

Comparison of Changes in Upper Airway Dimensions with Dexmedetomidine and Propofol in children undergoing MRI

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1.0 Introduction

Propofol is being successfully used to sedate children undergoing MRI (Magnetic Resonance Imaging) (1). Dexmedetomidine has also been shown to provide adequate sedation without affecting cardiovascular and respiratory stability (2). There are studies comparing the sedative, hemodynamic and respiratory effects of dexmedetomidine and propofol in children undergoing MRI, demonstrating that both drugs provide adequate sedation in most children although, propofol provided more rapid anesthetic induction, recovery and discharge. Dexmedetomidine better preserved MAP (mean arterial pressure) and RR (respiratory rate) and was not associated with desaturations (3). Studies in spontaneously breathing children undergoing MRI have also shown that increasing depth of propofol sedation resulted in a reduction in upper airway caliber (4). Therefore in children with airway compromise, dexmedetomidine may be a better option for sedation. This is supported by a study which demonstrated that MRI sleep studies were completed without artificial airways in a larger proportion of children with OSA (obstructive sleep apnea) receiving dexmedetomidine than with propofol (5). There are no studies, comparing airway dimensions in children sedated with propofol and dexmedetomidine.

2.0 Objectives

The objective of this study is to compare the changes in upper airway configuration at the level of soft palate, base of tongue and tip of the epiglottis in children sedated with dexmedetomidine and propofol while undergoing diagnostic MRI.

We hypothesize that the upper airway caliber will be smaller in children receiving propofol than with dexmedetomidine.

3.0 Study Design and Method

Single blind randomized controlled trial. (Two treatment parallel study)

A total of 40 Study subjects will be placed into two groups of 20 each. Patients in Group P will be sedated with propofol while those in group D will receive dexmedetomidine (open label). The person analyzing the images of the airway and taking measurements will not be aware of the sedation agent used on that subject. The person collecting and

analyzing the data will be aware of which drug is being administered. Patients will be randomly assigned, either propofol or dexmedetomidine. There will be two groups, group **P** and group **D**, 20 in each group. Group P will receive propofol and group D, dexmedetomidine. The physician analyzing the data will be aware of which drug is being administered. Patient will be randomly assigned, either propofol or dexmedetomidine. Randomization will be by a computer generated randomization table.

4.0 Inclusion and Exclusion Criteria

Inclusion criteria

- Children undergoing MRI brain
- Age 3 – 6 yrs inclusive
- ASA I – II

Exclusion criteria

- OSA
- Pathology of upper airway
- Severe Craniofacial anomalies that would affect airway management
- Severe Gastroesophageal reflux
- Increased intracranial pressure
- Body weight of 20% more than ideal
- Contraindication to the use of either drug

5.0 Recruitment and Consent Process

The parents of children scheduled for a diagnostic MRI of the head and neck will be approached to participate in this study

Participants will be recruited on the day they arrive for MRI by informed parental consent as per the inclusion and exclusion criteria.

The consent for the study will be obtained by a member of the research team from either the parent or the legal guardian on the day of the procedure. They will not be involved in obtaining consent for the procedure.

6.0 Study Procedures

Children arriving for MRI will have a preoperative evaluation performed including history and physical examination as for any child scheduled to have sedation for MRI. Those children meeting the inclusion criteria, after having obtained informed parental

consent, will be enrolled into the study. They will be randomly assigned, as described above, to receive either propofol or dexmedetomidine.

Sequence of study events will be as follows:

No premedication will be given.

All children will be induced with 70% N₂O and 6% sevoflurane in oxygen and an intravenous cannula will be inserted. N₂O and sevoflurane will be turned off and drugs will be administered as follows. Glycopyrrolate 10mcg/kg will be administered IV. Administer propofol bolus at 3mg/kg, or dexmedetomidine at 2 mcg/kg over 10min followed by an infusion of propofol at 240 mcg/kg/min, or dexmedetomidine at 3mcg/kg/hr respectively. In the propofol group, if the patient is unable to lay still at this dose, a further bolus of 1mg/kg will be administered to a total bolus dose of 5mg/kg. If the patient requires more than this dose, he/she will be excluded from the study.

