Original articles

Audit of practice in Australasian hyperbaric units on the incidence of central nervous system oxygen toxicity

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Central nervous system; Clinical audit; Diving tables; Hyperbaric oxygen therapy; Toxicity

Abstract
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Introduction: Central nervous system oxygen toxicity (CNS-OT) is an uncommon complication of hyperbaric oxygen treatment (HBOT). Different facilities have developed local protocols in an attempt to reduce the risk of CNS-OT. This audit was performed to elucidate which protocols might be of benefit in mitigating CNS-OT and to open discussion on adopting a common protocol for Treatment Table 14 (TT14) to enable future multicentre clinical trials.
Methods: Audit of CNS-OT events between units using different compression profiles for TT14, performed at 243 kPa with variable durations of oxygen breathing and 'air breaks', to assess whether there is a statistical diference between protocols. Data were collected retrospectively from public and private hyperbaric facilities in Australia and New Zealand between 01 January 2010 and 31 December 2014.
Results: Eight of 15 units approached participated. During the five-year period 5,193 patients received 96,670 treatments. There were a total of 38 seizures in 33 patients when all treatment pressures were examined. In the group of patients treated at 243 kPa there were a total of 26 seizures in 23 patients. The incidence of seizure per treatment was 0.024% (2.4 per 10,000 treatments) at 243 kPa and the risk per patient was 0.45% (4.5 in 1,000 patients). There were no statistically significant differences between the incidences of CNS-OT using different TT14 protocols in this analysis.
Conclusion: HBOT is safe and CNS-OT is uncommon. The risk of CNS-OT per patient at 243 kPa was 1 in 222 (0.45%; range 0–1%) and the overall risk irrespective of treatment table was 0.6% (range 0.31–1.8%). These figures are higher than previously reported as they represent individual patient risk as opposed to risk per treatment. The wide disparity of facility protocols for a 243 kPa table without discernible influence on the incidence of CNS-OT rates should facilitate a national approach to consensus.

Introduction

Hyperbaric oxygen treatment (HBOT) is defined as "*a treatment in which a patient breathes 100% oxygen whilst inside a treatment chamber at a pressure higher than sea level pressure*". For clinical purposes, the pressure must equal or exceed 142 kPa (1.4 ATA).[1] In Australia and New Zealand, most clinicians treating conditions published by the Undersea and Hyperbaric Medical Society (UHMS) or the Australian and New Zealand Hyperbaric Medicine Group (ANZHMG) use a treatment pressure with 100% oxygen at 243 kPa (2.4 ATA). This is equivalent to the pressure at 14 metres' sea water depth and commonly referred to as a Treatment Table 14 (TT14).

Complications of HBOT include barotrauma, pneumothorax, lung oxygen toxicity and central nervous system oxygen toxicity (CNS-OT). CNS-OT usually presents with prodromal symptoms such as sweating, twitching and tunnel vision, followed by a tonic-clonic seizure. It is most commonly brief and resolves spontaneously once the partial pressure of oxygen is reduced. However, patients are at risk of serious harm during a CNS-OT convulsion.

Air breaks are short periods of breathing air instead of oxygen that have been recommended traditionally to reduce the severity of pulmonary oxygen toxicity.[2] Extended air breaks or extra air breaks may be given with the physiological rationale that the length of exposure to higher oxygen pressures is one of the causes for CNS-OT. Recently

however, air breaks have been postulated as increasing the risk of seizure.[3] There are 10 public hospital and five private hyperbaric facilities in Australia and New Zealand that provide HBOT. Each facility uses a slightly different TT14, the main differences are in the provision of air breaks and total duration of therapy.

This retrospective analysis of data was undertaken to determine if different air-break practices significantly influenced the incidence of CNS-OT. Data concerning indications for treatment were also collected to ensure that similar demographics of patients and risk factors (known and hypothetical) were analysed to assess validity.

Methods

We contacted by phone and email the directors of the 10 public and five private facilities in Australia and New Zealand that provide HBOT inviting them to participate in this study. Nine facilities agreed to participate of which eight were able to contribute to this report. This analysis was deemed to be a quality assurance activity by the Royal Brisbane and Women's Hospital Human Research and Ethics Committee (HREC/15/QRBW/214) and all participating units applied for HREC approval prior to sharing de-identified data.

