COMPARISON OF OUTCOMES DURING MRI SEDATION WITH MIDAZOLAM-DEXMEDETOMIDINE VERSUS KETAMINE-DEXMEDETOMIDINE

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Background

Non-invasive radiologic studies such as MRI play an increasingly important role in the evaluation of pediatric patients with both acute and chronic disease. Due to their developmental capacities, procedure-related anxiety, and the need for a near motionless state during these studies, children often require moderate to deep sedation for the completion of these procedures.

Historically, many different sedative regimens have been used to sedate children for these studies. These regimens have included chloral hydrate (1, 2), sodium pentobarbital (3-5), and propofol (5-7). While each of these agents has been reported to be successful, they also have potential disadvantages. Chloral hydrate has a highly variable onset and dissipation of action (2), has been associated with a higher sedation failure rate in older children and those with various neuro-behavioral diagnoses (8) and is no longer available in the United States. Pentobarbital use has been associated with a risk of respiratory depression and significant recovery related agitation (2, 9). While propofol has become one of the most popular agents for pediatric sedation, it also can cause significant respiratory depression and/or hypotension (10, 11).

Dexmedetomidine is an α_2-adrenoreceptor agonist with both sedative and analgesic properties. It has been used to effectively provide pediatric procedural sedation for radiology procedures and has become an increasingly popular choice for non-invasive procedural sedation in recent years (12-14). Compared to other agents, the main appeals of dexmedetomidine include limited respiratory suppression, a simulation of more natural sleep, minimal effects on the EEG, and limited adverse behavioral

reactions, both during the induction and recovery phases. The most significant reported adverse effects with dexmedetomidine sedation have included hypotension and bradycardia (15, 16). While rarely requiring intervention, these effects may be managed by decreasing the infusion rate, fluid administration, or use of an anticholinergic such as glycopyrollate although profound hypertension has been reported with this intervention (17).

In response to the hypotension-inducing effects of several sedatives commonly used, practitioners have co-administered hypotension-sparing agents to ameliorate this effect. The primary agent used for this purpose is ketamine, a sympathomimetic agent which tends to cause hypertension, tachycardia, and, to a lesser degree, respiratory stimulation. While the addition of ketamine to propofol appears to have inconsistent effects on propofol-induced respiratory depression, the combination has been reported to result in improved hemodynamic preservation (18-20). However, because propofol is a very short-acting agent, the use of this combination may still be associated with the development of emergence reactions not uncommonly seen with ketamine.

More recently, interest has also increased in using ketamine as a co-sedative with dexmedetomidine in an effort to blunt the hemodynamic effects seen with dexmedetomidine alone or when combined with a benzodiazepine such as midazolam. Additionally, as dexmedetomidine has a longer duration of action compared to ketamine, emergence reactions could potentially be less problematic than during ketamine sedation alone or during propofol-ketamine sedation. Unfortunately, few data have actually described the results of this combination in pediatric sedation to date.

During cardiac catheterization, different dosing combinations of ketamine-dexmedetomidine were associated with good analgesia for catheter insertion and minimal adverse cardiovascular or respiratory adverse effects (21, 22). Similarly, when used for burn dressing changes, ketamine-dexmedetomidine provided equivalent analgesia and cardiovascular stability with improved respiratory preservation compared to ketamine-propofol (23). However, in these settings, ketamine was added to dexmedetomidine or propofol primarily for its potent analgesic effects. No data to date have compared ketamine-dexmedetomidine to dexmedetomidine alone or dexmedetomidine-midazolam sedation for non-invasive or non-painful procedures.

For the past 6-7 years, dexmedetomidine (with or without midazolam) has been the sedative regimen of choice for MRI sedation for our Critical Care-based sedation service (UCSS). In the last 2-3 years, we have also been incorporating ketamine into this regimen. It has been the impression of providers using this combination that with ketamine-dexmedetomidine, patients fall asleep more quickly, have less hypotension, and do not have emergence reactions when they wake up. The current study proposes to more rigorously evaluate these questions.

Study Purpose

The purpose of this prospective, double-blind, randomized trial is to compare the impact of midazolam or ketamine coadministration on various sedation-related outcomes during dexmedetomidine sedation for MRI studies.

Rationale

While this combination is being used more and more frequently by sedation practitioners, based on a presumption that the 2 together augment sedation efficiency and decrease sedation-related adverse events, the data supporting these assumptions remains lacking. The current study would specifically address these important questions.

Hypotheses and Research Aims:

1) We hypothesize that the coadministration of ketamine with dexmedetomidine for MRI sedation will result in improved sedation efficiency (decreased induction time), improved preservation of cardiovascular stability, and not increase sedation-related adverse recovery events when compared to sedation with midazolam-dexmedetomidine.

