# Seizure Incidence in 80,000 Patient Treatments with Hyperbaric Oxygen

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**Yildiz Ş, Aktaş Ş, Cimşit M, Ay H, Toğrol E.** ***Seizure incidence in 80,000 patient treatments with hyperbaric oxygen.*** **Aviat Space Environ Med 2004; 75:992–4.**

***Introduction:*** Hyperbaric oxygen treatment (HBOT) involves some risk of central nervous system (CNS) oxygen toxicity, which may be revealed by various signs and symptoms including seizures in patients breathing $O_2$ at pressures of 2 ATA or higher. The aim of this study was to determine the incidence of such seizures in the Underwater and Hyperbaric Medicine Departments of two university hospitals. ***Methods:*** We retrospectively evaluated 80,679 patient-treatments for 9 clinical indications to determine the incidence of seizures attributable to CNS $O_2$ toxicity. Because different protocols were used for HBOT, the treatments were studied in four groups according to the chamber type used and the medical facility at which it was located. ***Results:*** Only 2 seizures were documented, yielding an incidence of 2.4 per 100,000 patient-treatments. Both cases occurred in a multiplace chamber pressurized to 2.4 ATA with $O_2$ delivered by mask for three × 30 min with 5-min air breaks. ***Discussion:*** The seizure incidence reported here is lower than other studies published in the literature. The delivery of $O_2$ by mask rather than hood may be a factor. Nevertheless, it appears that the risk of seizures due to CNS $O_2$ toxicity during HBOT is very low as long as appropriate exclusion criteria and treatment profiles are used.

**Keywords:** central nervous system, oxygen toxicity, hyperbaric oxygen.



HYPERBARIC OXYGEN treatment (HBOT) is used for a variety of clinical conditions as well as decompression sickness and air embolisms from diving, mechanical ventilation, or certain invasive manipulations. The possibility of $O_2$ toxicity in the central nervous system (CNS) was first described by Paul Bert in 1878 (1), and has been a continuing concern. Such toxicity may be revealed by various signs and symptoms (7,11). Patients breathing $O_2$ at pressures of 2 ATA or higher can develop grand mal seizures either without warning or following premonitory signs of CNS irritability (11).

CNS $O_2$ toxicity is thought to involve the generation of reactive $O_2$ species that ultimately lead to alterations in cerebral energy metabolism and electrical activity due to lipid peroxidation at the membranes, enzyme inhibition, and/or enzyme modulation (14). Another possible mechanism is an increased concentration of nitric oxide (NO) in the brain, producing vasodilatation of cerebral vessels and counteracting the vasoconstrictive effects of $O_2$. The use of NO synthase inhibitors that block the production of NO has been shown to protect rats from hyperoxic seizures (2).

Although HBOT is associated with the potential risk of producing mild to severe toxic effects, it remains one of the safest therapeutic procedures in modern medicine (3,4,12). The aim of this study was to determine the incidence of seizures during HBOT in a large database available from two university hospitals in Turkey.

## METHODS

Records for HBOT between 1990 and 2003 were studied from the Departments of Underwater and Hyperbaric Medicine at the Gata Haydarpaşa Training Hospital and the Istanbul University Faculty of Medicine. Because different protocols were used for HBOT, the treatments were studied in four groups according to the chamber type used and the medical facility at which it was located (**Table I**). The study included a wide variety of clinical conditions but excluded diving pathologies such as decompression sickness and gas embolism because of the differences in treatment tables. No patient with pneumothorax or epilepsy was accepted for treatment. Relative contraindications included bronchial asthma, obstructive pulmonary disease, and pregnancy; when such cases were accepted, a multiplace chamber was used. Patients with fevers did not receive HBOT until the fever was under control.

Each patient-treatment was assigned to one of nine clinical indications as follows:

1. Wound: Diabetic and non-diabetic ulcers, venous stasis ulcers, and all non-healing chronic wounds.
2. Bone: Osteomyelitis of long bones, cranial bone and sternum, discitis, and avascular necrosis of bone, especially the head of the femur.
3. PVD: Peripheral vascular disease, vasculitis, Buerger's disease, and others.

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This manuscript was received for review in May 2004. It was accepted for publication in August 2004.

