The KetaBAN Trial: Nebulized Ketamine for Analgesia in the ED

REBEL EM

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Background: Intravenous sub-dissociative dosed ketamine has gained an expanded role in the management of a variety of acute painful conditions in the ED (REBEL EM). When IV access is not readily available or unobtainable, sub-dissociative dosed ketamine can be given through the intranasal route as well. Another non-invasive route of ketamine administration could be the nebulized route. Inhaled ketamine has a bioavailability of about 20 to 40% (compared to the IV route) and a duration of action of 20 to 40 minutes. There is currently no high-quality literature in the ED that evaluates or compares the analgesic efficacy and safety of nebulized ketamine.

Paper: Dove D et al. Comparison of Nebulized Ketamine at Three Different Dosing Regimens for Treating Painful Conditions in the Emergency Department: A Prospective, Randomized, Double-Blind Clinical Trial. Ann Emerg Med 2021. [Epub Ahead of Print]

Clinical Question: What is the analgesic effectiveness and safety of nebulized ketamine at 3 different doses for ED patients presenting with acute and chronic painful conditions?

What They Did:

- Prospective, randomized, double-blinded superiority clinical trial
- Comparing 3 doses of nebulized ketamine:
    - 0.75mg/kg
    - 1.0 mg/kg
    - 1.5 mg/kg
- All enrolled patients could receive up to 3 doses of nebulized ketamine for their pain control
- Ketamine inhaled through a breath-actuated nebulizer

Outcomes:

- **Primary:** Difference in pain scores on an 11-point numeric rating scale between all 3 groups at 30 minutes
- **Secondary:**
    - Need for rescue analgesia (additional doses of nebulized ketamine or IV morphine)
    - Adverse events at 30 and 60 minutes
        - Used the Side Effect Rating Scale for Dissociative Anesthetics (SERSDA) and Richmond Agitation Sedation Scale (RASS)

        - SERSDA scale includes fatigue, dizziness, nausea, headache, feelings of unreality, changes in hearing, mood changes, general discomfort, and hallucinations with severity graded on a 5-point scale, with 0 representing absence of any adverse effects and 4 representing severely bothersome side effects
        - RASS evaluates severity of agitation and/or sedation on a 10-point scale with scores ranging from -5 (unarousable to 0 (alert and calm) to +4 (combative)

Inclusion:

- Adult patients (≥18 years of age)
- Presenting to the ED
- Acute pain
    - Acute pain included: traumatic and nontraumatic abdominal, flank, back, and musculoskeletal pain and headache
- Exacerbation of chronic painful conditions
    - Chronic pain included: chronic abdominal pain, musculoskeletal, back, and neuropathic pain
- Initial pain score of ≥5 on a standard 11 point (0 to 10) numeric rating scale (NRS)
- Warranted use of ketamine analgesia as determined by treating physician

Exclusion:

- Painful conditions that required immediate intervention (treatment) by the treating physician
- Altered mental status
- Unstable vital signs (SBP <90 or >180mmHg, Pulse <50 or >150BPM, or RR <10 or >30BPM)
- Acute intoxication
- Received opioids within 4 hours prior to enrollment
- Allergy to ketamine
- Patients with actual body weight of >150kg
- Unable to provide consent
- PMH of alcohol or drug abuse
- Pregnant or breastfeeding patients

Results:

- 120 patients enrolled (40 per group)
    - 120 patients available at 30 minutes
    - 109 patients available at 120 minutes
- Difference in mean pain scores at 30 minutes:
    - 0.75mg/kg vs 1.0mg/kg: 0.25; 95% CI 1.28 to 1.78
    - 1.0mg/kg: vs 1.5mg/kg: 0.025; 95% CI -1.51 to 1.56
    - Change in pain score was similar among the 3 groups (mean value of 4.1)
    - Reductions in pain scores from baseline to 30 minutes were greater than 1.3 (Clinically significant)
    - BUT, there was no observed differences in the mean NRS pain scores between the 3 dose groups at 30 minutes
    - Decrease in mean NRS pain scores relative to baseline at all subsequent time points (15 to 120 minutes) in all patients
- 15 patients received rescue analgesia
    - 5 received additional dose of nebulized ketamine
    - 10 received IV morphine
    - 5 patients in the 0.75mg/kg cohort
    - 6 patients in the 1.0mg/kg cohort
    - 4 patients in the 1.5mg/kg cohort
- No serious adverse events occurred in any of the groups
    - Overall occurrences of psycho-perceptual effects were close to 25% at 30 minutes after nebulized ketamine however the proportions of subjects experiencing dizziness and fatigue were similar across all 3 groups

