Seizure incidence by treatment pressure in patients undergoing hyperbaric oxygen therapy

Marvin Heyboer III, M.D. [1], *Shane Jennings, M.D.* [1], *William D. Grant, EDD* [1], *Cindy Ojevwe, B.S.* [2], *Joseph Byrne, M.D.* [3], *Susan M. Wojcik, Ph.D.* [1]

[1] Department of Emergency Medicine, Division of Hyperbaric Medicine, SUNY Upstate Medical University, Syracuse, New York USA

[2] Medical Student, SUNY Upstate Medical University, Syracuse, New York USA

[3] Center for Wound Care and Hyperbaric Medicine, St. Joseph's Hospital, Fayetteville, New York USA

CORRESPONDING AUTHOR: Dr. Marvin Heyboer III – *heyboerm@upstate.edu*

ABSTRACT

Introduction: Hyperbaric oxygen (HBO_2) therapy uses different maximum treatment pressures. A side effect of HBO_2 is oxygen toxicity seizure. The purpose of this study was to determine the overall incidence of oxygen toxicity seizure and assess risk at different treatment pressures.

Method: A retrospective chart review was performed on patients who underwent HBO_2 at a university hospital and at an outpatient center. Statistical analysis was performed to determine overall incidence of seizure and identify risk factors including maximum treatment pressure.

Results: A total of 931 patients were identified representing a total of 23,328 treatments. The overall incidence of seizure was one in 2,121 treatments (five per 10,000). There were zero per 10,000 at 2.0 atmospheres absolute / atm abs (0/16,430), 15 per 10,000 at 2.4/2.5 atm abs (1/669) and 51 per 10,000 at 2.8 atm abs (1/197). There was a statistically significant difference for seizure between the different pressures (χ^2 (2, 23,540) = 31.38, $p < .001$).

Discussion: The overall incidence of oxygen toxicity seizure in this study is consistent with recent reports. This study demonstrated a statistically significant increased risk of seizure with increasing treatment pressure. Treatment at higher pressure should be chosen based on demonstrable benefit with a clear understanding of increased risk with higher pressure.

INTRODUCTION

Hyperbaric oxygen (HBO_2) therapy, treatment of patients with 100% oxygen (O_2) in a chamber at higher than atmospheric pressure, is recognized for treatment of various indications [1]. Examples include select problem wounds such as advanced non-healing diabetic foot ulcers, late-effect radiation injury (LER), decompression sickness and carbon monoxide (CO) poisoning. Different treatment pressures may be used depending on the indication. For example, advanced non-healing diabetic foot ulcers are commonly treated at 2 atmospheres absolute (atm abs), soft tissue radionecrosis (STRN) and osteoradionecrosis commonly at 2.4-2.5 atm abs, while emergent conditions such as decompression sickness are treated at 2.8 atm abs. The primary beneficial effects of HBO_2 are the result of hyperoxia [2,3]. HBO_2 has been shown to promote neovascularization through increased local growth factors and stimulation of progenitor stem cell release from bone marrow, improve leukocyte function and ameliorate ischemia reperfusion injury [4-14].

Patients receive benefits from HBO_2 through what can be described as a "controlled oxidative stress" [8]. However, oxidative stress has been known to produce adverse effects such as central nervous system oxygen toxicity in the form of seizures. The link between hyperbaric oxygen exposure and seizures was recognized as early as 1878 by Paul Bert [15]. Oxygen toxicity seizures are thought to be the result of the interactions of an increased number of free radical intermediates and other reactive oxygen species with the plasma membranes of neurologic cells as a result of the hyperoxia [16]. In particular, the reactive oxygen species lead to changes in electrical activity in the brain as a result of lipid peroxidation at the membranes [17]. In addition, there is evidence that increased

nitric oxide levels in the brain produce vasodilatation, which counteracts the cerebral vasoconstriction normally produced by the increased levels of oxygen [18].

Historically, O_2 toxicity seizures have been rare events, occurring in approximately one in 10,000 patient treatments [19]. However, more recent studies have reported an incidence of one in 1,800 and one in 2,844 patient treatments [20,21]. Previous publication has demonstrated an increased risk among patients treated for CO poisoning [22]. While there is an intuitive increased risk of seizure with increasing pressure, published studies demonstrating this risk are limited to the study by Banham in 2011 [23]. Further investigation and quantification of this risk would be helpful in standardizing treatment pressure among centers to minimize risk.