This is a retrospective cohort study of all consecutive patients who received treatments at eight hospitals in Australia and New Zealand over five years (01 January 2010 to 31 December 2014), examining the incidence of CNS-OT events. Data were collected using the Hyperbaric Technicians and Nurses Association (HTNA) data sets at each hospital. We collected data pertaining to the total number of treatments, treatment pressure, number of patients, conditions being treated and reported cases of CNS-OT. Cases with CNS-OT were analysed to obtain patient-level data. Since our aim was to analyse the effect of different air-break practices on the incidence of CNS-OT in patients treated at 243 kPa we prospectively decided to report events on all cases but restrict the analysis to events while on a 243 kPa TT14.

STATISTICS

The statistical analysis was performed using Stata version 13 (StataCorp, College Station, TX, USA) by an external biostatistician blinded to the hospitals. Means with standard deviation (SD) were used to describe patient characteristics. Poisson regression was used to model the rate of seizure events with hospital as the explanatory variable; Hospital 2 was defined as the reference as it had the most treatments and patients, to determine patient and treatment incidence rates for each hospital. An offset was introduced to account for difference in patient and treatment numbers between hospitals. A P-value of $< 0.05\%$ was considered significant. Hospital 5 and 7 were excluded from the statistical analysis as their incidence rate for CNS-OT was zero at 243 kPa. As this creates a numerator of zero when calculating the incidence rate, this cannot be accommodated in the calculation to compare facilities.

Results

Eight (seven public and one private) of the 15 facilities approached gained HREC approval and participated in the study. All hospitals used slightly different 243 kPa TT14 protocols. Differences included total duration of treatment, duration of 100% oxygen at 243 kPa, and the number, length and total duration of air breaks (see Table 2).

The range of treatment numbers between hospitals was 3,440–19,706, mean 12,083, with Hospital 5 having significantly fewer treatments compared to other facilities. One facility had a notably higher number of treatments per patient (31.5) compared to others, reflecting its chronic wound specialisation, whilst the overall mean number of treatments per patient was 19.

During the five-years, 5,193 patients received 96,670 treatments. There were a total of 38 seizures in 33 patients when all treatment pressures were included in the analysis (243 kPa, 284 kPa and Comex 30 – a helium-oxygen treatment with a maximum pressure of 405 kPa and oxygen partial pressure (PO_2) of 284 kPa). The overall incidence of seizures per patient was 0.039%. These data included emergent treatments of decompression illness (DCI) and toxic gas exposure; these groups of patients are thought to have a higher risk of CNS-OT due to the condition being treated and also a higher treatment pressure.

Table 1

Characteristics of 26 patients with CNS oxygen toxicity at a pressure of 243 kPa; data are shown as number (except age: mean ± SD); risk factors listed only for patients where the information was available; 'Any risk factor' includes those listed here and others, e.g., electrolyte disturbance or fever; ASA – American Society of Anesthesiologists risk grading

Characteristic	Number or mean (SD)
Female/Male	11/15
Age (years)	56.5 (± 2.9)
ASA 1	1
2	8
3	7
4	2
	No/Yes
Diabetes	22/4
Previous epilepsy	17/1
Previous O_2 toxicity seizure	22/4
>1 O_2 toxicity seizure	23/3
Steroids	24/2
Opioids	15/11
Any risk factor	14/12

Table 2

Characteristics of the 243 kPa hyperbaric oxygen treatment tables at the eight hospitals; treatments number and CNS oxygen toxicity (CNS-OT) incidence over a five-year period; some patients had more than one CNS-OT seizure. Total time is the total duration of the treatment from start of compression to end of decompression. Oxygen time is the time spent breathing 100% O_2 at 243 kPa; average treatment numbers rounded