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TABLE I. PATIENT-TREATMENTS 1990–2003 AT THE GATA HAYDARPAŞA TRAINING HOSPITAL (GATA) AND THE ISTANBUL UNIVERSITY FACULTY OF MEDICINE (ITF).

| Treatment Details Facility $O_2$ Route | Multiplace GATA Mask | Monoplace GATA Mask | Multiplace ITF Mask | Monoplace ITF Ambient |
|---|---|---|---|---|
| Normal Protocol | 3 × 30 min $O_2$ 5-min air breaks 2.4 ATA | 2 × 30 min $O_2$ 5-min air breaks 2.4 ATA | 3 × 20 min $O_2$ 5-min air breaks 2.4 ATA | 60 min $O_2$ no air breaks 2 ATA |
| Emergency Protocol | 3 × 25 min $O_2$ 5-min air breaks 2.8 ATA | None | 3 × 25 min $O_2$ 5-min air breaks 2.8 ATA | None |
| Years Studied | 1996–2003 | 1991–1996 | 1990–1998 | 2000–2003 |
| Number of Patient-Treatments | 35,786 | 12,285 | 26,973 | 5,635 |

4. Ischemia: Acute peripheral traumatic ischemia due to crush injury, frostbite, burns, reimplantation, compromised skin flaps, and grafts.

5. CRAO and SD: Central retinal artery occlusion and sudden deafness.

6. Infection: Fournier's gangrene, gas gangrene, and necrotizing fasciitis.

7. CO: carbon monoxide poisoning and smoke inhalation.

8. Radiation: Delayed radiation injury.

9. Other: Various diseases and study protocols including fibromyalgia, facial paralysis, and lymphedema.

Within each group, patients were assigned to either the routine or the emergency treatment protocol (Table I). Indications for the latter included CO poisoning, life-threatening soft-tissue infections, crush injuries, CRAO, SD, and acute acoustic trauma.



## RESULTS

A total of 80,679 HBOT patient-treatments were studied. Their distribution according to condition and group appears in **Table II**. Seizures occurred in 2 patients, or 1 in 40,339 patient-treatments. Both seizures occurred in a multiplace chamber; neither patient had a previous history of seizures. Details of the cases follow.

*Case 1:* A 22-yr-old man had a 10 × 15 cm infected decubitus ulcer in the sacral region. HBOT was applied for 30 sessions without signs of CNS $O_2$ toxicity. In the final session, he suddenly developed tonic-clonic convulsions and lost consciousness. The patient's source of breathing gas was immediately switched from $O_2$ to chamber air. After the tonic phase stopped, the patient was decompressed. He had a post-ictal confusion period of 45 min, after which he gradually regained consciousness. He was transferred to the Neurology Department where a neurological examination was performed and an EEG showed a generalized spike and slow wave paroxysms with no focal activity. Anticonvulsive therapy was initiated, but he continued having tonic-clonic seizures. A cranial CT scan revealed no pathology. The seizures were brought under control within 2 d and the patient was free from convulsions for 3 d. Serial EEGs showed persistent slow activity and occasional spikes in the temporal areas. On his fourth day in the Neurology Department, the seizures started again, increased in intensity, and became intractable; the patient eventually died in status epilepticus. No post mortem pathological examination was possible due to inability to obtain consent from the family. The underlying cause of the seizures in this patient could not be diagnosed, but they were most probably not due to $O_2$ toxicity.

TABLE II. TREATMENT NUMBERS FOR EACH INDICATION.

| Indications | Multiplace | Monoplace | Multiplace | Monoplace |
|---|---|---|---|---|
| Wound | 13,413 | 3,357 | 8,392 | 2,096 |
| Bone | 8,237 | 4,341 | 9,252 | 1,577 |
| PVD | 2,770 | 1,180 | 4,628 | 332 |
| Ischemia | 1,749 | 824 | 1,508 | 236 |
| CRAO and SD | 2,843 | 774 | 1,920 | 212 |
| Infection | 375 | 111 | 403 | 160 |
| CO | 302 | 199 | 144 | 3 |
| Radiation | 958 | 319 | 620 | 942 |
| Others | 5,139 | 1,180 | 106 | 77 |

PVD = peripheral vascular disease; CRAO = central retinal artery inclusion; SD = sudden deafness; CO = carbon monoxide poisoning.

