COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Protocol #: 16-1909

Project Title: A comparison of intranasal midazolam and Nitrous Oxide (N_2O) minimal sedation for minor procedures in a pediatric emergency department.

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I. Hypotheses and Specific Aims:

The objective of this project is to compare the sedative effects of intranasal midazolam versus inhaled nitrous oxide for minor procedures in the pediatric emergency department. Our primary outcome will be length of stay (LOS) in the emergency department (ED) stay for minor procedures. Secondarily we will compare patient/family and provider satisfaction between these two sedative agents. We hypothesize that the total length of stay for children undergoing minor procedures in the ED will be lower for nitrous oxide, as compared to intranasal midazolam. We also hypothesize that patient/family and provider satisfaction will be higher with nitrous oxide and adverse effects will not differ between N2O and intranasal midazolam.

II. Background and Significance:

Every day, infants, children, and adolescents undergo procedures in the pediatric ED that are anxiety producing, painful, or cause significant distress[1]. Providers must be cognizant of the anxiety, pain and significant distress caused by undergoing procedures; thus, the use of appropriate analgesia and sedation should always be considered. Not only will the use of appropriate analgesia and sedation reduce anxiety and emotional distress, but it may also improve the overall effectiveness and ease of the procedure. The use of mild to moderate sedation for minor ED procedures, such as fentanyl, midazolam, or ketamine has been well studied and shown to be safe in the pediatric population. Consequently, these medications are the typical sedative agents used for minor procedures in the pediatric ED.

Nitrous Oxide (N_2O) has had limited use in the pediatric ED despite being used for many years in pediatric dental clinics[2]. Nitrous oxide is a colorless gas, and has been described as odorless or having a pleasant, sweet odor and taste [2]. Given its favorable adverse effect profile, its ease of administration, and its ability to provide amnesia and analgesia, it is an attractive sedative for use in minor procedures [2]. It also provides rapid onset and rapid offset [3].

Intranasal midazolam is well studied and has been shown to be safe and effective for sedation in the pediatric ED. It is a short acting benzodiazepine that has anxiolytic, sedative, hypnotic, anticonvulsant, and anterograde amnestic effects[4,5]. Midazolam is most commonly favored for sedation, having a fast onset, short half-life (2 – 4 hours), steepest dose-response curve and a >50% incidence of amnesia[6]. It has a wide toxic/therapeutic ratio and safety margin and does not produce prolonged sedation associated with other benzodiazepines[7]. Respiratory depression is rare, as is cardiovascular depression with the exceptions of patients that have a history of hypovolemia or heart failure[6]. Paradoxical reaction to midazolam has been previously described in the literature. These may include hallucination, disorientation, uncontrollable crying or verbalization, agitation, restlessness, involuntary movement, self-injury, and aggressive or violent behavior, which sometimes require restraints[15].

Nitrous oxide has potential for safe and effective administration as a sedative agent for ED minor procedures that is superior to intranasal midazolam. Therefore, the primary objective of our study is to compare the total length of ED stay when using intranasal midazolam or nitrous oxide for minimal procedures. Secondary objectives include comparing patient/parent and provider satisfaction between intranasal midazolam and nitrous oxide and assessment of safety profile as measured by the rate of adverse effects.

III. Preliminary Studies/Progress Report:

There have been no previous studies comparing nitrous oxide and intranasal midazolam for mild sedation/anxiolysis in children requiring minor procedures.

Both intranasal midazolam and nitrous oxide have been well studied individually. Midazolam is a GABA receptor agonist and has been shown to be safe and effective for use in children to provide anxiolysis and pre-anesthetic sedation[8]. Studies evaluating midazolam have shown improvements with anxiety and crying, as well as need for restraint[9]. The most common complaint with intranasal midazolam is that it is noxious and painful to the nasal mucosa[10]. It also has a relatively low drug concentration (5mg/mL) leading to a respective large volume required for intranasal dosing. Primary adverse effects include respiratory depression. Cardiovascular depression is rare, except in patients with hypovolemia or heart failure[6].

Although classified as an anesthetic gas, the potency of nitrous oxide is significantly less than other inhaled drugs used to provide general anesthesia[11]. Several studies, one with >35,000 patients, have shown nitrous oxide delivered at fixed concentrations of 50% to 70% is safe and effective for minimal sedation[11-14]. Nitrous oxide has been shown to have a very rapid onset and rapid offset, with a very short half-life, thus making it an ideal sedative for minor procedures[3]. Numerous studies have shown that it provides anxiolysis and is a safe pre anesthetic sedation. It has also been shown to improve anxiety, crying and need for restraints.

