depression[56] and the mechanism underlying its efficacy may be through the attenuation of spreading depression. Additionally, a recent meta-analysis that included 201 patients in nine clinical studies confirmed that normobaric oxygen to be therapeutic for cluster headache, while hyperbaric oxygen even more effective for terminating acute migraine albeit not as routine therapy owing to costs and poor availability.[57]

Hyperbaric oxygen as treatment

Although several authors provide early descriptions of the use of oxygen therapy in the treatment of cerebral ischaemia as early as the 1960s, the reports were largely anecdotal clinical studies.[58–61]

A recent meta-analysis of clinical studies of hyperbaric oxygen in acute ischaemic stroke looked at outcomes of mortality, functional health outcomes and adverse effects from four randomised control trials, one controlled clinical trial and 17 observational studies deemed the majority of "poor quality". Their conclusions were that the current evidence, limited by "good-quality trials" and sample size, do not support a beneficial role of hyperbaric oxygen for patients with stroke.[62] Similarly, Bennett *et al.* meta-analysed data regarding effectiveness of hyperbaric oxygen as adjunctive therapy in acute stroke and did not find evidence to show that it improves clinical outcomes at 6 months when considering three randomised control trials (106 participants).[10]

On the other hand, meta-analysis of patients with TBI receiving hyperbaric oxygen revealed that the risk of death was reduced but not that of favourable clinical outcome. The authors concluded that based upon the modest numbers of patients and limitations of methodology, routine administration of hyperbaric oxygen could not be justified.[63]

Finally, problems with hyperbaric oxygen were mainly those pertaining to practicality and availability of such treatment along with their consequent costs. Additionally, some patients were lost to follow-up due to claustrophobia and patient discomfort. For example, the study by Anderson *et al.* was stopped prematurely because of poor tolerance and difficulties with administration of therapy.[64]

In light of these disappointing conclusions, normobaric hyperoxia has been proposed as a more feasible alternative.[12] Normobaric hyperoxia is non-invasive, easily available, inexpensive and simple to administer—all of which add up to make a practical therapy against stroke and TBI.

Clinical studies of normobaric hyperoxia

Clinical studies on TBI

Early studies showed that normobaric hyperoxia soon after TBI boosted brain PbtO2, which in turn

appeared to rescue aerobic metabolism as seen by decreasing extracellular lactate levels.[27,65] This gave the theoretical framework of efficacy and was the forerunner of many studies, as summarised in Table I.

The most cited study in this area is that of Tolias *et al.*[13], who performed a prospective study of 52 patients with severe TBI treated with 100% FIO2 for 24 hours starting within 6 hours of admission; comparing them to a historical cohort of 112 patients. Using intracerebral microdialysis, increased glucose levels and decreased glutamate and lactate levels, as well as reduced lactate/glucose and lactate/pyruvate ratios were found in microdialysate in the groups treated with hyperoxia.

Furthermore, significant reductions in intracranial pressure were seen in the treatment group, without changes in perfusion pressure (discussed below). Strengths of this study included their multifaceted study of various aspects of improvement—microdialysis, ICP measurement and clinical. Criticisms of this study pertained with safety concerns of pulmonary toxicity, which we discuss next, that it compares patients against historical controls. In many ways this study can be seen as a successful clinical translation of preceding animal studies (notably Chen *et al.*[66]), and proof of concept of the hypothesis that arterial hyperoxia attenuates the fall in glucose and rise in lactate. Although this study does not carry the power of a randomised control trial, it can be seen as a stepping stone.

Using similar microdialysis techniques, Magnoni *et al.* studied the effects of 3 hours of 100% on patients.[29] Therapy was initiated late in the natural