While there have been many advances in hyperbaric medicine, there continue to be various treatment protocols across institutions, which makes it difficult to compare various studies on therapeutic benefit. To this end, there is a need to increase our knowledge of risk *vs.* benefit at various treatment pressures. The goal of this standardization would be to minimize risk with maximum therapeutic benefit.

The purpose of this study was to determine overall incidence of O_2 toxicity seizures and assess whether there was a statistically significant difference in the incidence of O_2 toxicity seizures at various treatment pressures. In addition, this study evaluated other potential risk factors in treatment protocols, including total treatment time, air breaks and patient demographics.

METHODS

A retrospective chart review was performed on patients undergoing hyperbaric oxygen therapy from January 1, 2003, to June 30, 2011, at both an academic regional level 1 trauma center and an outpatient community hospital. All patients were treated in a monoplace chamber compressed with 100% oxygen. Patients were treated per institutional protocol for either 90 minutes or 120 minutes at 2 atm abs, 2.4/2.5 atm abs, or 2.8 atm abs as determined by the ordering physician. Air breaks were provided by mask for a total of 10 minutes when they were utilized.

Patients who experienced an oxygen toxicity seizure treated during this time period were identified. Information was collected on these patients and all others treated who did not experience an oxygen toxicity seizure during the same time period. Information collected included diagnosis, gender, age, total treatment time, maximum depth, use of an air-break, treatment time of seizure onset, and history of seizure, stroke, other CNS, diabetes, and alcohol abuse. The diagnoses were combined into five groups:

1) non-healing lower extremity ulcers;
2) chronic refractory osteomyelitis;
3) late effect radiation injury;
4) emergent conditions; and
5) other.

The overall incidence of oxygen toxicity seizure was determined. In addition, the incidence of oxygen toxicity seizure in patients treated at 2 atm abs, 2.4-2.5 atm abs and 2.8 atm abs was compared to determine the incidence of oxygen toxicity seizures at various pressures. Comparison of seizure incidence was also performed in patients who received air break[s] *vs.* no air break[s], diagnosis groups previously listed, and specifically CO poisoning patients.

All data was entered into a structured study-specific database. Data analysis was completed utilizing IBM® SPSS® v. 21 and MedCalc® v. 12.3 for summary statistics and statistical comparison between groups. Comparison between categorical groups was analyzed using χ^2 or Fisher's exact test when appropriate. Where indicated, individual χ^2 comparisons were further analyzed. Comparison of summary statistics were analyzed based on χ^2 test of proportions.

RESULTS

Overall Incidence

A total of 23,328 hyperbaric oxygen treatments on 931 patients were analyzed. Demographic data is shown in Table 1. Ten patients underwent 11 HBO_2 treatments that were associated with an oxygen toxicity seizure, and an additional 182 HBO_2 treatments without an associated seizure. There were 921 patients who underwent 23,135 HBO_2 treatments without associated seizure. There were a total of 23,317 HBO_2 treatments without seizure. The overall incidence of oxygen toxicity seizure was one in 2,121 or five per 10,000 treatments. Complete patient data for individual seizure cases including the time during the treatment and the treatment number when the seizure occurred are shown in Table 2. Seven patients continued treatment after their seizure, and one of those seven had a recurrent seizure.

Table 1: Demographic information on patients who did and did not experience an oxygen toxicity seizure during hyperbaric oxygen therapy

	Patients without seizure		Patients with seizure		
	N	*n* (%)	N	*n* (%)	*p*-value
GENDER	921		10		0.47
male		589 (64.0)		8 (80.0)	
female		332 (36.0)		2 (20.0)	
HISTORY					
past seizures	908	16 (1.8)	10	1 (10.0)	0.47
stroke	908	42 (4.6)	10	0	0.95
diabetes mellitus	908	355 (39.1)	10	4 (40.0)	0.79
alcohol use	910	51(5.6)	10	1 (10.0)	0.93
other CNS[a]	908	20 (2.2)	10	2 (20.0)	0.009
	N	*x* (SD)	N	*x* (SD)	
AGE	921	57 (18)	10	54 (17)	0.60

[a] Other CNS included transient ischemic attack (TIA), brain tumor, traumatic brain injury (TBI), soft tissue radionecrosis (STRN), dementia.

