

The efficacy of hyperbaric oxygen in hemorrhagic stroke: experimental and clinical implications

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Submitted: 30 June 2016

Accepted: 10 September 2016

Arch Med Sci 2017; 13, 5: 1217–1223

DOI: 10.5114/aoms.2017.65081

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Abstract

Hemorrhagic stroke, accounting for 10–30% of stroke cases, carries high rates of morbidity and mortality. This review presents the current knowledge on the efficacy of hyperbaric oxygen (HBO)-based modalities in the preclinical research on hemorrhagic stroke. Both preconditioning and post-treatment with HBO are considered as prospective therapeutic options. High efficacy of HBO therapy (HBOT) for brain hemorrhage has been noted. We found that moderate hyperbaric pressures appear optimal for therapeutic effect, while the therapeutic window of opportunity is short. HBO preconditioning offers more modest neuroprotective benefit as compared to HBO post-treatment for experimental intracerebral hemorrhage. We advocate for mandatory calculations of percent changes in the experimentally investigated indexes of HBO effectiveness and stress the need to design new clinical trials on HBO for hemorrhagic stroke.

Key words: intracerebral hemorrhage, subarachnoid hemorrhage, brain edema, preclinical research.

Introduction

Hyperbaric oxygen (HBO, 100% oxygen above 1.0 atm absolute; ATA) may not seem to be an intuitive intervention for intracerebral hemorrhage (ICH), as opposed to cerebral ischemia where it may augment oxygen supply to the ischemic territory [1]. It is more difficult to conceptualize the benefit from HBO therapy (HBOT) for bleeding in the brain. However, this type of stroke also involves a hypoxic component in the tissue surrounding the hemorrhagic lesion, with cells striving for oxygen [2]. Venules and arterioles contract in response to HBOT, which may theoretically attenuate the bleeding. It also may lead to a diminution in cerebral blood volume and edema, providing relief from increased intracranial pressure and thus an improved microcirculation [3]. The HBO may also target the phenomena underlying secondary brain injury after hemorrhage, including oxidative stress, apoptosis, autophagy, and inflammation, while boosting brain regeneration and functional performance [4].

Worldwide, across distinct human populations, from 10% to 27% of strokes are hemorrhagic [5]. In the category of hemorrhagic strokes is the subarachnoid hemorrhage (SAH), in which the blood, most often from a ruptured aneurysm of an intracranial artery, extravasates between the arachnoid and pia mater membranes [6]. The ICH refers to bleeding with-

in the tissue of the brain, most often the basal ganglia [7].

Animal models of hemorrhagic stroke are useful for assessing cerebral pathophysiological phenomena modified by investigational therapies as well as underlying molecular alterations [8]. These models also allow for determination of the effectiveness of HBO with respect to diverse and clinically relevant hemorrhagic brain injuries and treatment regimens, including both post-treatment and preconditioning approaches. Assessing HBO effectiveness requires clearly defined indexes of hemorrhagic injuries. Targeting brain edema, which is a good indicator of hemorrhage-induced brain injury, may provide a focus for therapeutic interventions. As for cerebral ischemia, infarct volume or the extent of cell damage in vulnerable anatomical brain regions is often evaluated. For hemorrhages, on the other hand, investigators must select the analyzed areas of cell damage, which can be subjective. In addition, lesion volume is not commonly determined in hemorrhagic stroke models. Instead, percent reductions in water content referenced to levels in the control tissue may provide an estimate of HBO effectiveness.

Preclinical studies have shown that edema severity strongly correlates with neurologic impairments after ICH [9]. Brain edema reduction also allows for an approximate comparison of HBO effectiveness between hemorrhagic and ischemic brain injuries. The purpose of this review was to identify hemorrhagic conditions and treatment regimens that are associated with the highest percent reductions in brain injury indicators with HBO therapy, with the goal of facilitating its transition to clinical trials.

Subarachnoid hemorrhage and hyperbaric oxygen

The SAH accounts for 5–10% of all strokes [10], affects relatively young people, carries high mortality, and leaves one third of patients with a lasting disability [11]. Upon the initial bleed, there is a profound decrease in cerebral blood flow, which could be considered as a mechanism for reducing bleeding; however, if the hypoperfusion persists beyond several minutes, brain ischemia arises and cell hypoxia ensues [12]. This phenomenon may explain the presence of injured cells remotely from extravasated blood collections. Especially because of this distant ischemic injury, HBO can be considered as a potentially beneficial therapeutic option.