The patient will breathe spontaneously throughout the study while O₂ is administered (3l/min) via a nasal cannula.

A best attempt will be made to position the child's head in the neutral position with a folded sheet beneath the neck or shoulders.

When immobile for 5 min and endtidal sevoflurane is 0%, airway images will be obtained as described later (T₁).

Throughout the procedure, arterial oxygen saturation, exhaled carbon dioxide tension, respiratory rate, heart rate and arterial blood pressure will be monitored continuously and recorded at 5-min intervals during the study period by the anesthesiologist.

The infusions will be discontinued at the end of the scheduled imaging sequence and the patient will be transferred to the recovery area.

Images will be acquired in inspiration and expiration at the level of:

1. the soft palate
2. base of the tongue
3. tip of the epiglottis

A routine axial T2 weighted sequence will be employed to obtain images. At each anatomic level, 8 measurements will be obtained and values will be averaged. No attempt will be made to obtain images at a certain point in the respiratory cycle. These images will be in addition to routine sequences obtained for the clinical study. Each slice will take approximately 1 second. We are estimating therefore, approximately 18

extra seconds of imaging time added to the study. Please note that MRI has no radiation exposure.

After image acquisition following will be calculated at each level by the radiologist on the radiology PACS workstation.

1. cross sectional area (CSA)
2. anteroposterior (AP) diameter
3. transverse (Tr) diameter

At each anatomic level, measurements will be obtained 8 times and average values will be calculated.

In each child transverse and anteroposterior dimensions will also be measured at the level of the vocal cords and the cricoid ring in the axial scan. An additional level may be measured between the vocal cords and the cricoid ring i.e. sub-vocal cord level.

The study should be completed in 18 months.

Data collection:

1. demographic data, age sex, weight, height, race
2. clinical parameters: heart rate, blood pressure, respiratory rate, SpO₂(by pulse oximetry) every 5 minutes.
3. temperature of the subject before and after the study
4. airway dimensions for each drug
5. emergence agitation score in recovery room at 5, 10, 15 and 30 mins
6. sedation score in recovery at 15,30 and 60 mins
7. recovery time (time from discontinuation of sedation to readiness to discharge)

7.0 Risks and Discomforts

Propofol is a substituted isopropylphenol administered intravenously as 1% solution to induce and maintain anesthesia. Studies have shown that anesthesiologist-administered propofol TIVA with oxygenation via nasal prongs in spontaneously breathing children is a reliable technique with good preservation of upper airway patency and rapid induction and recovery rates. At Hershey Medical Center, this technique is utilized in most children presenting for MRI.

Hypotension and bradycardia are observed occasionally when propofol is used as a single drug to achieve sedation (2, 6.). The decrease in MAP and HR reported after propofol induction is 15%-31% and 17%-24% respectively (7). In our study, if the MAP decreases >20% from the base line, a fluid bolus of 10mls/kg of lactated Ringer's solution will be administered. All patients will receive 10mcg/kg of glycopyrrolate after

placement of IV line for its antisialogogue effect. This should also prevent any bradycardia associated with propofol and dexmedetomidine. 5.5% of complications of sedation in children are respiratory events. Respiratory complications, though not consistent, reported with propofol are ventilatory depression, suppression of pharyngeal and laryngeal reflexes and transient respiratory arrest. (7, 8, 9.). This may be more pronounced in children with existing respiratory obstruction. We have chosen to exclude this group. Inadequate sedation is the most common adverse event (5%-15%) resulting in failure (3.7%) of MRI procedures. A study by Usher et al (1) demonstrated that movement during imaging was more likely at lower infusion rates (mean 175mcg/kg/min) than when mean infusion rate was 193mcg/kg/min (range 150-250 mcg/kg/min). In our experience at Hershey Medical Center, we frequently have to increase the infusion to 250mcg/kg/min to prevent movement during the scan. Therefore we have chosen to image the airway at this higher infusion rate, and then decrease to 200mcg/kg/min for the rest of the imaging. Other problems seen with propofol are burning, stinging or pain at the injection site. Some of the rare risks of propofol include irregular heart rate, rash, itching, agitation, increased blood pressure and increased heart rate.