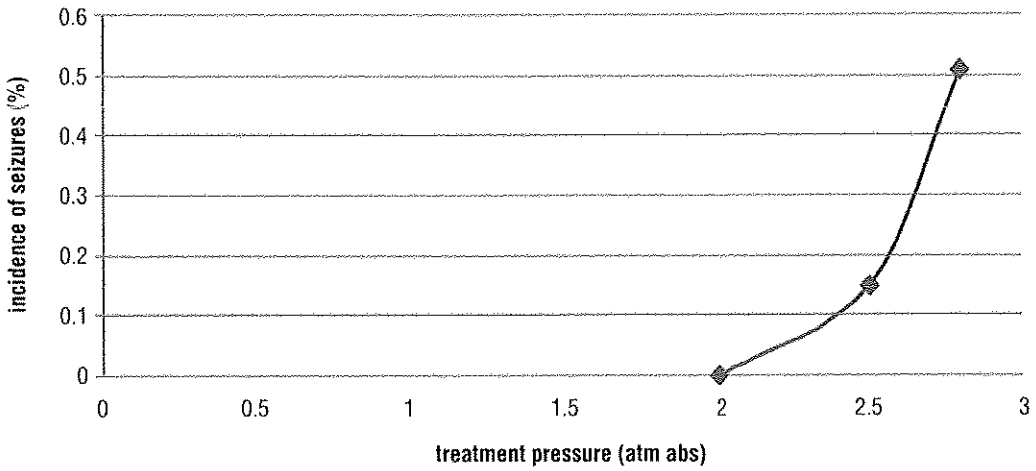
Table 2: Treatment details on patients who experienced an oxygen toxicity seizure during HBO_2 therapy

case	age	sex	indication for HBO_2* (atm abs)	maximum Tx pressure	total Txs*	Tx # of Sz (mins)	time to seizure	air break	past medical history*	prodromal symptoms reported
1	64	M	radiation cystitis	2.4	9	9	111	after	Type 2 DM	No
2	79	M	radiation cystitis	2.5	1	1	43	none	alcohol abuse	No
3	27	M	CRO	2.5	10	3	58	none	Type 1 DM	Yes
4	56	M	LER larynx	2.5	30	2	84	after	Type 2 DM	No
5	46	F	LER mandible	2.5	30	21	98	after	none	No
6	46	M	LER mandible	2.5	30	12	97	after	none	Yes
7	68	F	LER mandible	2.5	30	11	53	none	TIA, Type 2 DM	No
8	51	M	LER brain	2.5	22	14	68	none	astrocytoma	Yes
9	68	M	LER mandible	2.5	30	2/ 17	106/ 100	after/ after	none**	Yes/ Yes
10	32	M	CO poisoning	2.8	1	1	40	none	none	No

* CRO = chronic refractory osteomyelitis; LER = late effect radiation injury; CO = carbon monoxide poisoning; Tx = treatment; Sz = seizure; # = number; mins = minutes; DM = diabetes mellitus; T IA = transient ischemic attack; None = no reported history of seizure, stroke, other CNS, diabetes, alcohol abuse

** Patient experienced an oxygen toxicity seizure during two separate treatment encounters

Figure 1: Seizure incidence by hyperbaric oxygen treatment pressure



Pressure and time

The incidence of oxygen toxicity seizure increased with increased atmospheres absolute (Figure 1). There were zero per 10,000 at 2.0 atm abs (0/16,430), 15 per 10,000 at 2.4/2.5 atm abs (1/669) and 51 per 10,000 at 2.8 atm abs (1/197). There was a statistically significant difference for seizure between the different pressures (χ^2 (2, 23,540) = 31.38, p<.001). Individual comparisons resulted in a statistically significant difference between 2.0 atm abs and 2.4/2.5 atm abs (χ^2 (1, 23,342) = 21.2, p<.001) and between 2.0 atm abs and 2.8 atm abs (χ^2 (1, 16,628) = 20.25, p=.01).

While comparison of 2.4/2.5 atm abs *vs.* 2.8 atm abs did show a threefold increase in incidence, it did not reach statistical significance. Table 3 lists the number of patients, treatments and seizures by treatment pressure. In comparing treatment times, there was no statistical difference in seizure occurrence when comparing patients treated for 90 minutes *vs.* 120 minutes.

Air breaks

Receiving an air break was found to be a statistically significant risk factor for having a seizure (p<.001). There were six seizures out of 1,429 patient treatments (42 per 10,000, 0.42%) where an air break was given, while there were five seizures out of 21,899 patient treatments (2.3 per 10,000, 0.023%) where no air break was given. This was also analyzed by treatment pressure. At 2 atm abs there were 0/16,390 *vs.* 0/40 (no air break *vs.* air break, NS/not significant). At 2.4/2.5 atm abs there were 4/5314 (1/1329) *vs.* 6/1386 (1/231) (no air break *vs.* air break, p<.001). Finally, at 2.8 atm abs there was 1/195 *vs.* 0/3 (no air break *vs.* air break, p<.001). Among patients treated at 2.4/2.5 atm abs, those treated without an air break had a shorter treatment time of 90 minutes (98%), while those treated with an air break had a longer treatment time of 120 minutes (98%). The seizure occurred after the air break in all six treatments where seizure occurred in the setting of an air break.

