Central nervous system oxygen toxicity during routine hyperbaric oxygen therapy

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Hampson N, Atik D. Central nervous system oxygen toxicity during routine hyperbaric oxygen therapy. Undersea Hyperb Med 2003; 30(2): 147-153 - Hyperbaric oxygen therapy is associated with a recognized risk for clinically apparent central nervous system (CNS) toxicity. The risk for oxygen-induced convulsions during routine hyperbaric treatment of most routine conditions is extremely low. However, reports from the 1980's describing the incidence of CNS oxygen toxicity differ significantly from more recent reports since 1996. This retrospective study was conducted to determine the incidence of hyperbaric oxygen-induced seizures among patients treated at our facility for routine, non-emergent indications. In addition, the period studied was selected to examine the incidence of CNS oxygen toxicity between two brands of oxygen delivery hoods. We reviewed our treatment experience for approximately 10,000 routine patient treatments performed prior to and following a change in the brand of oxygen hoods used. Among 20,328 total patient treatments performed from 1992 to 2001, 6 patients experienced an oxygen-toxic seizure for an overall incidence of 1 in 3,388 treatments (0.03%). No difference in seizure incidence was seen between the two brands of oxygen hoods utilized. We conclude that the incidence of oxygen-toxic seizures in our patient population is approximately three-fold greater than historical reports and in agreement with more recent reports. The reason for this apparent increase in incidence of CNS oxygen toxicity is unknown.

Oxygen toxicity, hyperbaric treatment protocols

INTRODUCTION

Central nervous system (CNS) oxygen toxicity, as manifest by clinically apparent generalized seizure activity, is a recognized side effect of hyperbaric oxygen (HBO_2) therapy (1). Three reports from the 1980's describing large series of patients receiving HBO_2 therapy for miscellaneous routine and emergent conditions quote an incidence of CNS oxygen toxicity of approximately 1 in 10,000 hyperbaric treatments performed at 2.0 to 3.0 atmospheres absolute (atm abs) pressure (1-3). Two reports published since 1996 have described significantly higher incidences, ranging up to 1 in 1,800 treatments with certain protocols (4, 5).

The present study was conducted to examine the incidence of CNS oxygen toxicity among 20,000 patients treated with hyperbaric oxygen for routine, non-emergent indications, on an identical treatment protocol, and with oxygen delivery by head hood. As two brands of head hoods were utilized for oxygen delivery during the period studied, it additionally allowed for a comparison of the risk for CNS oxygen toxicity with use of each of the two devices.

METHODS

The study was approved by the Institutional Review Board of Virginia Mason Medical Center in Seattle. Data were obtained from treatment experience for patients who received hyperbaric oxygen therapy at the Virginia Mason Center for Hyperbaric Medicine. All patients were treated in a multiplace hyperbaric chamber. Patients included in the analysis were required to have been treated (1) for a routine, non-emergent indication, (2) on one specified hyperbaric protocol, and (3) with oxygen delivery by head hood. All included patients were treated at 2.36 atm abs, with 90 minutes of 100% oxygen delivery at treatment pressure, and with oxygen administration in three 30 minute breathing periods separated by 5 minute air breathing periods ("air breaks"). Patients were excluded if they were treated for an emergent indication, on a different hyperbaric treatment protocol, or had oxygen delivery via face mask, tracheostomy or endotracheal tube.

During the study period prior to October, 1997, the brand of oxygen delivery hood utilized was Sea-Long (model PN312). In October, 1997, the use of Amron hoods (model 8891) was begun. Both hoods were utilized interchangeably for two months, until the supply of Sea-Long hoods was depleted. All hoods were ventilated with 100% oxygen at a flow rate of 30 liters per minute. Carbon dioxide (CO_2) levels were not monitored inside the hoods.

Hyperbaric patient treatment logs were retrospectively reviewed to identify approximately 10,000 consecutive qualifying patients treated both prior to and following the change in brand of oxygen hood. Treatment indication was recorded for all patients. For patients experiencing CNS oxygen toxicity as defined by generalized seizure activity, medical records were reviewed in detail to extract information on patient demographics and medical history. Statistical comparisons were performed with using Fisher's Exact Test.