IV. Research Methods

A. Outcome Measure(s): The primary outcome measure of this study is to compare length of ED stay between intranasal midazolam and nitrous oxide, when used as minimal sedation for minor procedures. The total length of ED stay will be defined as time from intranasal midazolam or nitrous oxide administration to time of discharge readiness, collected by the research assistants. Additional time periods measured will include: time from anxiolytic/sedative given to time of procedure completion, and total time for recovery.

Secondary outcome measures will include patient/parent and provider satisfaction with sedation and adverse events with anxiolytic/sedative. Adverse events will be classified and defined as hypoxia, need for administration of reversal agent, nausea, vomiting, paradoxical reaction, airway obstruction, laryngospasm, inadequate sedation, allergic reaction, and cardiac arrest.

B. Description of Population to be Enrolled:

Inclusion criteria:

1. Patients ≥2 years of age and <18 years of age and Parent/legal guardian age ≥18 years of age to <80 years of age
2. Patients with an American Society of Anesthesiologists (ASA) Physical Status Classification System level 1, 2, and 3
3. Patients requiring anxiolysis and mild sedation for minor procedures
    a. Minor procedures will include simple lacerations less than 4 cm
    b. Lumbar punctures
    c. Minor incision and drainage of abscesses that do not require extensive debridement or require moderate sedation or surgical consultation.
    d. Must receive the standard of care dosing for either nitrous oxide or intranasal midazolam.
    e. Nitrous oxide up to 70% nitrous concentration will be allowed
    f. Intranasal Midazolam 0.2-0.5mg/kg with a max dose of 10mg

Exclusion criteria will include the following:

1. Nasal injury with deformity, nasal obstruction or significant congestion, which would make delivery of medication difficult or unpredictable.
2. Laceration that involves the nose and ears or come into contact with the scavenger device or nitrous oxide tubing
3. Allergy to benzodiazepines
4. Benzodiazepine dosing for any reason 24 hours prior to procedure

5. Epistaxis that causes significant obstruction that would make delivery of medication difficult or unpredictable. Or does not stop with direct pressure and requires other interventions for hemostasis.
6. Facial or nasal deformity that cause significant obstruction limiting delivery of anxiolytic medications.
7. Copious mucous
8. Recent (less than 1 week) tympanic membrane graft or middle ear surgery
9. Patients undergoing bleomycin therapy.
10. Patients known to be pregnant at time of enrollment
11. Patients with severe behavior problems, personality disorders or other mind-altering conditions as determined by administering provider. This would include a patient unable to cooperate with having nasal device on nose, or significantly distressed with device not allowing for proper use.
12. Closed space situations such as pneumothorax, air embolus, pneumocephaly or craniotomy in the last 3 weeks, intraocular surgery with retained gas, pulmonary bullae, severe emphysema, or bowel obstruction.
13. Patients with significant co-morbidities: severe pulmonary disease, cardiac disease, hematologic diseases associated with B12 deficiency, sickle cell disease.
14. Patients with acute otitis media and/or sinusitis
15. History of paradoxical reaction to nitrous oxide
16. Known MRSA (+) patients
17. Co-administration of additional sedation or analgesic medications

C. Study Design and Research Methods

Study Design, Setting, and Subject Enrollment:

We will use a prospective, observational study design with an alternating weekly suggested anxiolytic medication. As we will be encouraging an anxiolytic medication on certain suggested weeks, this study will not be strictly observational. The study however, is not intended to be an interventional study as both the administration of nitrous oxide and intranasal midazolam in the pediatric ED for anxiolysis intended for minor procedures is standard of care. We are not attempting to randomize the groups but are encouraging providers to consider nitrous oxide on certain weeks or intranasal midazolam administration on certain weeks in order to obtain patients in each arm to gain power in the study to show possible statistical significance. This study will take place in a large urban tertiary care Children's Hospital in Aurora, CO with over 72,000 visits annually. This is an academic institution and a multi-state referral center. Patients participating

will be enrolled over a one-year period. Trained research staff will obtain and collect data needed by enrolling patients meeting inclusion criteria as stated above.

Both nitrous oxide and intranasal midazolam are considered standard of care in the Children's Hospital Colorado (CHCO) ED. Although Nitrous Oxide is relatively new to the CHCO ED, greater than 20 providers have been trained on its use, and it has become a very popular method for anxiolysis for procedures to date. In coordination with our statistician, in order to ensure that there are evaluable numbers of subjects receiving each sedative agent, we will designate one medication as the primary agent for alternating weeks. For example, the first and third week of the month would be designated a nitrous oxide week and the other weeks of the month would be designated an intranasal midazolam week. However, if the patient/caregiver or provider is not comfortable with the minor sedative recommended for that week they may choose the one they wish to use.