Dexmedetomidine is a highly selective alpha-2 adrenoceptor agonist that has sedative and analgesic effects. Respiratory complications, reported with large and rapid (2mins) initial loading doses of dexmedetomidine include irregular respiration, respiratory depression and transient respiratory arrest. (9). Studies have also shown when bolus doses were administered over 10 mins; saturations were maintained at 95% or higher (5). We have chosen to administer the bolus over 10 mins. Data obtained from any patient unable to maintain a patent airway during the study will not be analyzed. Airway obstruction will be managed by insertion of either an oral or a nasopharyngeal airway. If that fails, a laryngeal mask airway will be inserted to maintain a patent airway. The hemodynamic effects of dexmedetomidine in healthy adults is biphasic, with an initial increase in systolic blood pressure and a reflex decrease in heart rate followed by stabilization of heart rate and blood pressure below baseline (12). In a study by Mason et al(16), although the incidence of bradycardia during dexmedetomidine sedation was 16%, the majority of patients had heart rate values within 20% of the age-adjusted values of 'awake' children. During these bradycardic episodes, the MAP of these patients was always within 20% of age-adjusted values (16). Review of 747 patients, comparing three different dosage protocols of dexmedetomidine, demonstrated dosages required to successfully complete MRI scans are significantly greater than dosages approved by the Food and Drug Administration.

In their study, at a bolus dose of 3mcg/kg and infusion of 2mcg/kg/hr, 2.4% of patients required adjuvant sedation as compared to 7.4% in the lower dose group. In a study comparing dexmedetomidine and propofol for MRI sleep studies in children (5), the median bolus dose of dexmedetomidine was 2mcg/kg and the median infusion rate was 2mcg/kg/hr. We have chosen the proposed dexmedetomidine dosage for our study from these findings. If the upper airway cannot be satisfactorily imaged at this dose of dexmedetomidine, propofol will be used as the rescue drug and the subject withdrawn from the study.

Since dexmedetomidine has a longer half-life than propofol, children receiving dexmedetomidine will be sedated longer after the procedure than with propofol. Other rare risks for dexmedetomidine include nausea, dry mouth, wheezing and irregular heart rate.

8.0 Benefits

When compared to dexmedetomidine, propofol sedation is associated with more desaturations and decreases in RR. The need for artificial airway support is significantly more when children are sedated with propofol (35%) than with dexmedetomidine (12%) (17). We hypothesize that the relaxant effects of dexmedetomidine on upper airway muscle tone are less than those with propofol for any given level of anesthesia. The effects of propofol and dexmedetomidine at high and low doses have been studied individually, however, there are no studies comparing the effect of the two drugs on upper airway dimensions. This study will shed light on this. Although there are no direct benefits to the patients in this study, the data obtained will be useful when we have to encounter patients with compromised airways.

9.0 Reporting of Adverse Events and Unanticipated Problems Involving Risks to Participants or Others

The PI will be responsible for the identification and reporting of any adverse events associated with the study. All reportable AE's and unanticipated problems will be reported to the IRB, per IRB policy.

10.0 Study Withdrawal/Discontinuation

If a parent chooses to withdraw consent or is discontinued from the study; the researchers will no longer use or share any medical information about the patient for this research study, except when the law allows them to do so. The researchers will be unable to take back anything they have already done or any information they have already shared with the parent's permission. The investigators may continue using and sharing the information obtained prior to the patient's withdrawal if it is necessary for the

soundness of the overall research. The investigators will keep records of the care that was provided as long as the law requires.