RESULTS

From August 6, 1992 to September 30, 1997, a total of 10,189 patient treatments meeting inclusion criteria were performed using the initial brand of oxygen delivery hood, complicated by 1 episode of CNS oxygen toxicity (0.01%). From January 1, 1998 to April 19, 2001, a total of 10,139 treatments were performed using the second brand of oxygen delivery hood, complicated by 5 oxygen toxic seizures (0.05%). The difference in incidence of CNS oxygen toxicity was not significantly different between the two periods ($p = 0.12$, Fisher's Exact Test). The overall incidence of seizures was 6 in 20,328 treatments, or 1 in 3,388 exposures.

Patient demographic information, diagnosis, and details relative to the time of seizure onset for each patient are listed in Table 1. Patient #1 was an 85 year old female receiving HBO_2 therapy for a nonhealing lower extremity wound. Her medical history was notable for hypertension and hypothyroidism. She experienced a seizure during her 1st HBO_2 treatment then completed 18 additional treatments without recurrence. Subsequent treatments were performed on a modified protocol which delivered 90 minutes of 100% oxygen at 2.36 atm abs in four 20 and one 10 minute breathing periods separated by 5 minute air breathing periods. Patient #2 was a 67 year old male being treated for soft tissue radionecrosis of the stomach following radiation therapy for esophageal cancer. He experienced a seizure during his 25th HBO_2 treatment then completed 10 additional treatments without recurrence. Post-seizure treatments were performed on the modified protocol. Brain computed tomography scan performed after his seizure was normal. Patient #3 was a 62 year old female receiving HBO_2 treatment for soft tissue

radionecrosis of the oral cavity following radiation therapy for head and neck cancer. She had received 40 hyperbaric treatments six months earlier without complication. She experienced a seizure during her 4th HBO_2 treatment in this course then discontinued therapy. Patient #4 was a 69 year old female receiving HBO_2 treatment for a compromised split thickness skin graft. Medical history was notable for rheumatoid arthritis being treated with low dose prednisone, chronic atrial fibrillation, hypothyroidism, hypertension, history of venous thromboembolism, and history of peptic ulcer disease. She experienced a seizure during her 1st HBO_2 treatment, then discontinued therapy. Patient #5 was a 54 year old female receiving HBO_2 treatment for soft tissue radionecrosis of the neck following radiation therapy for tongue cancer 18 years earlier. Medical history was otherwise notable for notable for hypertension, hyperlipidemia and history of stroke without neurological sequelae. She experienced a seizure during her 21st HBO_2 treatment, then completed 9 additional treatments without recurrence. Subsequent treatments were performed on the modified protocol. Patient #6 was a 76 year old male receiving HBO_2 treatment for soft tissue radionecrosis of the rectum following radiation therapy for prostate cancer. He experienced a seizure during his 16th HBO_2 treatment, then completed 29 additional treatments without recurrence. Subsequent treatments were performed on the modified protocol. All patients were neurologically normal after recovery from the acute seizure episode. None were administered anticonvulsant medication during post-seizure hyperbaric treatments.

Table 1 – Characteristics of patients experiencing CNS oxygen toxicity

Patient	Age	Sex	Indication for HBO_2	Total # Treatments	Treatment # with Seizure	O_2 Period with Seizure
1	85	F	Nonhealing wound	19	1	3
	67	M	Delayed radiation injury	35	25	2
3	62	F	Delayed radiation injury	4	4	3
4	69	F	Delayed radiation injury	1	1	1
5	54	F	Delayed radiation injury	30	21	2
6	77	M	Delayed radiation injury	45	16	3

Table 2 details number of patients treated for various routine conditions during the study period and the number of seizures that occurred. No diagnosis was associated with a significantly greater chance of seizure during hyperbaric treatment ($p = 0.51$, Fisher's Exact Test).

Table 2. Indications for hyperbaric treatment during study period.

Indications for HBO_2	Number of Treatments	Number of Seizures
Delayed Radiation Injury	12,882	4
Nonhealing wounds	5,813	1
Compromised flap/graft	1,208	1
Chronic osteomyelitis	425	0

DISCUSSION

The possibility that oxygen breathing under increased pressure can cause grand mal seizures was first described by Paul Bert in 1878 (6). Central nervous system oxygen toxicity resulting in generalized seizure activity is a well recognized complication of modern hyperbaric oxygen therapy. A number of factors relate to the risk for CNS oxygen toxicity. These include patient susceptibility factors, pressure at which 100% oxygen is administered, and duration of hyperbaric oxygen breathing periods. As seizures related to HBO_2 therapy are obviously undesirable, efforts are made to modify these factors to minimize risk for seizure activity.