The primary questions/outcomes of interest are:

1) Does ketamine coadministration, compared to midazolam coadministration, decrease or blunt the development of bradycardia and/or hypotension during dexmedetomidine sedation?

2) Does ketamine coadministration, compared to midazolam coadministration, improve the efficiency of sedation (decreased induction time, shorter recovery time) during dexmedetomidine sedation?

3) Does ketamine coadministration, compared to midazolam coadministration, increase the incidence of adverse recovery-related behaviors during dexmedetomidine sedation?

Outcomes

1) The primary outcome of interest will be to assess the impact of ketamine vs midazolam administration on cardiovascular changes during dexmedetomidine sedation
2) Our secondary outcomes will be to:
    a. Compare induction and recovery times between patients sedated with ketamine-dexmedetomidine vs midazolam-dexmedetomidine as a measure of sedation efficiency.
    b. Evaluate the incidence of adverse recovery-related behaviors between the 2 study groups, including overt emergence reactions.

Study Design

The will be a randomized, double-blind, prospective study. All patients referred to UCSS for brain MRI and for whom dexmedetomidine would otherwise be the sedation

regimen of choice will be eligible for enrollment. We propose to limit the study to patients undergoing only brain MRI as these studies are of a predictable length (25-30 minutes); therefore the sedation regimen can be more easily standardized. Parents of eligible patients would be approached prior to or during the pre-sedation assessment and told about the study and, if they agree to enroll, informed consent would be obtained. Assent will be obtained from children 7 years of age and greater, if they are otherwise developmentally capable of giving assent. The goal is to enroll 50 subjects (25 per treatment group) which would be sufficient to detect a 25% or greater difference in the mean maximal heart rate or blood pressure decrease from baseline between the 2 groups.

Following consent, subjects would be randomized to be sedated with either midazolam-dexmedetomidine or ketamine-dexmedetomidine and, upon achieving an appropriate depth of sedation, undergo their MRI. Monitoring during the MRI and subsequent recovery would occur in compliance with the current Norton Children's Hospital Sedation policy. Recovery-related behavior would be assessed using the Pediatric Anesthesia Emergence Delirium Scale (PAED, ref 24). This scale is described in Table 1.

Table 1: Pediatric Anesthesia Delirium Scale:

Item	Description	Not at all	Just a little	Quite a bit	Very much	Extremely
1	Child makes eye contact with caregiver	4	3	2	1	0
2	Child's actions are purposeful	4	3	2	1	0
3	Child is aware of his/her surroundings	4	3	2	1	0
4	Child is restless	0	1	2	3	4
5	Child is inconsolable	0	1	2	3	4

** a sum score of 12 or greater is indicative of emergence delirium

Inclusion Criteria

1) Inpatient at Norton Children's Hospital.
2) Order placed by treating team for MRI of the brain with sedation.
3) Age less than or equal to 18 years.
4) Plan to sedate with dexmedetomidine, regardless of study participation.

Exclusion Criteria

1) Previous adverse reaction to dexmedetomidine or clonidine
2) Current use of clonidine as a routine medication
3) Concurrent use of a heart-rate decreasing medication (digoxin, propranolol)
4) Contraindication to ketamine use
    a. Intracranial hypertension or traumatic brain injury
    b. Intraocular hypertension of eye trauma
    c. Pulmonary hypertension requiring medical management
5) Planned additional procedure during the sedation encounter (non-brain MRI, lumbar puncture, EEG etc)

Procedures

Study enrollment will last for 24 hours following completion of the MRI. During the study, the following procedures will take place:

1) Collection of demographic information: The study team will collect data regarding subject age, weight, BMI, gender, primary diagnosis and reason for MRI, comorbidities, and concomitant medications.
2) Following informed consent, subjects will be randomized to either midazolam-dexmedetomidine or ketamine-dexmedetomidine. Randomization will be done by

NCH pharmacy staff using a computer-based program. A log of which group (A or B) each study drug is assigned and which group each subject is randomized to will be maintained by pharmacy staff and will not be viewed by either study staff or sedation providers until completion of the study. As both midazolam and ketamine look similar to each other when drawn up in a syringe, it should be impossible for sedation providers to visibly distinguish between them. Additionally, the standard concentrations of each drug differ in the same proportion as their standard dosing (midazolam concentration = 1 mg/ml and dose = 0.1 mg/ml vs ketamine concentration = 10 mg/ml and dose = 1 mg/ml). Therefore, the volume of study drug administered to each subject will be identical (0.1 ml/kg to a maximum of 4 ml) without a need for dilution of the stock formulation. All of these factors (pharmacy maintenance of randomization assignment, similarity of drug appearance, and similarity between study drugs of volume to be administered) should ensure that study personnel, sedation providers, and subjects will remain blinded to which study drug they receive. In the event of a severe adverse reaction, it will be permissible for sedation personnel to contact pharmacy to break code for a given subject if necessary. However, because care for these reactions is always symptomatic support, it is difficult to perceive of a situation for which breaking the randomization code would be required to appropriately provide treatment.