Strengths:

- 1st study to evaluate feasibility and analgesic efficacy of nebulized ketamine in managing pain within the ED
- Volume of inhaled ketamine was standardized at 5mL for each group by adding normal saline to each syringe to not allow unblinding of dose
- ED providers, nurses, study participants, and investigators were blinded to the dosing of medication received

- Baseline characteristics with respect to age, sex, vital signs, and initial pain scores were similar between all 3 groups
- Authors measured the residual amount of drug in the BAN after each treatment and calculated actual dose received by the patients and compared to the ordered dose.
- Patients were allowed to receive rescue morphine (IV) if they did not want to have an additional dose of nebulized ketamine.

Limitations:

- Convenience sample with enrollment of patients only occurring Monday through Friday between 8am to 8pm and when an ED pharmacist was available for blinded medication preparation, could cause a selection bias
- Single center study with a specific protocol for nebulized ketamine that may not be generalizable to other health systems
- Large exclusion list making the results less likely to be generalizable
- Only 3 out of 120 patients had chronic pain as a chief complaint not allowing for meaningful conclusions in this patient population
- Small sample size did not allow for assessment of the variance of safety of the 3 different nebulized ketamine doses
- Participants monitored for 120 minutes. It is unclear how their pain was controlled after this time period
- No standardization of inhalation time or recording of actual treatment time make it difficult to assess compliance
- Use of breath-actuated nebulizers may not be readily available for use in other EDs

Discussion:

- Authors demonstrated that the administration of inhaled ketamine resulted in a significant reduction in pain across all 3 dosing groups and provided short-term pain relief (up to 120 minutes)
- 1.5mg/kg of nebulized ketamine did not provide better pain relief in comparison to the 0.75mg/kg and 1mg/kg doses for short-term pain management

Time	N	0.75mg/kg	1.0mg/kg	1.5mg/kg
Baseline	120	8.7	8.6	8.7
15 min	120	5.8	5.2	6
30 min	120	4.7	4.4	4.6
60 min	116	4.7	4.4	4.2
90 min	110	4	4.4	3.7
120 min	109	3.7	3.4	3.6

- The mean change in pain score at 30 minutes was 4 points and at 120 minutes was 5 points
- Authors were looking for a minimal clinically significant difference in pain score of 1.3 between the 3 groups at 30 minutes as the primary outcome.
- Majority of patients suffered from acute musculoskeletal pain from traumatic and nontraumatic origins
- In the 0.75mg/kg group more patients had complaints of flank pain and exacerbation of chronic pain compared to the other groups and the 1.5mg/kg group had more patients with abdominal pain
- No comparison to placebo or other active analgesics to see if inhaled ketamine better but not really a weakness since this is not what the authors set out to do
- No other analgesic medications were given as 1st line treatment. Ketamine isn't my 1st line agent for analgesia but, for study purposes it makes sense why this was done in this manner. It would be interesting to see how this works after we have tried standard analgesic medications first
- **IMPORTANT NOTE:** The occurrence of psycho-perceptual effects of 25% is significantly lower than what was seen in the previous study looking at sub-dissociative ketamine given as a slow infusion (54%) compared to IV push (92%) (REBEL EM)
- **IMPORTANT NOTE:** In this trial 10/120 patients required opioid rescue analgesia. This is lower than the total number of patients needing opioid rescue compared to IV sub-dissociative ketamine trial conducted in 2015 (17/90) [2]

Author Conclusion: "We found no difference between all 3 doses of ketamine administered through breath-actuated nebulizer for short-term treatment of moderate to severe pain in the emergency department."
Clinical Take Home Point: 0.75mg/kg of nebulized ketamine was both efficacious and safe in the control of acute pain in the ED. Additionally, compared to previous evidence looking at IV sub-dissociative ketamine there appears to be a signal of decreased levels of psycho-perceptual effects and need for rescue analgesia. However, these last two findings would need to be studied in a trial comparing nebulized vs IV ketamine.

References:

1. Dove D et al. Comparison of Nebulized Ketamine at Three Different Dosing Regimens for Treating Painful Conditions in the Emergency Department: A Prospective, Randomized, Double-Blind Clinical Trial. Ann Emerg Med 2021. [Epub Ahead of Print]
2. Motov S et al. Intravenous Subdissociative-Dose Ketamine Versus Morphine for Analgesia in the Emergency Department: A randomized Controlled Trial. Ann Emerg Med 2015. PMID: 25817884