11.0 Statistical Analysis of the Study

Study participants will be recruited among those presenting for MRI under sedation consistent with inclusion and exclusion criteria. Participants will be randomized to either receive propofol (Group P) or dexmedetomidine (Group D) for sedation.

Primary Outcome

To measure and compare the cross-sectional area (CSA) of the upper airway at the level of soft palate, base of the tongue and epiglottis in both groups of children at high doses of propofol and dexmedetomidine. **Secondary Outcomes**

To measure and compare the

- anteroposterior (AP) diameter
- transverse (Tr) diameter

of the upper airway at the three levels in both groups of children. To measure and compare AP and Tr dimensions at the level of the vocal cords and cricoid ring and may be an additional level between the vocal cords and the cricoid ring.

Statistical Power and sample size

For the estimation of sample size, we assumed an effect size similar to that reported in previous studies evaluating the airway dimensional changes occurring with propofol sedation. We assume that with dexmedetomidine, there will be minimal or no significant changes in airway dimensions. For a two-tailed α of 0.05 and a β of 0.2 (power = 80%), we estimated that 15 patients in each group would be required to demonstrate a 25% difference in CSA with high doses of propofol and dexmedetomidine infusions. Assuming dropouts due to incomplete data, a total of 40 patients, 20 in each group will be enrolled in the study.

Statistical Methods

Statistical Analysis: Continuous data will be presented as mean \pm SD. Two way repeated measures analysis of variance will be used to compare upper airway CSA and dimensions. $P < 0.05$ will be considered statistically significant.

12.0 Privacy and Confidentiality Considerations

The principal investigator will be solely responsible for data collection and verification, and review of cumulative adverse events. Confidentiality will be protected by utilizing a code number as the only identifier for each subject and list will be kept under lock and key with access limited to the PI and co-investigator, Dr. Hulse, and the clinical research nurse.

13.0 Data and Safety Monitoring Plan

This study involves low risk to subjects as it involves administering propofol to one group of patients for sedation of children undergoing MRI, which is, our routine

practice. The safety of dexmedetomidine for sedation in children is well documented in literature as mentioned earlier.

Risks associated with propofol include respiratory depression, transient apnea, hypotension, bradycardia, pain on injection. Very rare risks include rash, itching, and agitation. Risks associated with dexmedetomidine include irregular respiration, respiratory depression, hypertension, hypotension, bradycardia and prolonged sedation. Very rare risks associated with dexmedetomidine include nausea, dry mouth, and wheezing. Risks associated with propofol include respiratory depression, transient apnea, hypotension, bradycardia, pain on injection. Very rare risks include rash, itching, and agitation.

The total time to scan the airways will be less than 5 minutes. Therefore there is minimal risk of prolonging the total scan time.

Oversight for the conduct of the study will be provided by the PI, Dr. Uma Parekh and the clinical research nurse assigned to the study. They will ensure that all eligibility criteria and consent requirements are met prior to a subject's participation on study and that all study procedures and adverse event reporting occur according to the IRB approved protocol.

All data forms and study specific information will be kept in locked file cabinets and password protected database with access limited to the PI and clinical research nurse. Any presentation or publication of the data will be done in aggregate fashion without identifiers.

All adverse events will be documented on study specific case report forms and entered into a computer-based log. Risks associated with propofol include respiratory depression, transient apnea, hypotension, bradycardia, pain on injection. Very rare risks include rash, itching, and agitation. Risks associated with dexmedetomidine include irregular respiration, respiratory depression, hypertension, hypotension, bradycardia and prolonged sedation. Very rare risks associated with dexmedetomidine include nausea, dry mouth, and wheezing. Risks associated with propofol include respiratory depression, transient apnea, hypotension, bradycardia, pain on injection. Very rare risks include rash, itching, and agitation.