3) Following randomization, pharmacy staff will prepare the study drug doses; either midazolam (0.1 mg/kg, maximum dose 4 mg) or ketamine (1 mg/kg, maximum dose 40 mg) to be administered. Doses of study drug will be labelled with the

subjects name and group assignment (A or B), which will then be obtained by sedation providers prior to initiation of sedation.

4) Sedation induction. Per UCSS standard practice, sedation induction will occur by administration of study drug first, followed by dexmedetomidine 2 mcg/kg. The induction bolus will be administered over a 5 minute period to avoid development of significant hypertension and/or sinus pause which have been reported with rapid bolus administration (25). If sedation is inadequate to start the MRI after initial induction doses of study drug and dexmedetomidine, additional 0.5 mcg/kg doses of dexmedetomidine may be administered every 5 minutes until adequate sedation is achieved. If adequate sedation is not achieved following either 4 mcg/kg of dexmedetomidine or if clinically significant cardiorespiratory adverse effects develop, the encounter will be considered a sedation failure per our routine practice and the procedure will either be aborted or performed using alternative sedation as deemed appropriate by UCSS providers.
5) MRI examination: Upon induction of adequate sedation, the subject will be transported to the MRI suite where the scan will occur. Monitoring during the scan will be in accordance with the American Academy of Pediatrics and American Society of Anesthesiology sedation standards and Norton Children's Hospital policy for monitoring of patients undergoing procedural sedation. This will include, at minimum, continuous monitoring of heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2) and end-tidal CO_2 (ET-CO2) monitoring and intermittent non-invasive blood pressure (BP) measurement. Vital signs will be recorded at least every 5 minutes during induction and MRI scan and at least

every 15 minutes during the recovery phase. Similarly, standard pain and sedation depth assessments will be performed and recorded every 5-15 minutes.

6) Recovery: Upon completion of the MRI scan, subjects will be transported to the Norton Children's Hospital sedation unit which is adjacent to the MRI scanner for recovery. Vital signs and pain/sedation assessments will be performed during recovery as listed above. To assess for adverse recovery-related behaviors, the PAED will be administered and recorded every 15 minutes during recovery by study personnel. Per Norton Children's Hospital policy, recovery will be considered complete once subjects have achieved an Aldrete score of 8 or greater on 2 consecutive assessments, at which time they will be transported back to their room.
7) Follow-up: A follow up visit to ask the parents ± the subject about any problems or unpleasant experiences during the sedation encounter. Specific questions of interest will include:
    a. Prolonged sedative effects (sleepiness/grogginess lasting more than 120 minutes from the last dose of sedation administration)
    b. Observed (parent(s)) or recalled (subject) unpleasant visual or auditory experiences or hallucinations during the recovery phase.
    c. Persistent nausea/vomiting or inability to tolerate oral/enteral intake (if no other clinical contraindication to oral/enteral intake existed prior to study enrollment)
    d. Medical record will be reviewed for any signs of adverse events post-sedation.

Risks

The risks of undergoing procedural sedation in general have been well defined. These risks are outlined in Table 2 and are similar to those described with use of midazolam as well:

Table 2: General risks of procedural sedation

Common (>10%)	Uncommon (1-10%)	Rare (<1%)	Very rare (<0.1%) but clinically important
Dizziness during recovery	*Minor blood pressure decrease *Minor/transient decrease in oxygen levels *Minor decrease in HR Oversedation Increased salivation/secretions Agitation during recovery Burning at IV site with sedative administration	Nausea/vomiting Hallucinations Apnea (pause in respiration) Minor airway obstruction (resolves with minor repositioning) Prolonged sedation (>120 minutes) Ineffective sedation (unable to complete procedure)	Cardiac Arrest (0.003%) Gastric content aspiration (0.003) Seizure (0.04%) Laryngospasm (closure of the vocal cords obstructing breathing) (0.04%) Serious allergic reaction (rash/hives) (0.05%) Anaphylaxis (0.005%)

* Minor is defined as a change in parameter not requiring intervention

More specific risks associated with the use of either dexmedetomidine or ketamine are outlined in Tables 3 and 4:

