Title: EFFECT OF MONOCHROMATIC LIGHT ON THE INCIDENCE OF EMERGENCE DELIRIUM IN CHILDREN; A SINGLE BLINDED RANDOMIZED CONTROLLED TRIAL

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Background:

Emergence delirium/emergence agitation (ED/EA) is a behavioral phenomenon of unclear etiology consisting of short lived behavioral changes that can be both traumatic to families and pose a safety risk to patients and staff. ED is characterized by a variety of presentations, including crying, excitation and agitation, that occur during the early stage of recovery from general anesthesia, generally in the first 30 minutes.

Involuntary activity in the bed and even thrashing about during an episode of ED can lead to dislodgement of IV cannulas, surgical dressings and or surgically placed items such as drains and catheters.
Emergence delirium occurs in children of all ages following an anesthetic with halogenated agents (e.g. sevoflurane/isoflurane) with or without having undergone a surgical procedure (e.g. MRI patients). Electroencephalograms (EEG) in patients experiencing emergence delirium show diffuse background slowing. Presently, the treatment for ED is to revert the patient back to a hypnotic state mainly with sedatives so that they may "reset" themselves postulating that by re-inducing a hypnotic state, the brain has time to resolve this issue. The hypothesis of this study is that during ED, there is failure of organized EEG activity, especially alpha wave activity and that by enhancing alpha activity, the incidence of ED may be reduced without the need for additional pharmaceuticals which may be costly, delay recovery and are not without adverse effects specifically cardiopulmonary depression.

Monochromatic light (ML) has been used in a variety of clinical and non-clinical applications to affect a variety of changes. Exposure to light of short wavelength within the visible spectrum (450-470nm) has been associated with effects on circadian rhythm, neuroendocrine and neurobehavioral changes and enhanced cognitive performance. Blue ML has been studied safely to enhance work-place alertness and productivity. Clinically, blue ML has been used safely for decades in the neonatal intensive care unit to treat jaundice.

Blue ML, has been known to suppress melatonin secretion and enhance alertness and workplace performance. The effect occurs within the retinal photoreceptive ganglion cells which mediate

the observed responses. The effect is even present in visually blind persons lacking outer retinal function. Short exposure to bursts of blue light has revealed enhanced neural activity on functional MRI. Use of blue ML has been shown to enhance EEG activity in the alpha range (awake range) compared with light of greater wavelengths. If using blue ML in the operating room may enhance alpha EEG activity, (a circadian marker for alertness) it may be possible to reduce the incidence of emergence delirium in the post-operative period and therefore the amount of (non-pain) sedative medication needed in recovery.

Purpose:

Emergence delirium is associated with a safety risk to patients and staff members in the fact that these children are uncontrollable and often thrashing which may result in self-inflicted injury (falls and collision with bedframe) or perturbation of intravenous or surgically placed devices. At present, the treatment involves re-sedating these patients (e.g. propofol or dexmedetomidine). These medications are certainly not without risk. If intravenous access has been lost, intra-nasal or intra-muscular administration of medications can be dangerous or impractical to administer at times of delirium.

The primary aim of this study is to ascertain if perioperative exposure to non-invasive monochromatic blue light can reduce the incidence of emergence delirium.

The secondary aim involves assessing the need for rescue interventions (e.g. hypnotic agents – propofol or dexmedetomidine).

Protocol/Risk/Subjects:

Patient identification
Patients ages 2-6 years undergoing routine tonsillectomy and adenoidectomy requiring general anesthesia would be identified for inclusion. Exclusion criteria would include: American Society of Anesthesiology classification other than 1,2; history of migraine headaches, ocular disorders, seizure history, psychiatric conditions, parental refusal, developmental delay and those patients on medication for attention deficit disorders or caffeine stimulants. Patients with contraindications to receiving inhalation agents, use of premedication with midazolam or dexmedetomidine would also be excluded.

Randomization
After enrollment and consent, each patient will be randomized to either placebo or intervention group. 110 sealed envelopes randomizing patients to the exposure group A (monochromatic light) or bulb B (placebo) white light bulb with blue outer coating.

The machine used for the study will be the Drager Photo-Therapy 4000 currently in use through the NICU at Texas Children's Hospital. The bulb is the standard Drager approved Osram Dulux 18W/830 commercially available bulb. This bulb produced light of 450-470nm wavelength, well within the visible spectrum. The protective plexi shield will remain in place. The bulb for the placebo group contains white florescent bulbs Osram Dulux 18W/830 with a blue plastic covering that will produce light containing all wavelengths in the visible spectrum but will appear blue due to the outer cover. To ensure that this bulb does not produce any monochromatic light, a calibration meter, (Solarmeter Model 9.4 Blue Light Meter measuring 422-499nm with range from 0-199.9 mW/cm^2 Blue Light) will be used.

Patients will be evaluated for emergence delirium by two nurses blinded to the study arm.

Each patient will be given a study specific number for de-identification of data avoiding use of any identifiers (name, DOB, MRN, date of service etc.).