Hospital	Treatments	Patients	Average no treatments	CNS-OT patients	CNS-OT events	Incidence by treatment (%)	Incidence by patient (%)	Time at 243 kPa	No. of air breaks	Duration of breaks	Total air break	Oxygen time	Total time
1	13,046	953	14	3	3	0.023	0.31	75	1	5	5	70	95
2	19,706	1225	16	3	4	0.020	0.24	90	1	5	5	85	110
3	5,701	275	21	3	4	0.070	1.09	90	1	10	10	80	120
4	13,304	927	14	8	8	0.060	0.86	95	1	5	5	90	119
5	3,440	228	15	0	0	0.000	0.00	90	3	5	15	75	120
6	18,788	597	32	4	4	0.021	0.67	90	1	5	5	85	104
7	13,989	515	27	0	0	0.000	0.00	90	2	5	10	80	110
8	8,696	473	18	2	3	0.035	0.42	90	3	5	15	75	110

Nearly half (15 of 33) the patients with CNS-OT had at least one of the commonly described risk factors for CNS-OT such as opiate use or CNS disease. When restricting the analysis to patients treated at 243 kPa there were a total of 26 seizures in 23 patients; three patients had more than one seizure event. The characteristics of these patients are summarised in Table 1.

The incidence of seizure was 0.024% (2.4 per 10,000 treatments, range 0–0.06%) at 243 kPa and risk per patient was 0.451% (4.5 in 1,000 patients, range 0–1.0%). There were no statistically significant differences in the incidences of CNS-OT amongst the different hospitals at 243 kPa TT14. Table 2 describes the variability in TT14 between the eight hospitals in treatment profiles and the incidence of CNS-OT. Table 3 shows the incidence rate ratios per treatment and per patient by hospital, (excluding those with an incidence rate of zero). Figure 1 describes the incidence of CNS-OT events versus the number of air breaks used at the eight hospitals.

Discussion

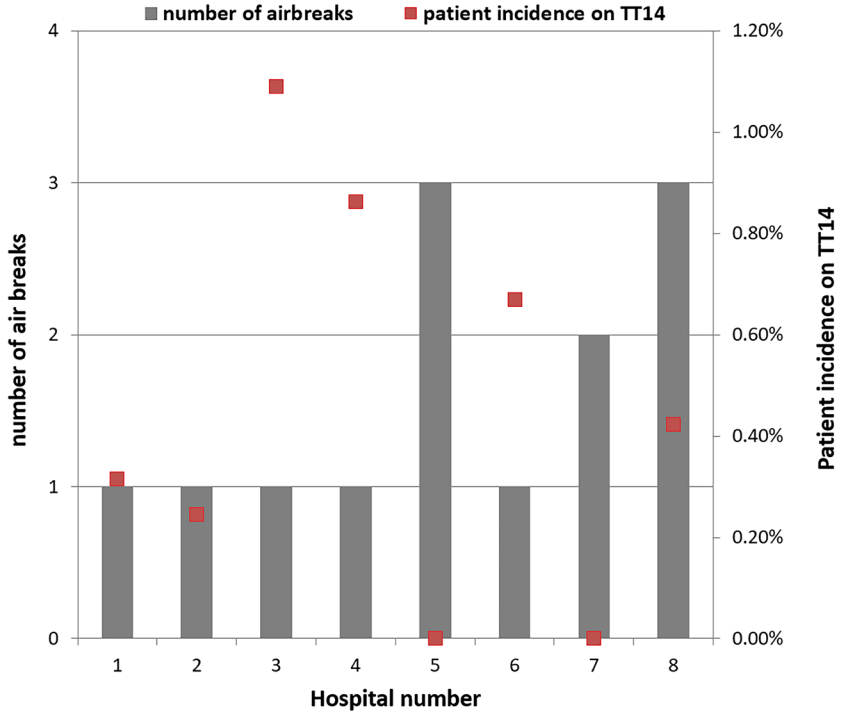
We report the incidence of CNS-OT events in 5,193 patients who have received over 96,000 hyperbaric oxygen treatments. The overall incidence of CNS-OT (irrespective of treatment pressure) when cited as 'risk per treatment' was 0.039% (33 events in 96,670 treatments). This is two-thirds of that reported previously in a single Australian facility (0.06%; 25 events in 41,273 treatments),[4] and 14% of what was reported in a cohort of children receiving HBOT (0.27%; 3 events in 1,099 treatments).[5] When restricting the analysis to treatments at 243 kPa, our cohort reports an incidence of 0.024% or 1 in 4,166 treatments which is 40% of that reported previously (0.06% or 1 in 1,719 treatments).[4]