As noted previously, a number of published reports have described the incidence of this complication of hyperbaric oxygen treatment. Previous reports are listed in Table 3. While the risk for oxygen toxic seizures is commonly quoted as 1 in 10,000 hyperbaric oxygen treatments (7), results from the prior reports are conflicting. The first three studies from the 1980's did demonstrate an average risk of seizure at approximately 1 in 10,000 exposures (1-3). Two more recent studies described significantly higher incidences (4, 5). When all the studies are reviewed in detail, it is apparent that the patient populations and hyperbaric treatment protocols differed significantly between and even within studies.

Table 3 – Reported incidence of CNS oxygen toxicity during hyperbaric oxygen therapy

Report (author, year)	Treatment Pressure (atm abs)	Number of Patient Treatments	Number of Seizures	Seizure Rate
Hart, 1987 (ref. 2)	2.0-3.0	Not stated	44	1 in 12,253
Davis, 1988 (ref. 1)	2.4	Not stated	Not stated	1 in 7,692
Davis, 1989 (ref. 3)	2.4	52,758	5	1 in 10,552
Welslau, 1996 (ref. 4)	2.4 - 3.0	107,264	16	1 in 6,704
Plafki, 2000 (ref. 5)	2.4 – 2.5	11,376	4	1 in 2,844

The first report by Hart and Strauss in 1987 described the authors' 20 year treatment experience (2). They broke the two decades into quartiles, noting a decrease in seizure incidence from 1 in 385 treatments to 1 in 12,253 treatments over time. They attributed this to improved patient selection and avoidance of conditions or medications which they believed increased risk for CNS oxygen toxicity. Treatment details provided in the paper indicate that a wide variety of conditions, both emergent and routine, were included. In addition, the analysis included treatments that were performed at pressures ranging from 2.0 to3.0 atm abs. Specific details about treatment protocols with respect to duration of oxygen breathing, the provision of air breaks, and equipment utilized for oxygen administration are not described in the paper.

In 1988, Davis and colleagues described a risk for seizure of 1.3/10,000 (1 in 7,692) hyperbaric treatments performed at 2.4 atm abs (1). The patient population and further details of the hyperbaric treatment protocol were not described. In 1989, Davis reported the side effects experienced during 52,758 hyperbaric treatments performed at two centers in San Antonio for a variety of conditions (3). Five seizures were noted. Patients were treated at 2.4 atm abs once or twice daily. Additional details of the treatment protocol are not available.

Conflicting with these results are two more recent studies from Germany. In 1996, Welslau and Almeling reported data collected from 19 hyperbaric centers in Germany described an incidence ranging from 1 in 1,800 to 1 in 9,000 treatments, depending upon the hyperbaric protocol utilized (4). Patients were treated for a variety of conditions, particularly acute otologic conditions such as acoustic trauma, sudden deafness, and tinnitus. In the entire experience, 16 generalized convulsions occurred in 107,264 hyperbaric treatments. Among 3,603 treatments performed at 2.5 to 2.6 atm abs and delivering 60 consecutive minutes of 100% oxygen without air breaks, 2 seizures occurred for a rate of 1 in 1,802 treatments. When 60 minutes of oxygen was administered at 2.5 atm abs in two 30 minute periods separated by an air break, the risk for seizure was 1 in 9,358 treatments. An intermediate risk for seizure at 1 in 3,725 was seen when 90 minutes of oxygen were administered in three 30 minute periods with air breaks at 2.4 atm abs. Equipment used for oxygen administration equipment was not described.

Finally, Plafki and co-workers described their experience from 11,376 hyperbaric treatments performed at two German hyperbaric treatment facilities (5). Patients were treated for a variety of non-emergent conditions, receiving either two 30 minute oxygen breathing periods at 2.5 atm abs or three 30 minute oxygen periods at 2.4 atm abs. Four seizures were seen, for an incidence of 1 in 2,844 treatments.