Table 3: Risks associated with ketamine use

Common (>10%)	Uncommon (1-10%)	Rare (<1%)	Very rare (<0.1%) but clinically important
Dizziness during recovery Double vision during	*Minor blood pressure decrease Agitation during	Hallucinations Minor airway obstruction (resolves with minor	Cardiac Arrest Gastric content

recovery Elevated heart rate (transient) Elevated blood pressure (transient) Increased salivation/secretions	recovery Nausea/vomiting Burning at IV site with sedative administration Muscle jerking (not seizure)	repositioning) Prolonged sedation (>120 minutes)	aspiration Seizure Laryngospasm (closure of the vocal cords obstructing breathing) Serious allergic reaction (rash/hives) Apnea (pause in respiration)

* Minor is defined as a change in parameter not requiring intervention

Table 4: Risks associated with dexmedetomidine use:

Common (>10%)	Uncommon (1-10%)	Rare (<1%)	Very rare (<0.1%) but clinically important
*Minor blood pressure decrease *Minor heart rate decrease	Blood pressure decrease possibly requiring intervention Heart rate decrease possibly requiring intervention	Nausea/vomiting Hallucinations Apnea (pause in respiration) Minor airway obstruction (resolves with minor repositioning) Prolonged sedation (>120 minutes) Ineffective sedation (unable to complete procedure)	Cardiac Arrest Gastric content aspiration Seizure (0.04%) Laryngospasm (closure of the vocal cords obstructing breathing Serious allergic reaction (rash/hives) Anaphylaxis

* Minor is defined as a change in parameter not requiring intervention

Statistical Analysis

Comparisons between baseline demographics will be performed using a *t-test*. To assess the impact of each sedation regimen on cardiovascular status, the minimum BP

and HR recorded during the sedation encounter in each subject will be identified and the percentage decrease from corresponding baseline or pre-sedation values will be calculated. Maximal percentage decrease in BP and HR between groups will be compared via *t-test*. Induction time (time from initiation of sedation administration to achievement of a sedation depth adequate to start the procedure) and recovery time (time from procedure completion to achieving sedation monitoring discharge criteria (see Procedures section, number 5)) will be calculated for each patient and comparison of each between groups will be performed using a *t-test*. Incidences of other adverse events (hypoxia, respiratory suppression, recovery-related emergence reactions) will be compared between groups using chi-squared analysis. A p value of <0.05 will be considered significant.

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Study Event Table

Study Event/Day	Screening	Baseline (Sedation Initiation)	Sedation Period	Recovery Period	End of Study (24 hours from end of MRI)
Informed Consent/Assent	X				
Inclusion/Exclusion Criteria	X				
Medical History & Demographics	X	X			
Concomitant Medications	X	X	X		
Physical Examination	X	X	X		
Vital Signs (BP, HR, RR, temperature & pulse oximetry)	X	X	X		
AE/SAE		X	X		X
PAED Scale				X	

CASE REPORT FORM

SUBJECT #_____ INITIALS_____

DOB: _____AGE:_____years

GENDER: ☐ M ☐ F

WEIGHT:_____kg HEIGHT: _____cm BMI: _____

PRIMARY DIAGNOSIS:_____

SECONDARY DIAGNOSES:_____

_____

INDICATION FOR MRI: _____

CURRENT MEDICATIONS:

Drug	Dose	Study Start Date	Indication

SUBJECT #_____ INITIALS_____

SEDATION ENCOUNTER:

Induction Drugs:

Study Drug: Group (A/B):_____

Volume (mL)_____

Time administered:_____

Dexmedetomidine:

Induction Dose: Dose given:_____mg/kg Total Dose: _____mg

Time administered:_____

Extra Doses:

Dose given:_____mg Time administered:_____

Dose given:_____mg Time administered:_____

Dose given:_____mg Time administered:_____

Dose given:_____mg Time administered:_____

Outcomes:

Sedation Effective: ☐ **Yes** ☐ **No**

Procedure completed: ☐ **Yes** ☐ **No**

Recovery-related problems (during 24 hours post MRI): ☐ **Yes** ☐ **No**

If yes, describe:_____

_____

_____

_____

Other adverse events (during 24 hours post MRI): ☐ **Yes** ☐ **No**

If yes, describe:_____

_____

_____

_____

Induction time (min):_____

Recovery time (min):_____

Vital Signs during Sedation/recovery: page _____ of _____

TIME	RR	HR	SpO_2	ET-CO_2	BP	Pain Score	Sedation Score	PAED Score

Vital Signs during Sedation/recovery: page _____ of _____

TIME	RR	HR	SpO_2	ET-CO_2	BP	Pain Score	Sedation Score	PAED Score