Effect of antiplatelet and/or anticoagulation medication on the risk of tympanic barotrauma in hyperbaric oxygen treatment patients, and development of a predictive model

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Abstract
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Introduction: Middle ear barotrauma (MEBt) is a common side effect of hyperbaric oxygen treatment (HBOT) and can result in pain, hearing loss, tinnitus and otorrhagia. The use of antiplatelet/anticoagulant drugs is thought to increase the risk and severity of MEBt during HBOT.
Methods: Single centre, retrospective observational cohort study of all patients treated with HBOT over a 4-year period (between 01 January 2015 to 31 December 2018) looking at the incidence of MEBt and the concurrent use of antiplatelet and/or anticoagulant drugs. MEBt was assessed by direct otoscopy of the tympanic membrane post-HBOT and scored using the modified Teed classification. Multivariate modelling assessed the relationship between antiplatelet and/or anticoagulation drug use, age, sex, and MEBt during HBOT.
Results: There was no evidence that antiplatelet and/or anticoagulation drugs increase the risk of tympanic barotrauma in HBOT patients. The prevalence of MEBt was higher in female patients than in males (χ^2 $P = 0.004$), and increased with age (χ^2 $P = 0.048$). No MEBt was recorded in patients undergoing recompression therapy for decompression sickness or cerebral arterial gas embolism.
Conclusions: In this retrospective single-centre study, antiplatelet and/or anticoagulation drugs did not affect the risk of MEBt, but both age and sex did, with greater prevalence of MEBt among older patients and females compared with younger patients and males. A predictive model, requiring further validation, may be helpful in assessing the likelihood of MEBt in patients undergoing HBOT.

Introduction

Hyperbaric oxygen treatment (HBOT) is a frequently used medical treatment with multiple indications outside of decompression illness. This has resulted in non-diving patients being administered HBOT with little or no experience in middle ear equalisation techniques. Middle ear barotrauma (MEBt) is a common side effect of HBOT. In the hyperbaric environment, rapidly increasing pressure during compression can "*overwhelm the ability of pressure regulation of the middle ear if active equalization is not often practiced*".[1] The unequal pressure gradient between the middle ear and external canal can lead to damage of the tympanic membrane and its structures, resulting in stretching, tearing and haemorrhage. Patients can experience symptoms ranging from mild discomfort, to ear pain, hearing loss, tinnitus and otorrhagia.

The incidence of MEBt is reported between 4.1–91% of patients.[2–7] The risk can be mitigated by assessment of patients with tympanometry, education around equalisation techniques and slow chamber compression (14–21 kPa·min^{-1} or less).

The use of antiplatelets/anticoagulants (AP/ACs) increase the risk of bleeding,[8,9] and are thought to increase the risk and severity of MEBt. A previous study looked at the risk of MEBt with the use of AP/ACs. It prospectively compared 73 patients from four hyperbaric centres: 34 participants on antiplatelet/anticoagulation therapy (treatment arm) versus 39 control patients who were not.[10] They reported no increase in MEBt-associated haemorrhagic complications between the two groups.

Methods

This retrospective, single centre observational study included all patients treated with HBOT between 01 January 2015 and 31 December 2018 at Fiona Stanley Hospital (FSH) Hyperbaric Medicine Unit (HMU). Approval was obtained via the FSH Clinical Audit Process (Activity number 28442). Data was collected via the BOSSnet (Core Medical Solutions, Adelaide, SA 5000) electronic medical record (EMR) system and the HMU's patient demographic cover sheet folder (Appendix 1*). This divided patients into their year of treatment and HMU identifying number. Information accessed included the HMU assessment and data form, referral letters and discharge letters. Patients receiving AP/ACs during their course of HBOT were included in the treatment group while all other patients constituted the control group.

Otoscopy was performed on all patients after their initial treatment and then in those who reported ear discomfort during a HBOT session as per the HMU's usual practice. Grading of MEBt was according to the modified Teed classification of MEBt (Table 1) and was documented in the patient's EMR and cover sheet (Appendix 1*).[11] HBOT was administered in either the multi-place chamber (Fink FETL-181, Fink Engineering Pty Ltd**,** Warana, Australia) or a mono-place chamber (Sechrist 3200 or 3600ER, Sechrist Industries Inc, Anaheim CA). Patients treated inside the multi-chamber were accompanied by a trained hyperbaric nurse. Assistance was offered if difficulty with equalisation occurred and compression was immediately halted and adjusted by the outside technician. Treatment tables and pressures used depended on the clinical indication for treatment (203–284 kPa). Compression rates for the multi-chamber were routinely 14 kPa·min^{-1} and in the mono-place chambers were set at 20.7 kPa·min^{-1} unless slowed on the advice of a hyperbaric physician.