TABLE I. Summary of studies using normobaric hyperoxia for TBI

Reference	Techniques	Main findings
Menzel *et al.*[65]	The effects of increasing tissue O2 by increasing FIO2 on PbtO2, lactate and glucose were measured. (n = 22 patients with severe TBI)	First microdialysis study to show that hyperoxia decreases lactate levels in the microdialysate, indicating that hyperoxia may promote aerobic metabolism
Menzel *et al.*[27]	The relationship between CBF (measured by Xe-CT), PbtO2, extracellular glucose and lactate (measured by microdialysis) were studied. (n = 47 patients with severe TBI, in total)	Increasing PaO2 by administering hyperoxia was shown to increase PbtO2 and decrease lactate in the microdialysate. This study introduced the concept of oxygen reactivity vis-à-vis proportional changes in PbtO2 in response to FIO2
Reinert *et al.*[28]	Effects of increasing FIO2 on cerebral perfusion pressure (CPP), PbtO2 and brain microdialysate glucose and lactate were studied using an intraparenchymal ICP device, oxygen sensor and microdialysis at the cortical-subcortical junction. Two 6- hour challenges to 100% oxygen – one early and one delayed were compared (n = 20 patients with severe TBI)	This study confirmed positive correlation between PbtO2 and FIO2, implying that PbtO2 can be improved by increasing PaO2. Moreover, PbtO2 was shown to positively correlate with CPP. Lactate levels were decreased by increasing FIO2 although glucose levels remained unchanged
Magnoni *et al.*[29]	Ventilation with 100% FIO2 for 3 hours delayed by 48 hours post-injury. Analysis by microdialysis of lactate, pyruvate, glucose, glutamate, brain tissue PO2 (n = 8 patients with severe TBI)	Delayed use of hyperoxia does not improve cerebral glucose oxygenation
Tolias *et al.*[13]	100% FIO2 administered with 6 hours of injury for a period of 24 hours. Analysis by intracerebral microdialysis and tissue O2 probes (n = 52 patients with severe TBI, compared with historical controls)	This study established the working hypothesis that early and prolonged hyperoxia improves TBI, as shown by improvements in microdialysate indices of brain oxidative metabolism and decreases intracranial pressure. Largest study of its kind to date
Diringer *et al.*[17]	Cerebral metabolic rate for oxygen (CMRO2) measured with positron emission tomography (PET) before and after 1 hour ventilation with 100% oxygen (n = 5 patients with severe TBI)	Hyperoxia curtailed to 1 hour is not sufficient to exert a beneficial effect on cerebral oxygen metabolism
Nortje *et al.*[67]	Cerebral microdialysis, brain tissue oximetry, 15O-PET performed during normoxia and hyperoxia (n = 11 patients with severe TBI)	Hyperoxia increases PbtO2 independent of changes in microdialysate lactate and lactate/pyruvate ratios
Rosenthal *et al.*[84]	Ratio of PaO2 to PbtO2 (PF ratio) determined before and after an ''oxygen challenge'' increase in FIO2 from baseline to 1.0 for 20 minutes (n = 37 patients with severe TBI)	First report to highlight the role of lung function, specifically the PF ratio, as a major determinant of the maximal PbtO2 attained during an oxygen challenge
Hlatky *et al.*[70]	The response of PbtO2 to hyperoxia was determined by measuring rCBF changes (using a stable xenon–enhanced computed tomography) in the vicinity of the PO2 probe. (n = 83 patients with severe TBI)	First report to suggest that ''at-risk'' peri-lesional brain tissue, which is most likely to benefit from the effects of hyperoxia is paradoxically the least likely to receive it
Tisdall *et al.*[69]	Cerebral microdialysis, brain tissue oximetry, broadband near-infrared spectroscopy (NIRS) to measure cytochrome C oxidase levels (n = 8 patients with severe TBI)	First report to use NIRS as well as microdialysis to show improved aerobic metabolism following brief exposure to hyperoxia

course of the injury. Another shortcoming of this study is the small sample size (n = 8) of patients which obviated analysis of aerteriovenous oxygen difference to a satisfactory statistical power.[12] The only conclusion we can derive from this otherwise good study is that short exposure to hyperoxia in the delayed phase of TBI likely does not cause improvement.

Another study that failed to show beneficial effects of hyperoxia in head injury came from Diringer et al.[17] This study must be lauded for the pioneering measurement of cerebral metabolic rate for oxygen. However, the study has several shortcomings, least of which is the small sample size of only 5 patients. The authors themselves admit that no patient was studied fewer than 12 hours post-injury and that the PET studies were done after only 1 hour at 100% FIO2. Similar to the study of Magnoni et al.[29], this study did not provide a suitable window to administer the therapy, namely early and prolonged.