Medication Administration:

Clinical pain management will not be restricted or limited in any way whether a patient receives intranasal midazolam or nitrous oxide. Analgesia will be provided per standard of care whether a patient is in the nitrous oxide arm or the intranasal midazolam arm. For example, for a laceration, local anesthetic will be applied per standard of care if either enrolled in the nitrous arm or the intranasal midazolam arm. If a patient complains of pain prior to any procedure requiring anxiolysis, Tylenol or Ibuprofen will be made available to the patient.

Intranasal midazolam with mucosal atomizer device administration will follow the CHCO established policy 'Intranasal Administration (atomization) of Medications,' which is 0.2mg/kg-0.4mg/kg, with providers' discretion when using 0.5mg/kg. Although standard of care is 0.2mg/kg-0.4mg/kg, it has been proven to be safe and effective when using 0.5mg/kg and we would like to study the normal practice of our providers. Due to variability in the dosing prescribed by providers, we will allow patients to receive a dose of 0.2-0.5mg/kg (maximum dose of 10mg) of intranasal midazolam with the mucosal atomizer device for all procedures.

For nitrous oxide administration, we will use an FDA approved device for delivery (Matrx Digital MDM (w/Bag Tee), (DMDM). The nasal hood with scavenger device will be placed over the patient's nose and the patient will help adjust the mask for comfort. The patient will be asked to close their mouth and breathe through their nose. Appropriate flow rate while delivering 100% (starting at 3L/min and increasing to 5L/min) will be established for 1-2 minutes while observing the reservoir bag for proper inflation and

pulsation. If a mouth breather continues despite instructions to nasal breath the nasal hood will be repositioned over the mouth to allow for gas administration.

Nitrous oxide will be delivered in one of two ways, using the titration method or rapid infusion method. Whichever method is used will be recorded. When using the titration method, starting at 20%, nitrous oxide will be added in 10% increments every 60 seconds until the ideal level of sedation has been met (not to exceed 70% nitrous oxide). Using the rapid infusion method, after the proper flow rate has been achieved with oxygen, the flowmeter will be increased to obtain 50% concentration of nitrous oxide. After 2-3 minutes if the patient does not have adequate sedation, nitrous oxide concentration will be increased to 70%.

Nitrous oxide concentration can be titrated up and down to meet adequate sedation levels at the discretion of the provider. Adequate sedation will be obtained by asking the patient questions (tingling of hands/feet, lightheadedness). Upon completion of procedure, nitrous oxide will be terminated and patient will be given 100% oxygen for 5 minutes to flush out remaining nitrous oxide. Once recovered and patient meets discharge criteria patient will be discharged. Nitrous oxide delivery will follow the standard CHCO standard practice procedures.

Patients will be monitored via standard of care in the CHCO ED. All patients will receive pre sedation vitals and continuous pulse oximetry for the duration of anxiolysis and mild sedation. Airway management equipment will be available at the bedside for all patients if needed.

Efficacy and side effects will be observed and recorded by a research assistant (RA) on a standard data collection sheet as well as a Standardized Adverse Event Reporting Form. Safety will be assessed by monitoring physiologic parameters (heart rate, respiratory rate, blood pressure, and pulse oximetry) as well as adverse effects (nausea, vomiting, laryngospasm, apnea, desaturation, and paradoxical reactions). The use of supportive interventions including airway re-positioning, supplemental oxygen or assisted ventilation will be recorded.
Data Collection:

Data will be collected by the RA on the total length of stay in the ED for all simple procedures using a start time of when sedation was administered to time of discharge readiness. Discharge readiness will be determined by a standard discharge readiness protocol as defined by our hospital for anxiolytic medications administered in the ED. In general, a patient will meet criteria if mental status has returned to baseline, cardiovascular/pulmonary and airway stability assured, neurologic stability, able to hold head upright,

sit up or ambulate with assistance dictated by age, and adequate hydration without excessive vomiting. In typical, the standard process in the ED, the RNs will make the provider aware of discharge readiness. We will use Epic time stamps to determine when the order placed by the provider for discharge was completed.

Recovery time from sedation as well as total length of ED stay will also be recorded. Procedures will occur within 10-15 minutes following intranasal midazolam administration and when adequate sedation with nitrous oxide has been met. All time stamps will be collected by the RA in real time.

We will also collect information on patient/parent satisfaction with sedation as well as provider satisfaction. Patient/parent satisfaction will be assessed for all patients; child satisfaction will be assessed for patients over 12 years of age. Satisfaction will be measured on a scale of 1 to 5 (1 being not satisfied and 5 being very satisfied). Specifically, parents (and children when applicable) will be asked "how satisfied with the means of sedation were you for the procedure performed". Research assistants will then ask the ED providers on a scale of 1 to 5 (1 being not satisfied and 5 being very satisfied) "how satisfied with the means of sedation were you for the procedure performed". Anxiolysis scores will be assessed and recorded by the RA for both nitrous oxide and intranasal midazolam. We will have the RA document an anxiety score and FACES score as reported by the provider prior to anxiolytic being given, after anxiolysis is given/prior to procedure (at time of actual procedure start time) and 5 minutes after procedure stop time. Complications will be observed and recorded, through discharge, by the RA.