Comparison of the incidence of CNS oxygen toxicity from different reports is complicated by differing patient populations, treatment pressures, protocol for oxygen administration, and probably equipment utilized for oxygen delivery. This is true not only between studies, but also within studies, as evidenced above. The present study was conducted in an attempt to eliminate some of this variability. Prior studies have demonstrated that specific subgroups of emergent patients treated with HBO_2 are at increased risk for CNS oxygen toxicity, presumably due to associated CNS injury (8, 9). All patients included in the analysis were routine, stable patients treated on an elective, non-emergent basis. It has been previously demonstrated in a population of patients with a single indication for hyperbaric therapy that the risk for HBO_2-induced seizures differs with treatment pressure (9). All patients in this analysis were treated on an identical hyperbaric protocol. Finally, none of the prior studies reviewed above described the equipment used for oxygen delivery to the patient. All patients in the present review received oxygen by one of two brands of hood.

The results from the present study are remarkably consistent with those of Welslau (4) and Plafki (5). If one looks at the subgroups receiving three 30 minute periods of oxygen breathing at 2.4-2.5 atm abs in the report by Welslau, two or three 30 minute oxygen periods in that pressure range in the report by Pflaki, and three 30 minute periods at 2.4 atm abs in the present report, seizure rates of 1 in 3,725 treatments, 1 in 2,844 treatments, and 1 in 3,388 treatments are seen, respectively. It would thus appear that the true incidence of CNS oxygen toxicity with this protocol is approximately three times greater than the 1 in 10,000 reported in earlier publications. The reasons for this finding are less clear. At least one prior report included acutely ill patients, some of whom had acute brain injury (2). However, they would have been expected to have experienced a higher rate of oxygen-induced seizures, not lower. Part of the explanation may lie in the fact that one prior study used lesser pressures of hyperbaric oxygen (2). A lower seizure rate would therefore be expected. However, two reports with low seizure rates (1, 3) used the same treatment pressure as the present and those of Welslau and Plafki (2.4 atm abs).

One can only speculate as to whether patients with greater inherent risk for seizure are being treated more recently than previously. It is possible that as hyperbaric facilities gain experience, they are accepting more ill patients, even for routine therapy. It is also possible that more patients are being treated with specific factors that might lower seizure threshold, such as a history of cranial irradiation. In the present analysis, however, no greater number of seizures was seen in the group with chronic radiation injury than those with other indications for treatment. Characteristics of patients who experienced seizures are detailed in the Results section above. As medical records of patients without seizures were not abstracted, it is not possible to compare the two groups for differences in characteristics other than treatment indication.

It is possible that the equipment utilized for oxygen administration plays a role. Most of the earlier reports do not clearly define the number of patients treated in monoplace vs. multiplace chambers. The current study did not include any patients treated in monoplace chambers, precluding comment on the present-day risk for CNS oxygen toxicity in that environment. It is conceivable that the oxygen administration equipment used in more recent studies is more efficient and that higher concentrations of oxygen are being delivered to the patient, increasing risk for oxygen toxic seizures.

An alternate explanation related to equipment would be that carbon dioxide accumulation in head hood delivery systems contributes to an increased risk for oxygen toxicity. Concurrent hypercarbia is well known to potentiate oxygen toxicity (10). Earlier studies do not report the brand or model of head hood utilized. It is interesting to note that the hoods used in the present study had different designs, potentially contributing to differences in gas mixing and CO_2 accumulation. The Sea-Long model had oxygen supply and exhaled gas ports placed on opposite sides of the hood, approximately 32.5 cm apart. Ventilation gas flowing through the hood coursed around the patient's head, presumably mixing well with exhaled gas. The Amron hood studied had oxygen supply and exhaled gas ports placed adjacent to each other on the neck ring, approximately 8.6 cm apart. Theoretically, ventilation gas could enter and exit the hood without mixing completely with exhaled gas. While the difference in rate of seizures between the two hoods reported in this study was not statistically significant, there was a trend toward more frequent seizures with the latter style. Because CO_2 levels were not monitored inside the hoods, it is not possible to say whether this truly played a role.

Whatever the explanation, it is clear that non-emergent patients treated routinely on the hyperbaric oxygen protocol studied and with oxygen administered by head hood have a risk for CNS oxygen toxicity approximately three-fold greater than is commonly quoted. As the protocol selected for this study is widely used in routine HBO_2 therapy in North American multiplace hyperbaric chambers (11, 12), this information is of great importance with regard to fully informing patients of the risk of treatment.

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