UAMS EM Journal Club
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Pre-procedural administration of Midazolam or Haloperidol to Decrease Recovery Agitation when utilizing Ketamine in Procedural Sedation

Clinical Bottom Line: If a patient is premedicated with midazolam or haloperidol during sedation with ketamine, there appears to be a decreased risk of recovery agitation, although the methods of measuring the agitation were biased. Premedication may come at a cost of increased total sedation time.

PICO Question:
P: Patients who are receiving sedation with ketamine
I: Premedication with midazolam or haloperidol
C: No premedication
O: Incidence of emergence reaction

Background: Ketamine is commonly used in emergency departments for procedural sedation. The medication has been in use since 1965 and has primarily been used in pediatrics. In adults however, it is known that ketamine, at times, causes post procedural recovery agitation. Many believe that administering medications such as midazolam or haloperidol prior to administering ketamine can reduce this agitation. It is not clearly understood the true benefit of premedicating patients prior to administration of ketamine for sedation.

Trial 1

Akhlagar, et al. “Premedication with Midazolam or Haloperidol to prevent recovery agitation in adults undergoing procedural sedation with ketamine: a randomized double blind clinical trail.” *Ann Emerg Med.* 2019 May;73(5):462-469

Pubmed link: https://www.ncbi.nlm.nih.gov/pubmed/30611640

Validity Rating: Low/Moderate Risk of Bias due to subjective nature of primary outcome

The Basics: Randomized control trial utilizing a single Sina Hospital in Iran. They randomized subjects into 3 groups. Placebo group receiving only ketamine, midazolam group receiving 10 mg of midazolam prior to the 1 mg/kg ketamine, or the haloperidol group utilizing 5 mg of haloperidol with the 1 mg/kg ketamine. Randomization was concealed and the clinician and the patient were blinded. They then used the Richmond agitation and sedation scale and the Pittsburgh agitation scale to measure post procedural recovery agitation.

Exclusion Criteria: <18 years of age, pregnant, history of CAD, CHF, CNS lesions, increased ICP, increased IOP, thyroid disease, acute intermittent porphyria, alcoholism, hepatic impairment, myasthenia gravis, parkinson's disease, structural brain damage, prolonged QT, torsades de pointes, neuroleptic malignant syndrome, psychiatric disease, bone marrow suppression, acute pulmonary infections, conditions requiring stimulation of the posterior pharynx, ingested solid food in the previous 4 hours or clear liquids in the previous 2 hours,

respiratory depression, moderate to severe dementia, epilepsy, intoxication based on the patients symptoms and physical exam, allergy to haloperidol, midazolam or ketamine.

Primary Outcome: Post procedure recovery agitation using the Richmond Agitation and Sedation Scale and the Pittsburgh Agitation Scale.

Secondary Outcomes: They looked at secondary outcomes of nausea, vomiting, CV events, changes in blood pressure, laryngospasm, apnea, and hypoxia

Follow Up: Patients were followed until complete sedation recovery. 1 individual was lost to follow up in the midazolam group secondary to incomplete documentation. Similarly, 2 were lost in the placebo group secondary to incomplete documentation.

Results:

1. In the midazolam vs placebo group the RRR for recovery agitation was 60.9% and the NNT was 2.57. The confidence intervals, although significant, were quite large (22.6-55.2).
2. In the haloperidol vs placebo group the RRR was 69.2% and the NNT was 2.03. The confidence intervals again were significant but similar to the midazolam group large, (28.6-59).
3. . The placebo group had 4.9% of patients who experienced nausea and 3.2% who experienced vomiting. Similarly, the midazolam group had 5% and the haloperidol group had 3.2% who also experience nausea without vomiting. No adverse events occurred in the other categories.
4. The placebo group did have 9.8% of it's patients who experienced severe agitation, described as a score of >8 on the PAS agitation scale. These 6 patients received midazolam, postprocedurally.

Limitations and Bias:

1. The population of patients is 90% male
2. Both the RASS and PAS agitation scales used in the study are subjective and also markedly inflate results if looking solely at the numbers.
3. We felt the doses of midazolam and haloperidol were higher than what is typically used in practice.

Trial 2

Sener, et al. "Ketamine With and Without Midazolam for Emergency Department Sedation in Adults: A Randomized Controlled Trial." Ann Emerg Med. 2011 Feb;57(2):109-114.e2

Pubmed link: https://pubmed.ncbi.nlm.nih.gov/20970888/

Validity Rating: Low Risk of Bias

The Basics: Randomized control trial utilizing a single Emergency department. They randomized subjects into 4 groups: Placebo group 1 receiving ketamine 1.5 mg/kg IV, placebo

group 2 receiving ketamine 4 mg/kg IM, Treatment group 1 receiving ketamine 1.5 mg/kg IV with midazolam 0.03 mg/kg IV, or Treatment group 2 receiving ketamine 4 mg/kg IM with midazolam 0.03 mg/kg IV. Both patients and providers were blinded. Adverse events and sedation characteristics were recorded, no specific agitation or sedation scales were used.

Exclusion Criteria: <18 or >50 years of age, or who had significant cardiovascular disease, central nervous system lesions or injuries, psychiatric disorders, pregnancy, ocular pathology, thyroid disease, acute pulmonary infections, conditions requiring stimulation of the posterior pharynx, and who had ingested solid food in the previous 4 hours or clear liquids in the previous 2 hours.

Primary Outcome: incidence of recovery agitation in groups receiving midazolam or placebo and the incidences of adverse event types in groups receiving IV versus IM ketamine. Recovery agitation was defined as any moaning, screaming, cursing, or unpleasant dreams or hallucinations.

Secondary Outcomes: effect of midazolam versus placebo on sedation times and satisfaction scores.

Follow Up: 182 had data collected for agitation, of those, 31 had missing data elements, a resultant 151 had analysis of sedation times and satisfaction scores

Results:

1. Recovery agitation was less common in the midazolam cohorts 8% versus 25%, 95% confidence interval 6% to 28%; NNT 6.
2. Incidence of adverse events, including respiratory events, nausea/vomiting, and agitation were similar (recovery agitation 13% versus 17%, 95% CI – 8% to 16%).

Limitations and Bias:

1. Data only applies to relatively healthy patients between ages 18-50 years.
2. Recovery agitation had no scale and may have been perceived differently by different recorders.
3. Small number of patients in the trial with very few incidence of recovery agitation (N30).