Previously CNS-OT has been reported as the risk of seizure (numerator) divided by total number of facility treatments (denominator). This is likely to underestimate the risk to the patient in facilities treating chronic conditions with a large number of treatments (e.g., chronic wounds) when compared with emergent indications that receive a lower number of treatments (e.g., decompression illness (DCI)). We have chosen to present the incidence both as the risk per *patient* and the risk per *treatment*, as the former is a more appropriate patient-centred outcome. When receiving information on HBOT, the patient wants to know what is the risk to them. For CNS-OT it is the risk of seizure (numerator) in the population, which is calculated from the number of patients (denominator). This converts the risk in our audit to one per 222 patients (0.45%) as opposed to the higher figure of 0.06% as previously quoted in Australia per treatment (single unit data[4]). This is a relatively low risk when compared to other interventional medical and surgical therapies, e.g., the incidence of stroke after general surgery is reported as 2.9% (29 per 1,000).[6]

Table 3
Incidence rate ratios (IRR) for treatments and patients by hospital. Hospital 2 was the reference hospital as it had the most patients; as such, it does not appear in the table

	Treatments			Patients		
Hospital	**IRR**		***P*-value**	**IRR**		***P*-value**
1	1.13	(0.25–5.06)	0.25	0.96	(0.22–4.31)	0.24
3	3.46	(0.86–13.82)		4.45	(1.11–17.81)	
4	2.97	(0.89–9.84)		2.64	(0.80–8.78)	
6	1.05	(0.26–4.19)		2.05	(0.51–8.20)	
8	1.7	(0.38–7.59)		1.94	(0.43–8.68)	

Figure 1
Incidence of CNS oxygen toxicity and air breaks at the different hospitals (1–8) during a Treatment Table 14 (TT14)



Interestingly, the incidence reported recently for another large retrospective audit in Israel was considerably lower at seven in 62,614 treatments (0.01%). However, the majority (> 57%) of treatments in this report were at a pressure of 151 kPa; which is lower than the minimum therapeutic pressure used in Australia or New Zealand and likely to underestimate the incidence of seizures if applied to our population. In another recent report of a cohort of patients being treated for similar conditions but at the lower pressure of 203 kPa the incidence of seizure was 0.005 % events per treatment or 0.5% events per patient (1 in 200).[7] This is similar to our data at 243 kPa. The same group published a retrospective analysis of all adverse events (including CNS-OT) in the same population as event/treatment as opposed to event/patient in the same year. The overall adverse risk of any complication was published as 0.77% per treatment but would increase to 1.12% if corrected to only include patients treated at > 203 kPa and to give the risk as per patient.[8]

Retrospective audit data for risk of seizure at 243 kPa and 253 kPa reported a risk of 0.04% when results were presented as per treatment and considerably higher (1.07%), when recalculated as per patient.[2] A lower risk of CNS-OT per treatment was published over a decade ago (0.02%); however, this could not be converted to risk per patient as this study did not provide patient numbers.[9] The overall risk of seizure per patient at all pressures in the present audit (inclusive of Comex 30, and all types of 284 kPa profiles) was higher at 0.73% (range 0.19–1.8%) as expected since the risk of CNS-OT increases with increase in pressure.[3]

As consent forms usually list all common or serious side effects of therapy irrespective of treatment pressure, we

recommend that the overall risk of seizures per patient is reported, especially if therapy is at 283 kPa as is often the case for DCI. This risk is considerably higher than previously published. This equates to overall risk of 7.3 per 1,000 patients (almost 1 in 150) per individual.

We found a large variability in TT14 protocols at different facilities, both in terms of time at pressure and oxygen dose, and in relation to number (range 1–3), timing, duration and combined duration of air breaks (range 5–15 min). We did not find any correlation between number of air breaks and the risk of CNS-OT risk and there was no effect of centre on the risk of CNS-OT. This conflicts with previous studies.[3] The two facilities with zero incidences at 243 kPa reported three patients and one patient, respectively, who had a seizure at 283 kPa.