*Case 2:* A 14-yr-old boy had a crush injury to his left toes. HBOT was completed during 13 sessions without complications. During the 14th session, he suddenly developed convulsions, lost consciousness, and became cyanotic during a transient respiratory arrest. Afterwards, he developed tonic and tonic-clonic convulsions that lasted about 3 min. The patient's $O_2$ mask was removed so that he was breathing chamber air. After the tonic phase stopped, the patient was decompressed. No anticonvulsive therapy was given during the seizures or the hyperbaric session. After the patient was removed from the chamber, he was observed to have bitten his tongue. His post-ictal confusion lasted for about 35 min, after which he gradually and spontaneously regained consciousness. This seizure was regarded as a primary generalized epileptic seizure (grand mal). HBOT was discontinued for 2 d, after which the therapy was resumed and 20 additional sessions were completed using the same treatment protocol with no further seizures.

## DISCUSSION

Our study revealed 2 seizures in 80,679 patient-exposures. Both occurred in the same multiplace chamber, where patients were treated at 2.4 ATA with three 30-min periods of $O_2$ delivery by mask (Table I). Patients in the other multiplace chamber were treated at the same pressure, but the $O_2$ periods there lasted only 20 min. Only in the monoplace chamber at ITF was ambient 100% $O_2$ provided throughout the treatment, but there the pressure was only 2 ATA.

In Case 1, persistent and worsening seizure activity

occurred. Although the patient had no known history of epilepsy, he may have had a subclinical cerebral electrical abnormality that was triggered by HBOT. Even if the first event is attributed to $O_2$ toxicity, the subsequent seizures cannot be so linked.

The seizure incidence in our database was 2.4 per 100,000, considerably lower than the commonly accepted value of 10 per 100,000 (10), which was based on 3 reports from the 1970s (3,4,12). [Note: In comparing various studies, we report actual numbers followed by the incidence in parenthesis (using 100,000 as denominator)]. However, two later studies showed higher rates, 1 in 6,704 (14.9) (15) and 1 in 2,844 (35.2) (13). The variation reflects differences in patient selection criteria and specific treatment protocols, which have changed with time. Hart and Strauss reported that over their 20 yr of experience with HBOT, the seizure rate decreased from 1 in 385 treatments (259.7) to 1 in 12,253 (8.2); they attributed the change to improved patient selection to exclude conditions or medications thought to increase the risk of CNS $O_2$ toxicity (9). More detailed comparisons are difficult because the above reports provide little detail regarding the duration of $O_2$ breathing, length of air breaks, and the equipment used for $O_2$ administration.

Davis et al. reported CNS $O_2$ toxicity of 1.3 in 10,000 (13.0) in 1988 (6) and 5 in 52,758 (9.5) in 1989 (5). Neither report described other details regarding treatment or patient characteristics. In 1996, Welslau and Almeling reported occurrences ranging from 1 in 9,000 patient-treatments (11.1) to 1 in 1,800 (55.5), depending on the specific treatment protocol (15).

One reason for the low incidence of seizures in our study may be the fact that we use masks to deliver $O_2$ in our multiplace chambers. Unless the fit is very tight, masks—even with demand valves—deliver only about 80% $O_2$, whereas hoods deliver 100%. CNS toxicity with hoods has been reported as 1 in 3,388 (29.5), even when emergency protocols are excluded from the database (8). It has been suggested that the risk of $O_2$ toxicity may be further increased by $CO_2$ accumulation in the hood, $CO_2$-NO-peroxynitrite reaction, and a peroxynitrite-mediated tyrosine nitration (2).

We think that, apart from the partial pressure of $O_2$ and length of exposure, the most important factor in CNS toxicity is individual susceptibility. The incidence of seizures reported here, lower than any value we could find in the literature, may reflect the fact that our series did not include patients with stroke, head trauma, high fever, or cerebral palsy, pathologies that are known to lower seizure threshold.

In conclusion, as long as appropriate treatment profiles are used, the risk of central nervous system $O_2$ toxicity in HBOT is very low. In fact, for patients with no previous history of neurological or systemic disease that may predispose to seizures, the risk of such a complication for HBOT with $O_2$ delivery by mask is negligible.



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