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Protocol Title: Pseudoephedrine Prophylaxis for Prevention of Middle Ear Barotrauma in Hyperbaric Oxygen Therapy
NCT Study No.: NCT04332211

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Protocol

The initial study design employed a 1:1 pseudoephedrine to placebo ratio. At exactly half enrollment (42 out of 84) the research team recognized that the capsule prepared requires 15 minutes to be dissolved, in addition to the 20-30 minutes it takes for the pseudoephedrine tablet to be absorbed and take effect. Therefore, the following two changes have been applied to the protocol: 1. The study capsule will be administered 45 minutes prior to initiation of hyperbaric oxygen therapy; 2. The ratio of pseudoephedrine to placebo will be changed to 2:1 starting with enrollment #43; The total number of enrollments will be increased from 84 to 105. (Because the participants who received the Sudafed tablet did not have enough time for the study capsule and tablet to be digested and take effect we can not use their data for a reliable comparison of Sudafed to placebo. To reiterate, we have enrolled 21 with placebo, and 21 with badly-timed Sudafed. Overall, we need 42 with placebo and 42 with well-timed Sudafed based on our power calculation. Thus, we need another 21 (placebo) and 42 (well-timed Sudafed). This will require us to enroll another 63 patients with a 2:1 ratio. Thus we will need to increase the total number of participants we enroll for the protocol because the initial 21 with badly-timed Sudafed can not be used in the direct comparison calculations. In summary, in order to increase the number of Sudafed enrolled patients, we plan to change the enrollment ratio starting with #43 to 2 (Sudafed) to 1 (placebo). To reach statistical significance, based on our power calculation, we will need to increase our enrollment to a total of 105 (from initial 84) with the next 63 capsules packaged in the 2 Sudafed to 1 placebo ratio.)

Additionally, given the December 2021 RNI IRB recommendations, Dr. Moayedi (PI) will be the only study member who reviews and sings the eligibility criteria checklist for each enrolled participant (this was the case previously, but now is officially in the protocol)

Research Design and Methods

The study will employ a prospective randomized double-blind placebo control study design (enrollment ratio 1:1 – this ratio is changed to 2 Sudafed to 1 placebo starting enrollment #43 given the explanation above) to compare whether pseudoephedrine is more effective than placebo in preventing barotrauma during HBOT.

Setting: The study will take place in the UMMC Center for Hyperbaric and Dive Medicine.

Subjects: Convenience sample of patients undergoing their first HBOT.

Inclusion criteria:
New patient requiring HBOT (either inpatient or outpatient)
Age greater than or equal to 18 years and less than 80 years
Fluent in English
Full decision capacity
Able and medically cleared to swallow a pill

Exclusion criteria:

Enrollment would delay hyperbaric therapy more than 30 minutes in patients with emergent indications (example: CRAO, CO, AGE)
Contraindication to pseudoephedrine (MAOI use, pregnancy, glaucoma, heart disease, allergy to drug class)
SBP >160
DBP > 90
HR >100
Decongestant/antihistamine/pseudoephedrine/nasal steroid/oxymetazoline use within 12 hours.
Prisoner
Intubated
Unable take PO meds

Enrollment:
Trained research assistants will approach patients scheduled for their initial HBOT. If the patient is interested in participation, informed consent will be obtained. A copy of the informed consent will be given to the patient, and the signature page will be collected and kept in a secure location. Enrolled patients will be de-identified and assigned a consecutive study number starting with the number one. A record on the total number of potential eligible participants approached will also be kept. In order to confirm decision making capacity, the patient will be asked the following three questions prior to signing the consent form: 1. Why are we doing this study?; 2. What medication are we testing in this study?; 3. Who can you contact if you have further questions about the study? If the patients are able to answer these questions and the attending hyperbaric physician has them sign an informed consent form for the scheduled hyperbaric therapy, then they are deemed competent to be enrolled in the study. In order to prevent enrolling pregnant patients, the attending hyperbaric physician will be asked to check the result of the pregnancy test. If positive, or not available in a female patient of child bearing age, the patient will be excluded from the study. The PI will be the only study member who will review and sign the eligibility criteria for each enrolled participant.