Until recently, HBO was not used in the early period after SAH, and its clinical utility for SAH was limited to patients who developed cerebral vasospasm following the subarachnoid bleeding [13]. The SAH pathophysiology includes global cerebral ischemia arising by a mechanism of an

immediate increase in the intracranial pressure and a drop in cerebral perfusion pressure after bleeding, which induces robust expression of hypoxia-inducible factor-1 α that peaks at 24 h after the ictus [14, 15].

The robustness of endpoint measures for SAH is limited because morphological injury after SAH is not clearly delineated. Therefore, in the assessment of HBO efficacy after hemorrhage, researchers have used cell counts and indexes of brain injury that relate to brain edema and swelling in predefined regions of interest. In one study [15], HBO administered at 2.8 ATA for 2 h starting at 60 min after an experimental SAH reduced the increase in wet brain weight by 56.3% and reduced the increase in blood volume by 61.45%. The use of HBO was also associated with a statistically significant improvement in neurological function in that study. In another investigation, the action of HBO at the above parameters led to a decrease in malondialdehyde concentration in the cerebral cortex by 64.6% at 6 h and by 81.75% at 24 h after bleeding, as compared to the untreated group. That study confirmed that HBO can reduce oxidative stress-induced brain damage after SAH [16].

In a single hemorrhage SAH model producing 50% or more angiographic vasospasm, HBO at 3 ATA for 1 h, applied one day after SAH, reduced the increment in neurological severity score by 62.5% at 3 days after SAH, and by 72.6% at 10 days after SAH, compared to the results with a normobaric oxygen treatment [17]. However, not all indicators of SAH-induced brain injury have proved amenable to HBO. One-hour-long hyperbaric oxygen treatment at 3 ATA, which was first applied at 24 h after SAH and repeated daily over 7 days, exerted no effect on cerebroventricular volume expansion (experimental hydrocephalus), as determined on day 21 in the endovascular perforation model of SAH [18]. Nevertheless, HBO improved neurological deficits in hydrocephalic animals 14 days after SAH and improved spatial learning and memory abilities between days 17 and 21 [18]. Although it may seem clear that HBO does not ameliorate hydrocephalus after SAH, other treatment regimens (with the inclusion of acute treatment) and modified hyperbaric parameters need to be tested before an ultimate conclusion can be drawn.

Hyperbaric oxygen for intracerebral hemorrhage

Nontraumatic ICH accounts for about 15% of all strokes [19] and is associated with a 50% mortality rate at 1 year [20]. Preclinical studies have compared different hyperbaric levels for oxygen treatments to reduce ICH brain injury. Following intracerebral injection of 200 μ l of blood, HBO

treatment was used at 1.0, 1.8, 2.0, and 2.2 ATA to alleviate brain edema determined on the third and fifth days after hemorrhage in rabbits. These authors found that HBO at 2 ATA exerted an optimal effect. At 2 ATA, the excess in brain tissue water content over the sham level was reduced by 67.7% on day 3 and 79.5% on day 5 as compared to the untreated control [21]. The HBO at other pressures (1.8 ATA and 2.2 ATA) reduced brain water content by about 40% on the third and fifth days. A reduction in aquaporin 4 (AQP4) expression in the hemorrhagic brain accompanied the reduction in brain water content. Interestingly, the 2 ATA level has been adopted in several other studies of HBO's effects on ICH.

In addition, HBO for ICH is associated with a rather short therapeutic window of opportunity, although it appears to be longer (hence the better translational potential) in younger individuals. Zhou *et al.* determined that in adult mice with experimental ICH (30 μ l of autologous blood injection), HBO (60 min at 3 ATA) initiated within 30 min but not 60 min after the ictus alleviated edema and improved neurological outcomes [22]. With this early HBO treatment, the excess of brain water content with respect to the nonhemorrhagic hemisphere was reduced by 50% on day 3. Also at 3 days, early HBO reduced the excess of brain water by 53% after collagenase-induced bleeding (0.03 U). In a neonatal model of hemorrhage to the subependymal germinal matrix, HBO (2.5 ATA for 1 h) administered at 1 h after collagenase injection was associated with an improvement in cognitive function at 3 weeks after the hemorrhage (T-maze and Morris water maze testing) and in sensorimotor function at 4 weeks. HBO also had a reducing effect on brain atrophy, splenomegaly, and cardiac hypertrophy determined at 1 month after injury [23].