All awake patients were educated in the techniques used to equalise as well as being supplied with water bottles to assist in swallowing during compression and decompression. At the FSH HMU the multiplace chamber inside nurse attendant is mobile and vigilant, and the technician is on constant audio and visual contact with the patients inside the monoplace chamber. The unit policy during the study period stated "*as soon as ear pain or difficulty in equalisation is flagged, compression is to be halted, with the potential for decompression to 5–10 kPa below the ceased pressure prior to either abandoning or recommencing at a slower compression rate*".

STATISTICAL ANALYSIS

Data were compiled using MS Excel® and imported into SAS (Statistical Analysis System, Cary, NC version 9.4) for analysis. Differences in mean age between sub-groups were tested using Student's *t*-test with pooled standard deviation.

Table 1
Modified Teed classification of MEBt

Grade	Manifestations
0	Symptoms without signs
I	Injection of the tympanic membrane, especially along the handle of the malleus
II	Injection plus slight haemorrhage within the substance of the tympanic membrane
III	Gross haemorrhage within the substance of the tympanic membrane
IV	Free blood in the middle ear as evidenced by blueness and bulging
V	Perforation of the tympanic membrane

Unweighted Chi-square tests assessed proportions in binary variables (e.g., AP/AC use by sex). To assess the potential association between AP/AC use and MEBt, MEBt was collapsed to three levels; none, mild (Grade I), or involving haemorrhage (Grad II or above). An ordered (ternary) logistic regression model was weighted according to the number of HBOT treatments each patient (i) had completed and these weights (w_i) were normalised (w'_i) by multiplying them by the sample size ($n = 642$) divided by the sum of the weights (the total number of treatments) (Eq. 1).

$$w_i' = \frac{n.w_i}{\sum_{i=1}^{n} w_i} \quad \text{(Eq. 1)}$$

This ensured the covariance matrix of the parameter estimates was not disproportionately affected by the scale of the weighting variable (number of HBOT treatments). The initial model, which also considered potential interactions, is shown in Equation 2. The model was optimised through backwards elimination with least significant variables and interactions (identified by joint tests and conforming to the hierarchical principle) removed until all remaining variables were significant at $P \leq 0.05$

$$ln\left[\frac{P_{MEBt_i'}}{1-P_{MEBt_i'}}\right] = \alpha_j + \beta_1 Sex_i + \beta_2 Age_i + \beta_3 Med_i + \beta_4 Sex_i * Age_i + \beta_5 Sex_i * Meds_i + Age_i * Meds_i + \beta_7 Age_i * Sex_i * Meds_i \quad \text{(Eq. 2)}$$

Where MEBt' = the outcome MEBt (0, 1 or 2) scaled by w', α_j = the intercept for outcome *j*, β_{1-7} = the respective estimates for each independent variable, Sex = male (0) or female (1), Age is in whole years, and Meds = 1 for AP/AC medication use and 0 = no AP/AC medications. A Hosmer and Lemeshow goodness of fit test assessed if the expected outcomes significantly differed from the observed outcomes. $P \leq 0.05$ was accepted as significant, when deciding whether to reject the null hypothesis (that the expected outcomes significantly differ from the observed outcomes).

Table 2
Indications for hyperbaric oxygen therapy for patient included in the present study. ISSHL = idiopathic sudden sensorineural hearing loss

Pathology	Frequency *n* (%)
Non-healing wounds	145 (23)
Pre/post dental clearance	109 (17)
Radiation cystitis/proctitis	89 (14)
Osteoradionecrosis	77 (12)
Decompression illness	70 (11)
Necrotising fasciitis	32 (5)
Carbon monoxide poisoning	26 (4)
Radiation tissue injury	26 (4)
Retinal artery occlusion	14 (2)
Cerebral arterial gas embolism	13 (2)
ISSHL	9 (1)
Burns	6 (1)
Osteomyelitis	6(1)
Acute spinal infarction	6 (1)
Calciphylaxis	5 (1)
Avascular necrosis	2 (< 1)
Disseminated fungal disease	2 (< 1)
Crush injury	2 (< 1)
Pyoderma gangrenosum	1 (< 1)
Supranuclear palsy	1 (<1)
Bell's palsy	1 (<1)
Total	642

Results

There were 642 patients treated at FSH HMU over the four years, receiving a total of 13,989 HBOT treatments (median 27, IQR 25). There was a greater proportion of males (n = 450, 70%) treated compared with females and their mean age was greater (58 y vs. 53 y, SD 17.2, t = -3.16, P = 0.002). The prevalence of indications for HBOT are shown in Table 2.