Protocol:
Consenting patients enrolled in the study will receive the de-identified intervention medication at least 45 minutes and within 120 minutes of the HBOT. The medication will be either a 60mg pseudoephedrine tablet or a placebo prepared and de-identified by the UMMC Investigational drug pharmacy. Both patient and all investigators and hyperbaric department staff will be blinded to the de-identified intervention medication. Prior to HBOT, patients will be asked questions from the data collection form (see appendix A). Study subjects will have vital signs checked prior to enrollment. Otoscopy and grading of their tympanic membrane evaluation will be performed by the hyperbaric physician on duty prior to HBOT. During compression phase of HBOT, research assistants situated outside the chamber will document the need to stop compression for study patients and use of rescue oxymetazoline spray. If the study subject is unable to achieve compression to therapy depth, they will document the reason. Once pressurization has been achieved, the depth of the therapy will be documented. The inside tender will ask if the patient has any ear pain and rate is from 0-10. This information will be communicated via the intercom system to the research assistant. Once HBOT is complete, the

hyperbaric physician will perform another otoscopic evaluation and provide a second Teed score. At the conclusion of the study UMMC Investigational drug pharmacy will supply the key to identify the placebo versus medication.

Data Collection (see appendix A):

- Intervention medication ID
- HBOT depth
- Age
- Sex (M/F/Other)
- Pregnancy test result (+/ - / na)
- Heart rate (beats/min)
- Blood pressure
- Previous trouble clearing ears on airplane (Y/N not applicable)
- Active smoker – smoked cigarette w/in 24 hours (Y/N)
- History of sinus disease (Y/N)
- Current nasal/sinus congestion
- Visual inspection of tympanic membrane prior to HBOT (Teed score)
- Ear pain score prior to treatment

Outcome Variables:

- Use of rescue pseudoephedrine during compression (Y/N)
- Complaint of ear pain at pressure (0-10)- categorized into severe (greater than 7/10) or not severe (less than 7/10) on the standard pain scale.
- Completion of compression (Y/N if no, reason: ear pain, anxiety, other)
- Visual inspection of tympanic membrane immediately after HBOT (Teed score)

Statistical analysis:

The sample size of 42 was calculated for enrollment into each group (use of pseudoephedrine, no use of rescue pseudoephedrine) to detect a significant difference in pain score between the treated and untreated groups. We use the standard Alpha=0.05, and power of 80%.
This calculation was based on the incidence of barotrauma in placebo groups based on prior publications in scuba divers (32%). The incidence in pseudoephedrine treated group was 8%.

Sample Size	
Group 1	42
Group 2	42
Total	**84**
Study Parameters	
Incidence, group 1	32%

Incidence, group 2	8%
Alpha	0.05
Beta	0.2
Power	0.8

We will screen 90 patients (5% oversample) to obtain the required subjects in each group.

The primary outcome variable will be the frequency of severe pain and need for oxymetazoline rescue therapy, between the two groups. These frequencies will be compared using chi-square or Fisher's exact test, as appropriate. We will calculate 95% confidence intervals for the difference in frequencies between groups using normal binomial approximation.

Model building will be based on the results of the univariate analysis of independent and outcome variables. During model building, we will also test variables in a stepwise fashion into the model to identify confounders and effect modifiers. We will then use logistic regression analysis to build the final model between our independent variables to our dependent or outcomes variable.
Timeline:
IRB application will be completed by mid-April 2020.
Medical student and RN research assistant will complete CITI training and be added to the IRB protocol by May 2020
UMMC Investigational drug pharmacy will be notified about the need for manufacturing and de-identification of placebo and pseudoephedrine by mid-April 2020.
Study will be registered with ClinicalTrials.gov by May 2020.
Patient enrollment will begin by mid May 2020 (end of first year of medical school)
We anticipate reaching goal of 84 enrolled patients prior to November 2020.
Data analysis and abstract will be complete by February 2021.
Manuscript will be submitted to Undersea and Hyperbaric Medicine Journal by March 2021.

Limitations:
Given the small sample size, it is possible that some factors, measured or unmeasured, that may affect ear pain or request for rescue therapy will randomly differ between pseudoephedrine and placebo groups. Such factors may bias the study.
There is inherent bias in the pain scale. This is addressed by also examining the patient's tympanic membrane and asking pain score before the patient's treatment starts. Finally our results may not be generalizable given the small sample size and single center patient cohort.

Human Subjects

New patients requiring HBOT who will be approached about enrollment based on inclusion/exclusion criteria. We are avoiding vulnerable study populations such as children and prisoners. Informed consent will be obtained by trained study team members.

We will de-identify the enrolled subjects. We are only asking information about age, sex, smoking history, sinus disease, airplane flight history and current nasal congestion. We will also document limited physical exams findings including heart rate, blood pressure and tympanic membrane evaluation. None of these data points will provide any identifiers.

With respect to the intervention, pseudoephedrine is an over the counter widely used medication. We have ensured that through our exclusion criteria, we will not any significant cardiovascular risk to our enrolled patients.

