ARTICLE:
- Country: USA
- Funding Sources: Not disclosed

PURPOSE:
- Research Question(s):
  - What is the nature and severity of ED recovery agitation in children after ketamine sedation?
  - Does adjunctive midazolam reduce recovery agitation?
  - What is the difference in ketamine efficacy, adverse effects, and recovery duration when used with and without midazolam?
  - Are preprocedure agitation and external stimulation during recovery associated with recovery agitation?

DESIGN:
- Study Design: prospective, randomized, double-blind, placebo-controlled trial
- Dependent / outcome Variable(s): Recovery agitation
- Independent / research Variable: Adjunctive midazolam

SETTING / SUBJECTS:
- Research Setting: EDs of combined university medical center and children’s hospital
- Subjects:
  - Study population: Consecutive children aged 12 months – 15 yrs requiring procedural sedation
  - Inclusion / Exclusion criteria: Standardized ketamine exclusion criteria, reported in previously published paper:
    - Age ≤3 mo
    - History of airway instability, tracheal surgery, or tracheal stenosis
    - Procedures involving stimulation of the posterior pharynx
    - Active pulmonary infection or disease (including upper-respiratory infection)
    - Full meal in 3 hours preceding procedure
    - Cardiovascular disease including angina, heart failure, and hypertension
    - Head injury associated with loss of consciousness, altered mental status, or emesis
    - Central nervous system masses, abnormalities, or hydrocephalus
    - Poorly controlled seizure disorder
    - Glaucoma or acute globe injury
    - Psychosis, porphyria, thyroid disorder, or thyroid medication
      (Green 1998)
  - Number (control / intervention groups): 51 control (placebo); 53 intervention (midazolam)
  - Demographics: Limited, but similar (see Table 2) between two groups
Attrition: No attrition

METHODS:

- **Interventions:** Intervention group received intravenous midazolam (0.05 mg/kg, 2 mg maximum) 2 minutes after IV ketamine (1.5 mg/kg) loading dose. Both groups also received atropine as an antisialagogue
- **Study Groups:** Control (placebo, saline) and intervention (adjunctive IV midazolam)
- **Instruments:** Various 100-mm unmarked visual analog scales (VAS) (e.g. pre- and post-sedation)
- **Data Collection:** Untrained physicians and nurses participating in the procedural sedation recorded their impressions on the VAS

DATA ANALYSIS:

- **Level of Data:** Ordinal and categorical data
- **Statistics Used:**
  - Recovery agitation with or without adjunctive midazolam, time to recovery, and time to discharge were assessed by using the Wilcoxon rank-sum test.
  - Separate calculations were made for physician and nurse assessments.
  - Confidence intervals (CIs) of the difference between medians were calculated by using methods described by Daniel.
  - Categoric outcome measures were assessed with the \( \chi^2 \) or Fisher exact tests.
  - The relationships between preprocedure and recovery agitation and the level of external stimulation and recovery agitation were assessed by using the Spearman correlation coefficient.
- What, if any, variables were controlled for? Age, gender, weight, type of procedure, ASA class, and preprocedure agitation

RESULTS:

- **Brief answers to research questions:**
  - No evidence of benefit with adjunctive midazolam in improvement of recovery agitation, character, or duration or in the efficacy of sedation itself.
  - Midazolam VAS was 4 mm and placebo VAS was 5 mm (difference –1; 95% confidence interval –3 to 2; \( P= .705 \)).
  - This was a well-designed trial, was sufficiently powered, answered original question
- **Additional findings:**
  - Recovery agitation is low and likely of no clinical importance (VAS ratings of 5 out of 100)
  - Moderate correlation between preprocedure and recovery agitation, but children at the highest risk for recovery agitation (Figure 3) did not demonstrate benefit from midazolam use.
  - No correlation between recovery period stimulation and recovery agitation
  - Substantial interrater reliability for the VAS between nurses and physicians
- Other possible explanation for findings:
  - Suggested that altering the delivery time (prior to ketamine) or dosage may yield other results; however, noted that the recovery agitation with ketamine is already very low
- **Limitations:**
  - Does not investigate psychic or delayed behavioral effects post-discharge, whether these exist or not.
• VAS assessment of recovery agitation has not been validated
• Majority of children were under 10 years old (median 6 years old)

IMPLICATIONS FOR PRACTICE:

• Applicable to this clinical practice: This is applicable to pediatric patients at MMC receiving conscious sedation

• Feasible (cost, resources, etc): This is feasible. Of note, they also mention that they prefer IM route for short procedures (<20 minutes), such as a typical laceration repair, citing that it is simple, reliable, and economical. If procedures are estimated to take longer than 20 minutes, they administer the first dose intramuscularly and then painlessly initiate intravenous access for subsequent doses while the procedure is under way.

• Clinically Relevant: This could definitely make a clinically significant impact on MMC patients.

LEVEL OF EVIDENCE / DECISION FOR USE:

• Background Consider Replication Ready for use

• Level of Evidence:
  □ Ia Evidence obtained from meta-analysis of randomized controlled trials
  X Ib Evidence obtained from at least one RCT
  □ IIa Evidence obtained from at least one well-designed controlled study without randomization
  □ IIb Evidence obtained from at least one other type of well-designed quasi-experimental study
  □ III Well-designed non-experimental studies
  □ IV Expert committee reports, opinions of experts