Anesthetic Description

A standard and routine anesthetic will ensue for these patients in line with routine operative practices at Texas Children's Hospital, including an inhalational induction (mask) using sevoflurane 8%v/v with oxygen/nitrous oxide 3/7 L/min respectively, followed by intravenous cannula placement. Propofol will be administered if needed to facilitate oral endotracheal intubation at the discretion of the anesthesia attending. Dexamethasone (0.5mg/kg), ondansetron (0.1mg/kg) and morphine (0.1-0.2mg/kg) will be administered for anti-inflammatory, antiemetic and analgesic effects respectively. Intravenous fluid (lactated ringer solution) will be continuously infused with the appropriate volume to be determined by the anesthesia provider. Maintenance of anesthesia will be with sevoflurane with the concertation titrated to maintain an appropriate level of hypnosis as determined by the anesthesia provider. At the conclusion of the surgery, the patient will undergo routine deep extubation according to the routine practice of the anesthesia providers of record. On arrival to the PACU, the Drager phototherapy lamp will be illuminated over the patients head and neck. Randomization will determine if the patient will be exposed to ML blue light or the placebo bulb (white bulb with blue over coating). The PACU staff and the anesthesiologist will be blinded to study arm. The placebo bulb will provide blue light of all wavelengths as to not compromise blinding. The light will remain active and over the patient until the patient has been in the post anesthesia recovery unit (PACU) for 30 minutes.

Postoperative evaluation for emergence delirium

Two PACU nurses blinded to the patient group will be asked to complete the PAED scoring scale for evaluation of emergence delirium. They will be asked to complete the scoring evaluation upon arrival to the PACU and at 10 minutes, 20 minutes and 30 minutes following arrival. Two nursing evaluations will be used to reduce inter-observer bias. A patient

experiencing emergence delirium will receive standard pharmacologic treatment as determined by the anesthesiology provider irrespective of study participation. Blinding of the nurse and anesthesia team will help to ensure that the nursing staff will call the anesthesia providers with any and all usual questions and the anesthesia provider to react and treat potential ED as per usual practice without being biased by the study.
The study will end at this point without the need for additional follow-up or patient contact related to the study.

Statistical Analysis Plan

Sample size/Data Analysis:

The PAED behavioral scale will be used to assess the incidence of emergence delirium. The PAED scale is a reliable tool to measure ED and involves five items: eye contact, purposeful actions, awareness of the surroundings, restlessness, and inconsolability. While other scales exist, the PAED scale is the standard for assessment of ED and is the only validated scale. A PAED score of >12 will be used to define ED.

Cohort means and standard deviations (SD) or counts and frequencies as appropriate for the variables collected. We will compare the blue light and Sham groups using the Student's t-test for continuous variables (e.g., age, PAED score) and the chi-square test for categorical variables (e.g. % female, ASA category). For counts < 5, the Fisher's exact test will be used. For baseline comparisons, absolute standardized differences instead of p-values will be used to compare the groups.

Given the prospective collection of data, missing data for the PAED scores over time indicated a patient woke up or experienced emergence delirium and so no imputation will be performed. To adjust for any remaining confounding among the variables collected, a logistic regression model with the outcome being emergence delirium and a second logistic regression model with the outcome being either ED or the patient had a PAED score of 12 or more at time periods 10, 20, and 30 min. Both regression models used as independent predictors the following variables: treatment group, age, weight, gender, and ASA category. Robust standard errors were derived to account for any within-cluster correlation at the individual nurse level given the possible serial correlation of outcomes within each nurse caring for his or her patients.

An a priori calculation of sample size was done using an incidence of 40% of emergence delirium in similar patient population. We assumed an absolute reduction of 25% (ie, 40% to 15%) in incidence of emergence delirium to be clinically significant. To detect this difference at 80% power with a two-sided alpha of 0.05, required a sample size of 98 participants.

All p-values < 0.05 were considered statistically significant.

Risk/Discomfort:

The study procedure poses no additional risk to patients. The major risk is loss of confidentiality.

Use of monochromatic light has been safely tested in numerous human studies and used routinely in the NICU without identified patient risk using the same Drager machines at TCH. The moment the patient is awake and making purposeful eye contact with the PACU RN, the lights will be terminated. The risk of phototherapy is well known from nearly 40 years of clinical use in neonates. The risk of phototherapy is predominantly in neonates, especially preterm infants with jaundice, all requiring prolonged and continuous exposure to high intensity light for many days. This study will not include any neonates (with immature retina) or long term exposure of >30 min. The study will be terminated the moment the patient is awake and making purposeful eye contact with the PACU RN to avoid unnecessary discomfort.

Benefits:
The study benefits include improved understanding of emergence delirium and potential for both reduction in the incidence of emergence delirium and the use of pharmacologic agents.

Consent procedures:
The parental or legal guardian permission form will be signed prior to the beginning of surgery.

Confidentiality:
Personal Health Information(PHI) will be safeguarded at all times. Patients will be assigned a study ID number; their name or other identifying information will not be used in any presentations or publications resulting from this research. Data will be kept in a locked office to which only departmental personnel have access. Data files will be stored on a secure hospital network drive.

Sample collection:
Patients will be enrolled prospectively and randomized to either study or placebo arms. In addition, each patient will be assigned a random non-identifiable study number to ensure anonymity.
The following information will be recorded:
Age in months, gender, duration of procedure, duration from induction to extubation,
Recovery time (defined as arrival in PACU to first spontaneous eye opening or response to verbal command)

PAED behavioral scoring sheet will be completed at: (T=0 on PACU arrival, 10, 20 and 30 minutes post PACU arrival). Nurse determination of occurrence of ED.
Administration of supplemental dexmedetomidine, propofol, opioid or benzodiazepine in PACU will be noted if given. Opioid given to treat pain will be noted as such.

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