AP/AC use was reported by 180 patients (28%). The most common prescription was aspirin alone (n = 88, 14%) with a further 11 patients were prescribed AP/AC simultaneously. Other types of AP/ACs included clopidogrel, dipyridamole, warfarin, unfractionated heparin infusion (inpatients), low molecular weight heparin and the newer direct acting oral anticoagulants (DOACs). Males were more commonly prescribed AP/ACs than females (30% vs. 23%, χ^2 P = 0.059).

MEBt occurred in 84 patients (11% males vs. 19% females) with the majority consisting of grade I or II according to the modified Teed criteria (87%). Two patients experienced grade IV or V MEBt. One patient twice had documented barotrauma during their course of treatment with bilateral MEBt on one of those events. The higher Teed grade from this patient was put into our analysis, while the other 83 patients with MEBt had a single documented barotrauma each. All grade III MEBt and above with evidence of gross haemorrhage or perforation occurred in the control group. Mean age was greater among patients with MEBt (63 vs. 56, SD 17.2, t = -3.48, P = 0.0005). No other bleeding complications were recorded for any patients that were unrelated to their current hyperbaric indication. No MEBt was recorded in patients undergoing recompression therapy for decompression sickness or cerebral arterial gas embolism (CAGE). Patients undertaking HBOT for osteoradionecrosis (ORN) prophylaxis pre/post dental treatment or established ORN were assessed for increased prevalence of MEBt, compared with the remainder of the cohort. There was no association with increased MEBt in the pre/post dental group (16% vs. 13%%, χ^2 P = 0.402), nor in the ORN group (14% vs. 13%%, χ^2 P = 0.475), or when the two groups were combined (15% vs. 12%%, χ^2 P = 0.355).

Ultimately, the model (Eq. 2) was optimised and the following variables were removed, in order: Age*Sex*Meds (χ^2 P = 0.208), Sex*Meds (χ^2 P = 0.727), Age*Sex (χ^2 P = 0.180), Age*Meds (χ^2 P = 0.187), then finally Meds (χ^2 P = 0.736). The resulting model is shown in Equation 3. Sex and age were significantly associated with MEBt (χ^2 P = 0.004, OR 2.0, 95% CI 1.2, 3.2) and (χ^2 P = 0.048, OR^{10} 1.2, 95% CI 1.0, 1.3) respectively. The Hosmer and Lemeshow goodness of fit test showed P = 0.36 therefore, the null hypothesis was rejected and model fit accepted.

$$ln\left[\frac{P_{MEBt_i^t}}{1-P_{MEBt_i^t}}\right] = \alpha_j - [0.3421 * Sex_i\ (M = 0,\ F = 1) - [0.0148 * Age_i\ (yrs)] \quad \text{(Eq. 3)}$$

The estimate for the intercept (α_1) comparing no MEBt with (MEBt I or ≥ II) was 2.5246 (SE 0.4752), and for comparing (no MEBt or MEBt I) with MEBt ≥ II the (α_2) intercept was 3.2009 (SE 0.4853). Confidence intervals for parameter estimates were 0.000–0.030 for age and 0.109–0.576 for sex. Examples of translating Equation 2 into odds and probabilities are given in Appendix 2*. The percentage of patients in the three older age groups is shown in Table 3, by MEBt status. These percentages are weighted by number of treatments, to account for differences in exposure and MEBt in different age groups and sexes, but the unweighted percentages showed the same trend, (to an even greater degree). Patients aged ≥ 50 y accounted for 11,210 (80%) of the 13,989 HBOT treatments in this study.

Discussion

The most common complication of HBOT is myopic ocular changes, occurring in 25–100% of patients and dependent on the number of treatments and method of oxygen delivery.[12,13] MEBt is the second most frequent complication, with less common side effects including sinus and dental barotrauma, anxiety, cataracts, hypoglycaemic events during treatment and oxygen toxicity seizures (1/3,000–1/10,000 treatments).[2,4-7,12–16] The present study, looking at the largest cohort of patients, supports previous findings that MEBt is a common complication of HBOT.