The effectiveness of early HBO against brain edema was also examined in a minipig model of ICH at high altitudes. The HBO (2.5 ATA for 1 h) was administered 30 min after a 3 ml blood injection. The intervention resulted in a 38.7% reduction in perihematomal edema 24 h after ICH [24]. Thus, the brain water reduction was more modest than the complete reduction achieved with 2 ATA and the 74.8% reduction with 2.2 ATA as shown previously by Wu *et al.* at 24 h after ICH in rabbits [21].

Of note, the research on HBO for ICH has addressed possible interactions between oxygen and blood degradation products, which may pose a risk of aggravating brain injury. Researchers at the University of Michigan found diverse effects of treatment with HBO for ICH (attenuated or enhanced brain edema) depending on the type of blood components administered [25]. The HBO (3.0 ATA for 1 h), initiated 1 h after autologous

blood injection, produced a beneficial effect. In contrast, HBO aggravated brain edema induced by ferrous iron (released upon clot lysis). These data may suggest that more research is needed regarding the safety of HBO use upon hematoma degradation and absorption phases.

Hyperbaric oxygen conditioning for intracerebral hemorrhage

One way to target ICH-induced brain injury is HBO preconditioning (HBO-PC), which has also been analyzed for effectiveness. Conditioning for ICH allows interactions of HBO with the blood clot to be avoided, although currently the applicability of preconditioning is limited to a few hospital and pre-hospital scenarios. Qin *et al.* addressed the issue of an optimal HBO-PC regimen by using an autologous blood (100 μ l) model of ICH. They showed that with five 1-h sessions of 3 ATA HBO-PC, the increment in perihematomal brain water content was reduced by 52.1% (from 3.2% excess to 1.5%) on day 1, followed by a 23.2% reduction (from 4.3% to 3.3%) on day 3 after blood injection. Two or three HBO sessions were ineffective [26].

In another study in rats, HBO-PC (5 sessions; 5 HBO) at 2 ATA reduced brain edema by 40% and 22% in the ipsilateral cortex and basal ganglia, respectively, 72 h after autologous blood injection (80 μ l). In addition, the HBO-preconditioned group exhibited a significantly reduced neuronal degeneration count around the hematoma, decreased by 20.7, 13.3, and 14.6% as compared to the ICH group at 12 h, 24 h, and 24 h, respectively [27].

The ICH produced with a smaller hematoma volume (50 μ l) in rats was preconditioned with 5HBO at 2 ATA. The conditioning reduced excessive peri-hematoma brain water content by 53.9% at 72 h after the hemorrhage [28] as compared to the untreated group.

In these studies, preconditioning yielded smaller reductions in brain water content than with early post-treatment with HBO at 2 ATA, associated with a 67.7% reduction rate on day 3 [21]. Likewise, the reductions in AQP4 expression were smaller with 2 ATA HBO-PC as compared to 2 ATA HBO treatment: 39.2% vs. 66.7% and 52.83% vs. 89%, as determined on days 3 and 5, respectively [21, 28].

These results may indicate greater efficacy of HBO when it is given after the hemorrhage as compared to its use as preconditioning. The findings may also indicate synergy of HBO post-treatment mechanisms with endogenous defenses that are activated by the injury itself.

In addition, the postconditioning approach with HBO should be considered after the hemorrhage in order to stimulate brain adaptation to injurious sequelae of the bleeding [29–31]. The HBO post-

conditioning stimulus would most likely be the repeated HBO exposures, of short duration, and ATA levels that are relatively high although adjusted so as not to induce convulsions [32, 33]. Such a procedure applied shortly after the bleeding could rapidly activate antioxidant and anti-inflammatory defenses, later used against blood-induced oxidative stress and neuroinflammation.