From first principles, peri-lesional tissues are the foci propagating secondary damage and their salvage represents a neuroprotective effect. Oxygen-15 positron emission tomography (^{15}O-PET) has been used to show that normobaric hyperoxia administered following TBI confers a preferential metabolic advantage to this "at risk" peri-lesional tissue as measured by improved local cerebral metabolic rate of O2 (CMRO2) and PbtO2.[67] Authors claim reduction in lesion volumes by as much as 100ml in some patients as a result of normobaric hyperoxia.[67] Although some criticism has been raised on statistical grounds,[68] the observed improvements were independent of microdialysate and global ^{15}O-PET changes, suggesting additional, undetermined mechanisms.[67]

Notwithstanding, this hypothesis has been further confirmed by Signoretti et al. using ^{1}H-MR spectroscopy to detect N-acetylaspartate, a surrogate marker of neuron-specific mitochondrial impairment in patients with TBI.[20] In this study, ^{1}H-MR spectroscopy revealed areas of reduced N-acetylaspartate within brain tissue peripheral to the traumatic lesion (undetected by CT) suggesting that the hyperoxia therapy is likely to have a more potent effect on these peri-lesional areas.[20]

Further confirmation of this hypothesis comes from the study of Tisdall et al.[69] who used broadband near-infrared spectroscopy (NIRS) to measure cytochrome C oxidase concentrations indicative of mitochondrial function alongside microdialysis. Exposure to hyperoxia in 8 patients with severe TBI, even though it was of brief duration, resulted in significant increases in cytochrome C oxidase levels, as well as improved lactate to pyruvate ratios all suggestive of improved mitochrondrial function.[66]

However, cerebral PbtO2 increases in hypoperfused peri-lesional areas to a lesser degree when compared to areas with unimpaired CBF as shown by measuring cerebral blood flow changes using Xenon-CT.[70] This again suggests the possibility of more than one beneficial pathophysiologic mechanisms.

Normobaric hyperoxia in acute stroke

In a pilot study, Singhal et al.[71] showed that if started within 12 hours, normobaric hyperoxia transiently improved clinical features and MRI parameters of ischaemia. This study built on previous animal models of stroke which confirmed normobaric hyperoxia to decrease infarct volume[72,73] and MRI abnormalities.[74] A caveat is that Singhal et al.[71] did not note significant difference in outcome between control and treatment groups at 3 months. However, hyperoxia might offer stability in the short-term and thus increase the therapeutic window for other treatments such as thrombolysis.[75] Interestingly, intermittent use of hyperoxia was shown to promote ischaemic tolerance in a rat model.[76,77]

Building on their previous work, Singhal et al.[78] performed multivoxel magnetic resonance spectroscopic imaging and diffusion/perfusion MRI in patients with stroke exposed to normobaric hyperoxia or room air with imaging performed before, during and after therapy. By demonstrating decreased lactate levels and preserving N-acetylcysteine levels, they confirmed a neuroprotective role and concluded that normobaric hyperoxia improves aerobic metabolism.

Indeed, a small study in patients with middle cerebral artery strokes given 40% FIO2 oxygen by venturi masks has shown decreased mortality and fewer complications.[79] As with TBI trials, further studies are mandated.

Other benefits

The effects of normobaric hyperoxia on postoperative wound infections is an interesting albeit controversial topic. The premise for defence against surgical site infections is that oxidative killing of pathogens by neutrophils depends on tissue oxygen partial pressure, which is topped-up by arterial hyperoxia. Another prospect is that hypoxia can be prevented or reversed, thereby limiting local necrotic changes which are likely to become infected. Although there is some evidence (albeit controversial) that hyperoxia prevents wound infections in general surgery patients,[80,81] this is lacking in neurosurgery. Additionally, hyperbaric oxygen has been shown to improve neovascularisation[82] and bone remodelling[83] and a similar role of normobaric hyperoxia may be hypothesised.

Adverse effects

We will now review potential problems with high O2 therapy.