List of Variables:

1) Efficacy
   a) Anxiolysis score (Table 1)
   b) Need for additional sedatives
   c) Ability to complete the procedure
   d) FACES score (Table 2)
   e) Parent/patient satisfaction
   f) Provider satisfaction
   g) Whether or not child life specialist was present or not

2) List of complications
   a) Hypoxia (<90%)
   b) Paradoxical reaction (increased anxiety, awareness, pain)
   c) Need for administration of a reversal medication
   d) Vomiting with aspiration
   e) Prolonged sedation
   f) Airway obstruction
   g) Inadequate sedation
   h) Allergic reaction

i) Nasal Reaction
j) Nasal Irritation
k) Cardiac Arrest

3) Nothing by mouth (NPO) Status

4) Duration of procedure

5) Patient Demographics
   a) Weight
   b) Age
   c) Gender
   d) Race/Ethnicity
   e) Underlying diagnoses
   f) ASA level

Table 1: Anxiety Score

1	Agitated, clinging to parent, may or may not be crying
2	Awake, clinging to parent, whimpering, but not crying
3	Calm, sitting or lying comfortably with eyes closed but responding to minor stimulation
4	Drowsy, sitting or lying comfortably with eyes closed but responding to minor stimulation
5	Asleep, eyes closed, able to be aroused but not responsive to minor stimulation

Table 2: FACES scoring

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Anticipated Risks

Participation in this study is of minimal risk to study subjects. There is an unlikely risk of loss of confidentiality.

Intranasal midazolam has the following listed adverse effects: Hypotension, drowsiness, headache, over-sedation, seizure like activity, nausea, vomiting, myoclonic jerks, nystagmus, apnea, cough, hiccups, paradoxical reaction, agitation, amnesia, bronchospasm, emergence delirium, euphoria, hallucinations, laryngospasm and rash.

Nitrous Oxide has the following listed adverse effects: hypotension, headache, dizziness, confusion, nausea, vomiting and apnea.

Describe plan to minimize risk

The risk of loss of confidentiality will be minimized by only allowing research personnel to have access to the data and storing data in a HIPAA compliant REDCap database.

Justification

The potential benefit of this study is that by implementing nitrous oxide for minimal sedation we can shorten the total length of stay in the ED and thus improve patient and provider satisfaction. We also hope to strengthen the support for use of nitrous oxide in the pediatric ED by showing it is as safe and effective as intranasal midazolam.

F. Data Analysis Plan:

In this study we will measure a clinical significance as a difference in total length of ED stay as 15 minutes. Total length of stay will be measured and compared for statistical significance using t-test analysis**.** Patients will be enrolled over a one-year period. Based on annual CHCO ED estimates of candidate procedures, we estimated a total of 300 patients will be eligible. Considering possible attrition from refusals and RA availability we have calculated a range of possible samples needed to achieve adequate power to find a significant difference in Length of stay (Table 3)

Table 3: Power Calculation

Two-Sample T-Tests Allowing Unequal Variance

Numeric Results for Two-Sample T-Test Allowing Unequal Variance
Alternative Hypothesis: $\delta \neq 0$

Power	N1	N2	N	Target %N1	Actual %N1	δ	σ1	σ2	Alpha
0.99994	50	50	100	50.0	50.0	15.0	10.0	15.0	0.050
1.00000	75	75	150	50.0	50.0	15.0	10.0	15.0	0.050
1.00000	100	100	200	50.0	50.0	15.0	10.0	15.0	0.050
1.00000	125	125	250	50.0	50.0	15.0	10.0	15.0	0.050

Patient/parent and provider satisfaction scores will be compared and measured for statistical significance by completing chi-squared analysis. Demographics and baseline patient characteristics will be measured using means and standard deviation for continuous variables and frequency and percentage for categorical variables. We will also attempt to control for confounding variables: including tracking if our child life team is present, % of nitrous oxide used, use of local anesthetic, age, gender, weight, NPO status, ASA status, as well as FACES score and anxiety score.

G. Summarize Knowledge to be Gained:

By completing this study, we will better understand the potential benefits of using nitrous oxide for minor procedures in the ED. Because of its fast onset and rapid offset we anticipate its use for these procedures will significantly decrease the length of stay in the ED, therefore improving work flow, as well as improving patient/parent and provider satisfaction. While more studies need to be completed, this study will potentially increase provider's awareness of other anxiolytic methods that are safe and effective in the pediatric ED.

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