It can be quite insightful to compare the anti-edematous effects of HBO in cerebral hemorrhage and cerebral ischemia. When HBO at 2.5 ATA for 2 h was initiated at 1 h after endothelin-induced focal cerebral ischemia, a 38.6% reduction in excess brain water content was noted in the ischemic hemisphere at 24 h [34]. One hour of 3 ATA HBO administered after 2 h middle cerebral artery occlusion (MCAO) in rats led to a 43.1% reduction in focal edema volume at 24 h [35]. This 30–40% edema reduction range with HBOT (or closer to 20% in permanent ischemia) has been reported by most experimental studies of focal ischemic stroke [36, 37]. Thus, reductions in brain water content with HBO seem smaller after focal brain ischemia than after hemorrhage, with over 70% reductions reported with HBOT and 50% with HBO-PC at 24 h after hemorrhage [21, 26]. This result may indicate that relatively mild, predominantly perihematomal edema after hemorrhage more effectively responds to HBOT.

Clinical findings

Clinical treatment for brain edema after ICH remains mostly supportive (steroids, hyperventilation, mannitol). Several major clinical trials of investigational therapies for ICH did not use hyperbaric oxygen. Those studies, such as INTERACT-2, ATACH-II and CLEAR-III, yielded predominantly disappointing results. INTERACT-2 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2) investigators reported that the early, intensive lowering of blood pressure (BP) did not result in reduced rates of the primary outcomes [38]. Also the ATACH-II (Antihypertensive Treatment of Acute Cerebral Hemorrhage II) trial showed no benefits of intensive BP lowering in patients with intracranial hemorrhage [39]. CLEAR III (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III) tested the use of alteplase to quickly remove blood from ventricles after ICH, which however did not significantly improve the primary endpoints [40]. In STICH (Surgical Trial in Intracerebral Haemorrhage) no overall improved clinical benefit was seen from early hematoma evacuation [41].

Limited benefits from clinical trials conducted so far for brain hemorrhage leave room for testing other therapies, and HBO is certainly one of the treatments to consider. Previous authors have suggested that responsiveness to HBO may help to

determine the surgical intervention for putaminal hemorrhage [42]. Others have suggested a role of HBO in arresting the spread of hemorrhage [43]. Moreover, more recent clinical trials examined the effect of HBO on ischemic and hemorrhagic stroke. Repeated sessions of hyperbaric oxygen (40 daily sessions, 5 days/week, 90 min each, 100% oxygen at 2 ATA), initiated 6–36 months after stroke, improved neurological functions and life quality of patients with hemorrhagic or ischemic stroke [44]. Multiple HBO treatments (40–60× at 2 ATA) started 3–180 months (median: 19–23 months) after stroke also reduced memory impairments in hemorrhagic and ischemic strokes [45].

However, HBO also shows repair and regeneration potential in clinical studies of neurologic conditions other than brain hemorrhages, including autism, traumatic brain injury and post-concussive symptoms (PCS). All these studies stress the repair and regeneration properties of HBOT. Also, hyperbaric oxygen therapy has long been cleared by the FDA and Undersea and Hyperbaric Medical Society for use in decompression sickness (DCS) by countering pathophysiological sequelae of decompression including injury to the endothelia [46]. Studies have shown that HBO may regenerate endothelial function, which may provide an important mechanism of HBOT for DCS [47].

There are several positive studies of HBO for PCS. A study by Boussi-Gross of HBO for PCS after mild traumatic brain injury showed an improvement with a delayed treatment of 40 to 60 daily HBO sessions at 2 ATA [48]. However, the study titled “Hyperbaric Oxygen Therapy (HBO2T) for Post-Concussive Symptoms (PSC) After Mild Traumatic Brain Injury (mTBI)” used 40 once-daily hyperbaric oxygen sessions at 2 ATA over a 10-week period and found no effect on post-concussive symptoms, whereas an improved total score in the hyperbaric groups could be due to nonspecific effects [49]. As for those ineffective trials, inappropriate sham groups and small sample size have been a concern to other researchers [50]. Lack of effectiveness of HBO for PCS in some studies was suggested to depend of several factors including a delayed treatment time [50]. Likewise, even though the “Hyperbaric Oxygen Therapy in Chronic Stable Brain Injury” (HYBOBI) study reported safety of HBOT (60 daily HBO sessions at 1.5 ATA 100% oxygen) for stroke, anoxia or trauma, the neurological results were inconclusive, despite many participants showing improvement. The investigators expressed a need for more compelling evidence from carefully designed clinical trials [51].