MATERIALS AND METHODS (from accepted manuscript for Journal of Undersea and Hyperbaric Medicine)

Study design

This was a prospective randomized, double-blind, placebo-controlled trial of pseudoephedrine prophylaxis in patients undergoing their first treatment of HBO2 treatment. The study was conducted between May 2021 and July 2023 in the multiplace HBO2 facility at the University of Maryland Medical Center. The study was approved by our institutional research board and registered with ClinicalTrials.gov (NCT04332211).

Enrollment

A convenience sample of new patients requiring HBO2 treatment (inpatient and outpatient) were approached about enrollment at the time of initial consultation. We included English-speaking patients between the ages of 18 and 80 years. We excluded patients with contraindications to pseudoephedrine (monoamine oxidase inhibitor use, pregnancy, glaucoma, heart disease, allergy), hypertension (systolic blood pressure >160mmHg, diastolic blood pressure >90mmHg), tachycardia (pulse >100/minute), decongestant/antihistamine/nasal steroid use within 12 hours, prisoners, intubated patients, those unable to swallow a pill, history of hyperbaric treatment, SCUBA divers, those with pressure-equalizing tubes, and patients requiring emergent treatment.

Protocol

Consenting patients enrolled in the study ingested a study pill at least 45 minutes, and no longer than 120 minutes, before starting their first multiplace treatment. The pill contained either 60 mg of pseudoephedrine or a placebo, prepared and de-identified by the hospital investigational drug pharmacy. Patients, investigators, and hyperbaric department staff were blinded to the intervention medication. Before treatment, patients self-reported age, sex, whether they smoked tobacco within 24 hours, whether they had acute sinus congestion and any history of chronic sinus disease. We also measured their heart rate and blood pressure. Pre-treatment ear pain ratings were collected using a verbal numerical scale (0=no pain, 10=worst pain imaginable), and Teed scores (0 = normal; 1 = erythema of TM; 2 = erythema and slight hemorrhage within

TM; 3 = gross hemorrhage within TM; 4 = hemotympanum; 5 = perforation of TM) were documented on every patient. The rate of compression change was constant for all participants (0.15 atmospheres absolute per minute). Patient education about methods to equalize ear pressure and not succumbing to "peer pressure" (and thus not declaring inability to equalize) when other patients were in the multiplace hyperbaric chamber was standardized for every enrollment. Patients unable to equalize ear pressure during compression were given oxymetazoline nasal spray as rescue therapy. The need to pause compression for the use of oxymetazoline was documented. We documented the reason why the study participant could not achieve compression. Pain ratings at target or maximum pressure tolerated were collected. Teed scores were documented on every patient after treatment upon exiting the chamber (by the same physician that performed the pre-treatment Teed evaluation). We considered severe pain as >7/10 or requiring abortion of HBO2 treatment.

Statistical analysis

Our comparisons were based on our primary outcome measures (pain ratings, Teed scores, and oxymetazoline rescue therapy) between placebo and pseudoephedrine. Our sample size, based on power 0.8, significance 0.05, and effect size 8% versus 32%, was 42 patients in each group. The effect size was based on barotrauma measured in SCUBA divers [10]. Initial allocation was 1:1, but by the 42nd enrollment, we learned that the capsules prepared by the investigational drug pharmacy required additional dissolution time, necessitating a 45-minute wait rather than the original 30-minute protocol. Because of inadequate time for drug effect, patients assigned pseudoephedrine up to that point were not considered for the primary outcome comparison. Thus, we subsequently changed our allocation to 2:1 to increase the number receiving pseudoephedrine, starting with subject #43. This increased our total enrollment from 84 to 105.

For comparisons of placebo versus pseudoephedrine, we used only subjects with pseudoephedrine ingested at least 45 minutes before HBO2 treatment. We used data from subjects provided pseudoephedrine less than 45 minutes before treatment only for estimates of the incidence of complications of HBO2 treatment.

We compared frequencies of primary outcome measures using chi-square or Fisher's exact test, as appropriate. We calculated 95% confidence intervals for the difference in frequencies between categories using normal binomial approximation. We compared ordinal variables using the Wilcoxon rank sum test.

We used logistic regression to adjust for potential confounding by baseline variables (age, sex, HBO2 pressure, history of obstruction, sinus disease, smoking, and inpatient status). We used backward selection, aiming for a precise and unbiased estimate of the pseudoephedrine effect. We removed only variables whose removal would not change this estimate by >10% or increase the standard error by >20%.