Intravenous access for the study participants will be obtained using oxygen and nitrous oxide. Nitrous oxide will then be switched off and the study drug administered.

Nitrous oxide is a good analgesic and will be helpful to prevent the pain from propofol which will be given as a slow bolus. The commonest irregularity in heart rate seen is bradycardia. Glycopyrrolate is going to be administered to all patients and will prevent the bradycardia in both groups. Hypotension (< 20% from baseline) will be treated with a 10ml/kg fluid bolus with crystalloids. All anesthetic agents are respiratory depressants. Respiratory depression will be treated if it affects oxygenation (SpO₂ < 95%) as monitored by pulse oximetry. A nasopharyngeal airway will be inserted first. If it fails to improve oxygenation, a laryngeal mask airway will be used. If an airway

intervention is required, the participant will be excluded from the study. If the child fails to be sedated with the maximum doses mentioned in the protocol, the participants will be excluded from the study. The other risks are extremely rare.

The PI and clinical research nurse will review all adverse events regularly and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review report.

Cumulative adverse events and study progress will be reported to the IRB at the time of continuing review.

14.0 Compensation

There are no payments or compensation to participants.

15.0 Drugs

Propofol and dexmedetomidine will be obtained from the pharmacy. The amount of drug infused will be recorded in the anesthetic record. The unused drugs will be disposed in accordance with the departmental policies by Dr Parekh/Dalal.

Propofol is not recommended for induction of anesthesia in children <3 years or for maintenance of anesthesia in infants <2 months of age, and not recommended for monitored anesthesia care sedation in children. However there are enough studies as referenced throughout the protocol regarding the safety of its use in this age group. It is regularly used at Hershey Medical center as well as most children's hospitals around the world for sedating children undergoing MRI.

Dexmedetomidine is FDA approved in age's ≥ 18 years. Again there are many studies demonstrating use of dexmedetomidine in all age groups. (2, 14)

16.0 Records and Study Monitoring

Oversight for the conduct and monitoring of the study will be provided by the PI, Dr. Uma Parekh/Dr. Dalal / Research coordinator (Chris Mulvey) will be solely responsible for the data collection and verification.

17.0 Facilities

All studies will be conducted in MRI suite and its recovery area at PSMSHMC.

18.0 References

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Appendices

Appendix A

ASA Physical Status Classification System

ASA Physical Status 1 - A normal healthy patient

ASA Physical Status 2 - A patient with mild systemic disease

ASA Physical Status 3 - A patient with severe systemic disease

ASA Physical Status 4 - A patient with severe systemic disease that is a constant threat to life

ASA Physical Status 5 - A moribund patient who is not expected to survive without the operation

ASA Physical Status 6 - A declared brain-dead patient whose organs are being removed for donor purpose

Appendix B

The following measurements will be made for each drug at both high doses at the following levels

Soft palate	
CSA (mm²)	1
	2
	3
Mean CSA	
AP (mm)	1
	2
	3
Mean AP	
Tr(mm)	1
	2
	3

Mean Tr	
Base of tongue	
CSA (mm²)	1
	2
	3
Mean CSA	
AP (mm)	1
	2
	3
Mean AP	
Tr (mm)	1
	2
	3
Mean Tr	
Tip of epiglottis	
CSA (mm²)	1
	2
	3
Mean CSA	
AP (mm)	1
	2
	3
Mean AP	
Tr (mm)	1
	2
	3
Mean Tr	

Appendix C

Scoring system for emergence delirium (ED)

- 1 Sleeping
- 2 Awake, calm
- 3 Irritable, crying
- 4 Inconsolable crying
- 5 Severe restlessness, disorientation

Appendix D

University of Michigan Sedation Scale

- 0 Awake and alert
- 1 Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
- 2 Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
- 3 Deeply sedated: deep sleep, arousable only with significant physical stimulation
- 4 Unarousable

	On arrival	15 min	30 min	60 minutes
ED score				
Sedation score				