The exact mechanism of CNS-OT is poorly understood but increased cerebral blood flow via nitric oxide (NO) mediated responses is a critical factor and it has been hypothesised that reactive oxygen species may cause neuronal damage.[10] Phosphodiesterase inhibitors (which potentiate endogenous NO) have been implicated in opposing the protective vasoconstriction which is the initial response to hyperbaric hyperoxia.[11] Studies in rats have demonstrated a reduction in dopamine levels in the *substantia nigra pars compacta* which may be linked to seizure activity.[12] Dopamine is reduced in proportion to the increased PO_2. Recent studies in rats looking at striatal blood flow did not support the hypothesis of increased regional blood flow as the pathogenesis of CNS-OT.[13] A recent review suggests that an increased PO_2 saturates protective enzymes and causes neural network overstimulation.[14] Recent studies to develop drugs to reduce CNS-OT have focussed on the effects of pressure on astrocytes and adenosine metabolism which is thought to be crucial in the process of epilepsy.[15,16] Prevention of seizures has become increasingly important with the mounting evidence that seizures may cause cognitive dysfunction and apoptosis.[17,18]

We used seizure as our endpoint for CNS-OT as it is a clear, objective manifestation of toxicity. The experience in our own unit is that the more subjective prodromal symptoms which may precede a seizure are too difficult to confidently call oxygen toxicity. Known risk factors for CNS-OT include medical conditions or medications which are known to decrease seizure threshold.[19] These include electrolyte disturbances, epilepsy, hypercapnia, uraemia, narcotic use, fever and treatment with serotonin reuptake inhibitors. Treatment with corticosteroids has previously been hypothesised to be a risk factor for CNS-OT based on the results of a hypophysectomised rodent model demonstrating increased convulsion thresholds to HBOT.[20] There have been no trials to support the opposite effect (steroids reducing convulsion threshold) in humans. Our report did not find evidence of this association as only two of the patients with CNS-OT were receiving corticosteroids; too small a number for any useful conclusions to be drawn.

LIMITATIONS

Seven facilities were able to provide the condition being treated by broad category although there were discrepancies between total number of patients and patients by category, suggesting either 'off label' conditions being treated, poor data collection methodology or both (discrepancy in patient count ranged from 5 to 597). This highlights the need for an accurate national database, the adoption of which would allow trends in practice to be monitored for adoption of best evidence-based practices. The lack of accurate data in relation to indication for treatment is a flaw of this study; although CNS-OT is an uncommon enough event it is usually accurately recorded.

This audit also collected information regarding indications for HBOT. The facilities that were able to provide indications for treatment appeared to have a similar pool of conditions with the notable exception of idiopathic sudden sensorineural hearing loss. This condition has been on the UHMS indications list since 2014 and was recently endorsed by the European Committee for Hyperbaric Medicine as a valid indication for treatment with Level B evidence.[1,21] Despite this, between 2010 and 2015 two facilities did not treat any patients with this condition, whilst it accounted for 10% of the patient load in another facility. This may reflect a lag in the adoption of recommendations by Ear, Nose and Throat surgeons in different regions at the time of the survey and may not reflect the current situation.[22] A national database would also provide a better understanding of variations in practice.

Eight facilities were able to participate after their ethics committees agreed that this work constituted a quality assurance activity and was exempt from full ethics review. One public hospital facility was unable to participate as their ethics board deemed this to be low risk research and thus would require a lengthy full ethics review. It highlights the inconsistencies between hospital ethics committees when interpreting the National Statement on Ethical Conduct in Research in accordance with the National Health and Medical Research Council Act and institutional differences in governance.[23,24] No explanation was given for non-participation from other units invited to participate.

Conclusions

HBOT is safe and CNS-OT is uncommon. The risk of CNS-OT per patient at 243 kPa was 1 in 222 (0.45%; range of 0–1%) and the overall risk irrespective of treatment table was 1 in 137 (0.73%; range 0.31–1.8 %). These figures are higher than previously reported, as they represent individual patient risk as opposed to risk per treatment. The wide variation in facility protocols for a TT14 without discernible influence on the incidence rates of CNS-OT should facilitate an Australasian approach to consensus. Such consensus would simplify participation in multicentre trials and allow meta-analysis of smaller trials.

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