Pulmonary considerations

Lung function is a crucial determinant of PbtO2. Rosenthal *et al.*[84] elegantly showed that the ratio of PaO2 to PbtO2, named the PF ratio, is a major determinant of the maximal PbtO2 attained during an oxygen challenge, with higher PF ratios achieving greater PbtO2. The major concern regarding the clinical use of normobaric hyperoxia is its pulmonary side-effects. Hyperoxia has been shown to reversibly induce reactive oxygen species in rat lung capillary endothelial cells following 90 minutes' exposure to 70% oxygen.[85] The unit pulmonary toxic dose (UPTD) is the measure of cumulative oxygen toxicity for various exposures to O_2 and normobaric hyperoxia appears to increase this significantly greater than hyperbaric oxygen therapy,[11] further fuelling the normobaric hyperoxia versus hyperbaric oxygen debate. Furthermore, a recent study on mice showed that hyperoxia increases ventilator-induced lung injury.[86]

Additionally, severe chronic pulmonary disease also presents a theoretical contraindication to hyperoxia therapy because their respiratory drive may have switched from hypercapnic to hypoxic drive—hyperoxia would abolish this drive to initiate breathing and respiratory acidosis would ensue. However, this is a controversial area and as such these speculations may be premature.[87]

In practice, however, the resulting clinical manifestation is pulmonary absorption atelectasis,[88,89] which, in gestalt, is likely to be transient and abated by positive pressure ventilation.[90] However, none the clinical studies on hyperoxia have reported evidence of atelectasis. Moreover, this setback can be mitigated by use of a lesser FIO2, for example 60%.[91] Second, in a cohort of 52 terminally brain-damaged patients exposed to prolonged normobaric hyperoxia, no pathological evidence of lung damage was noted at autopsy.[92] Additionally, other forms of lung comorbidity such as aspiration pneumonitis, lung contusion and adult respiratory distress syndrome all too often coexist and the potential contribution of oxygen toxicity may be eclipsed and objective evidence of oxygen toxicity may be hard to ascribe.[93]

Oxidative stress

Although free radicals are key to the pathophysiology of neuronal death in TBI[94] and stroke,[19] and hyperbaric oxygen therapy is known to increase oxidative stress,[95] there is only preliminary evidence that hyperoxia may increase this via hydrogen peroxide production.[96] In contrast, FIO2 of 100% did not increase free radical production in a rat model of acute subdural haematoma,[97] and this was confirmed by Singhal *et al.*[73] who showed that normobaric hyperoxia in a rat model of ischaemic-reperfusion injury did not increase oxidative stress. On the other hand, free radical scavengers have been used as an adjunct to hyperbaric oxygen on a small clinical stroke study[98] and an animal study[99] and were found to be of benefit and indeed they may also show benefit as adjunct therapy to normobaric hyperoxia.

Hyperoxia in paediatrics

In cerebral palsy, stroke-like damage is believed to occur in the context of foetal distress perinatally and cell death is similar to that seen in stroke and TBI in many ways.[100] However, the use of hyperoxia is unlikely as yet in paediatrics for any indication (including TBI and the rare juvenile stroke syndromes) because of the risk of retinopathy of prematurity, which is caused by hyperoxia, particularly in the neonate.[101] Despite controversy on when to use oxygen therapy even for cardiorespiratory parameters,[102] a clear risk-benefit analysis is hard to establish.

Conclusion

In this paper we have reviewed normobaric hyperoxia therapy for TBI and stroke. Throughout, we emphasise our working hypothesis that normobaric hyperoxia must be administered early in the injury and for a prolonged period of time to prevent secondary damage since the pathophysiology of acute neuronal death is no longer considered an instantaneous irreversible event occurring at the time of injury.[103] Some supporting evidence comes from animal studies, which is suggestive but clearly not interchangeable with human studies. Nonetheless, all studies testing this particular hypothesis have suggested efficacy in improving stroke and TBI. Despite theoretical concerns, particularly those of oxygen toxicity, all studies have found normobaric hyperoxia to be safe and further mechanistic studies are clearly mandated.

So long as adverse effects such as pulmonary toxicity are not found, a megatrial similar to the MRC CRASH trial,[104] testing a simple methodology would be called for,[68,91] for example an increased FIO2 of 60%, administered within 1 hour of TBI for a duration of 24 hours. A multicentre trial would have further benefits and we would welcome collaboration on a project as such. In conclusion, as it represents a simple, minimally invasive, and easily applicable adjunct in the early management of TBI, we believe evidence presented in this review justifies such a trial.

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