Our unit cohort experienced a relatively low prevalence of MEBt compared with previous reports.[2–7] All of our patients underwent a thorough health check prior to commencing HBOT and education on equalising techniques. This included assessment of tympanic membrane movement under direct vision during Valsalva, as well as tympanometry. Several patients including intubated patients had myringotomies performed prior to commencing HBOT.[17] This may have slightly reduced the incidence of MEBt, but with 558 no-MEBt patients their effect upon the results would have been negligible, and non-directional regarding AP/AC use. A French unit treating a majority of acute cases reported a 13.6% incidence of MEBt with no influence of age, sex or mechanical ventilation.[18]

No patients treated for decompression illness suffered MEBt or had pre-existing evidence of MEBt prior to HBOT. Although speculative, this could be assumed to be from prior experience at equalising. The results reported remain valid even when patients treated for DCI were excluded. Another potential confounder for our observed prevalence could have arisen when patients asked for equalisation support prior to notifying of pain, which may have resulted in otoscopy not being performed post treatment. This could have reduced the actual total MEBt numbers and could explain why modified Teed scores of 0 were not recorded. A comparable HBOT unit in Australia experienced a 43.4% incidence of MEBT over the study period with similar characteristics of patient demographics and indications.[19] Grade 0 was reported in that study, although exact numbers were not stated.

ANTIPLATELET/ANTICOAGULATION USAGE

A small study of the prevalence of AP/AC usage in general practice patients showed 11.3% (95% CI 9.5, 13.1%) were prescribed AP/AC medication.[20] Indications for antiplatelets include coronary artery disease, cerebrovascular disease, arterio-venous shunt thrombosis, peripheral vascular disease with or without grafts.[21] Indications for anticoagulants include deep vein thrombosis, pulmonary embolism, atrial fibrillation, valvular disease or replacement and cardiomyopathy. Both AP and AC increase the risk of bleeding and are included in the bleeding risk stratification scoring of HAS-BLED and HEMORR2HAGES.[8,9] Our study showed no increased risk of MEBt associated with the use of AP and/or AC.

Table 3
Percentage of patients in three older age groups, by MEBt status and sex (and weighted by number of treatments)

Age group	No MEBt (%)	MEBt (%)	Males (% MEBt)	Females (% MEBt)
≥50 yrs	84	16	14	22
≥60 yrs	83	17	15	24
≥70 yrs	82	18	15	31

This observational study is the largest published cohort looking at the use of AP/AC and risk of MEBt in patients receiving HBOT. As reported in a previous study, males were more commonly prescribed AP/AC medication (30% vs. 23%) and this may be due to the higher incidence of MI and stroke seen in the aging male population compared with females.[22] In our study, males were more commonly prescribed AP/AC but it was statistically non-significant compared with females (30% vs 23%, χ^2 $P = 0.059$). Even so, the percentage of females in the three older age groups that suffered MEBt increased with age (Table 3). Sex and age have not been shown to influence prevalence of MEBt in other studies.[18] With the large number of patients included in the observation period, we were able to develop a statistical model to assess the likelihood of MEBt. This equation may be used to help assess an individual patient's risk of MEBt and thus develop strategies to prevent it. Sex and age were a secondary finding not included in the null hypothesis, so when using the above equation to estimate probability of MEBt, it should be remembered that the cohort described in this study may not be representative of patients at hyperbaric chambers in other locations. Furthermore, the probabilities generated assume patients will receive the same types and number of treatments as those patients upon whom the model was calibrated. We plan to look at validation of this statistical model involving a more heterogeneous patient mix.

AGE AND SEX

The tympanic membrane (TM) changes with age, with thinning, reduced vascularity, cellular atrophy and increasing TM stiffness.[23] The resultant decrease in compliance could account for the increasing risk of MEBt seen with age. Eustachian tube (ET) function is also affected by age-related atrophy. The tensor veli palatini muscle shows increasing fat tissue replacement with age and increasing ET cartilage calcification.[24–26] These two factors could represent increasing ET dysfunction leading to a higher MEBt risk due to pressure dysequilibrium. What is difficult to explain is why females are at a higher risk than males. There are no studies that differentiate the ageing subjects into sex.

Conclusions

In this single-centre study, AP/ACs did not affect the risk of MEBt, but both age and sex did, with greater prevalence

of MEBt among older patients and females, compared with younger patients and males. A large, multi-centre trial would be required to validate the above findings and the use of a predictive model to determine risk. A predictive model, requiring further validation, may be helpful in assessing the likelihood of MEBt in patients undergoing HBOT.

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