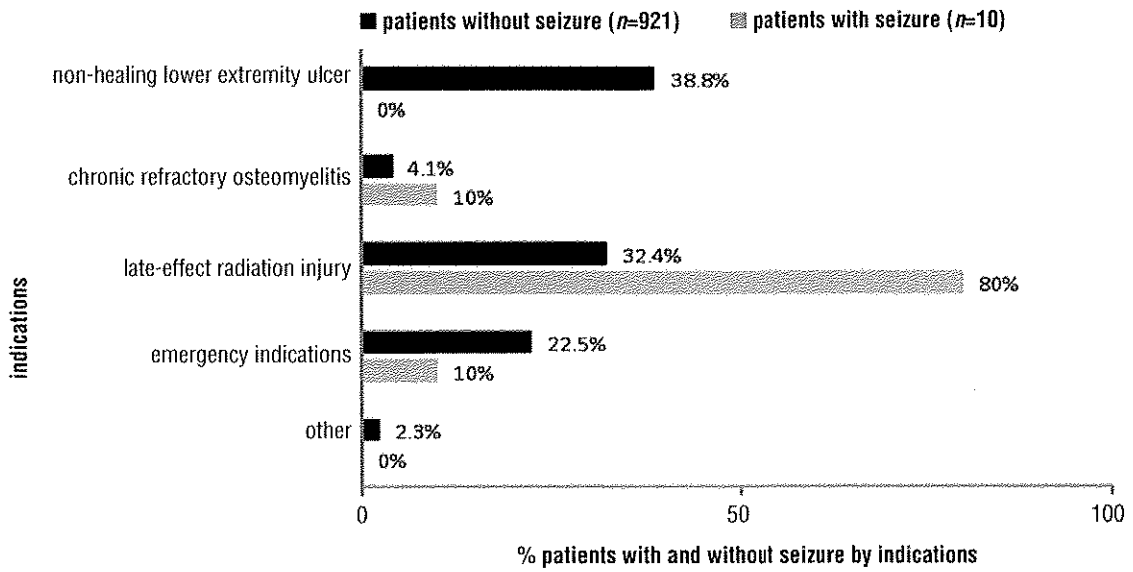
Table 3: Number of patients, treatments and oxygen toxicity seizures at each treatment pressure

Treatment pressure (atm abs)	# of patients	# of Tx	# of seizures
2.0	483	16430	0
2.4/2.5	271	6700	10
2.8	177	198	1

Treatment indication and patient characteristics:

Treatment diagnosis was organized into five treatment categories (non-healing lower extremity ulcers, chronic refractory osteomyelitis, late-effect radiation injury, emergent indications, and other) based on the assigned ICD-9 in the medical record. Figure 2 shows the percentage of patients with and without seizure treated in each treatment category. Table 4 demonstrates the number of patients treated by treatment indication and treatment pressure. When CO poisoning was compared to all other treatment indications at various

Figure 2: Seizure incidence by treatment indications



pressures, there was an increased incidence of oxygen toxicity seizure. The seizure rate was 55 per 10,000 (1/181, 0.55%) treatments for CO poisoning and four per 10,000 (1/2,315, 0.04%) treatments for other indications. This was not statistically significant (p=.154). CO poisoning represented 87% of emergent indications with the other 13% made up of necrotizing fasciitis, air gas embolism and decompression illness. When subgroup analysis was performed on CO poisoning *vs.* other emergent indications, there was no statistically significant difference in the incidence of seizure (p=.3).

There was a statistically significant increased risk of oxygen toxicity seizure in patients with a history of "other CNS," 2.2% of controls and 20% of seizure patients (p=.009). There was no statistically significant increased risk of oxygen toxicity seizure in patients who had past seizure, stroke, diabetes mellitus or alcohol use.