In one study of HBO for autistic children it was noted that the participants improved on the Clinical Global Impression scale as well as the Autism Treatment Evaluation Checklist (ATEC) with 40 hyperbaric treatments at 1.3 atm [52]. Another clin-

ical trial confirmed improved cerebral flow in the white matter of children and improved neurological performance on ATEC [53]. In addition, by now there have been around 10 positive studies of HBOT for cerebral palsy, with over 600 participants [54]. However, it needs to be noted that 40 HBO treatments at 1.5 ATA over an 8-week period in children with cerebral palsy was no more effective than hyperbaric air (HBA) in improving motor function [55]. Others have pointed out an improvement in both HBA and HBO groups in that study, and argued that 14% oxygen at 1.5 ATA should not be considered a placebo group, while the role of hyperbaria alone should be meticulously addressed in further studies [54, 56].

It is difficult not to note that novel clot removal approaches may create new opportunities for HBO use for these patients. With the clot gone, the risk of interactions between oxygen and blood degradation products is much attenuated. New research will evaluate whether oxygen side effects can indeed be reduced after blood clot evacuation. Genetic factors which play a role in cerebral hemorrhages [57] should also be considered as potentially determining the response to HBOT.

As for SAH, studies have shown that clinical outcomes of endovascular coiling of a ruptured aneurysm may even surpass those associated with open skull surgery [58]. The advent of endovascular coiling also creates a more suitable therapeutic option than surgery for a combination with HBO to improve outcomes, which should be further tested clinically.

Future research directions

To evaluate HBO-based modalities and optimal treatment regimens for hemorrhagic stroke, experimental studies should calculate percent reductions in brain water contents as well as other indexes of brain protection with the treatment.

Further research will establish the hemorrhagic injury characteristics that are most responsive to HBO treatment. The use of MRI, where available, may increase quantitation confidence, by allowing total lesion assessment between treated and untreated groups, and also stratifying the impact of HBO depending on revealed penumbral patterns. New translational research needs to evaluate the effectiveness of HBO for hemorrhage with comorbidities, which may challenge the results most often established in young and healthy laboratory animals [59].

In addition, studying the effect of HBO on hemorrhage-induced brain inflammation appears to be a plausible research direction. The inflammatory response greatly contributes to perihematomal edema and secondary brain injury after ICH [60]. The HBO, by reducing HIF-1 α expression and func-

tion, may target regulatory mechanisms of inflammatory cells dependent on HIF-1 [61]. Translational studies showed that HBO effectively reduced inflammation in the brain in traumatic brain injury and cerebral ischemia as well [62–64]. As for underlying mechanisms, HBO reduces excessive microglial activation [65], reduces proinflammatory cytokines IL-1 β and TNF- α , and activates anti-inflammatory IL-10 [62, 66].

One clinical study showed markers of reduced inflammation in patients pretreated with HBO at 2.4 ATA before cardiac procedures on cardiopulmonary bypass [67], and several clinical trials directed at targeting diseases of musculoskeletal and gastrointestinal systems with an inflammatory component also showed clinical improvement of treated patients [68, 69]. The potential of HBO to target inflammation, and thereby to prevent the exacerbation of hemorrhagic injuries, needs to be further verified.

The effects of HBO on hematoma enlargement additionally need to be examined in further studies. To this end, new models replicating these phenomena are needed [70, 71]. Another issue to be determined is what mechanisms of HBO-induced tissue regeneration are at play after hemorrhage [4].

Regardless of the options pursued, good laboratory practice needs to be maintained for all preclinical studies to advance to clinical trials. To this end, the updated STAIR and RIGOR criteria provide guidelines that are useful in preclinical hemorrhagic stroke research, despite being originally focused on ischemic stroke [72].

Conclusions

Preclinical research shows that HBO exerts a neuroprotective effect against hemorrhagic brain injuries. The impact of HBO on the brain water content and other indices, as reviewed here, reveals a higher effectiveness of the post-treatment approach involving moderate pressures of oxygen (~2 ATA) in experimental ICH, and a tendency to higher pressures for beneficial effects to occur after SAH. A short therapeutic window characterizes both applications, however.

The robust brain-protective effects of HBO for hemorrhagic injuries, not limited to relief from hypoxia, may justify its use for hemorrhagic stroke, which awaits verification in clinical trials.

Conflict of interest

The authors declare no conflict of interest.

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