Table 4: The number of patients treated by treatment indication and treatment pressure

treatment indication	2.0 atm abs	2.4/2.5 atm abs	2.8 atm abs
non-healing lower extremity ulcer	339	19	0
chronic refractory osteomyelitis	31	8	0
late-effect radiation injury	94	207	4
emergency indications	3	29	176
other	16	5	0

DISCUSSION

The overall incidence of oxygen toxicity seizure based on this study is estimated at one in 2,121 (five per 10,000) treatments. This is consistent with more recently reported incidence of one in 1,800 and one in 2,844 treatments [20,21]. However, this study is one of the few to demonstrate a statistically significant increased risk of oxygen toxicity seizure at higher treatment pressures. In particular, it is in accordance with the findings of Banham, which also demonstrated a statistically significant increased risk of oxygen toxicity seizure at pressures greater than 203kPa (2 atm abs) [23]. There was a demonstrable increased risk when going up in treatment pressure from 2 atm abs to 2.4/2.5 atm abs to 2.8 atm abs It would be prudent to consider these findings when designing and implementing treatment protocols.

These findings would also seek to foster discussion about when the perceived increased benefit of higher treatment pressures is worth this documented increased risk of oxygen toxicity seizure. This might be a more urgent discussion, especially since it was noted in this

study that the indications that were typically treated at higher pressure had a greater incidence of oxygen toxicity seizure. Consider late-effect radiation injury compared to non-healing lower extremity ulcers. While late-effect radiation injury represented 32.4% of patients treated, it represented 80% of the seizure patients. The higher trend may represent the increased maximum pressure typically used to treat these conditions (2.4/2.5 atm abs) as opposed to non-healing lower extremity ulcers (2 atm abs) which represented 38.8% of patients treated but 0% of the seizure patients.

Consider the issue of elective treatment of the majority of hyperbaric medicine patients with late-effect radiation injury and non-healing lower extremity wounds. There are both local and systemic effects that result in the benefits of HBO_2 for wound healing. These include increased local growth factors and systemic progenitor stem cell release resulting in neovascularization and healing [4-13]. These beneficial effects have been demonstrated at both 2 atm abs and 2.4/2.5 atm abs. There should be documented evidence of increased benefit when prescribing the higher pressure with the knowledge that there is an increased risk. The specialty continues to have non-standardized protocols that vary institution to institution, and the resulting clinical trial results become more difficult to interpret based on varying treatment protocols. Obtaining and applying a more objective understanding of risk *vs.* benefit at varying treatment pressures based on treatment indication is of tremendous benefit to our patients and the field.

Of course, there are indications, primarily emergent, that warrant treatment at higher pressure (2.8 atm abs) when seeking a particular effect such as amelioration of ischemia-reperfusion injury. Knowledge of the increased risk is still important in discussion of risk *vs.* benefit with patients. This study assists in this discussion. While there was evidence suggesting an increased risk of oxygen toxicity seizure in the CO-treated patient population which correlates with findings in other studies [22], this increased risk may simply be related to the higher maximum pressure used to treat this condition.

The results of this study also suggested that air breaks correlate with a higher incidence of seizure. The incidence of seizure in the group receiving air breaks was 42 per 10,000 (1/238) compared with an incidence of 2.3 per 10,000 (1/4380) in the group not receiving an air break. This may be the result of longer treatments at higher pressure associated with a need for air breaks. It may be the result of chance and not reproducible. It may induce seizure in some way. Indeed, the documented increased incidence of oxygen toxicity seizure over the past decade does correlate with an increased availability to utilize air-breaks [20-23]. When analyzed by treatment pressure, the evidence was more mixed, with an increased risk associated with air breaks at 2.4/2.5 atm abs while there was a decreased risk associated with air breaks at 2.8 atm abs. In addition, 98% of the patients who received an air break had a longer, 120-minute treatment time among those treated at 2.4/2.5 atm abs. This subgroup analysis is limited by the limited number of seizures available to analyze and longer treatment times among those patients who received an air break at 2.4/2.5 atm abs. Interpretation of these results should be tempered by these limitations.

This study did demonstrate an increased risk of seizure in patients with a varied history of brain tumor, STRN of the brain, transient ischemic attack/TIA and dementia. A history of alcohol trended toward increased risk but did not reach statistical significance. There was no evidence in this study that a history of seizure increased one's risk of oxygen toxicity seizure.

CONCLUSION

There are a variety of HBO_2 protocols utilized at different centers. The current study has demonstrated a statistically significant increased risk of seizure with increasing treatment pressure. To improve patient care it is important that we better quantify risk and benefit at different treatment pressures and times. This knowledge should be used to standardize treatment protocols for elective and emergent indications based on a better understanding of risk and benefit. It would have the secondary benefit of standardization and improved interpretation of clinical trial results. Based upon the findings here, treatment at higher pressure should be chosen based on demonstrable increased benefit, with a clear understanding of potential risks should higher pressures be used.

Conflict of interest

The authors have declared that no conflict of interest exists with this submission.

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