Critical Review Form
Therapy

Subdissociative-dose Ketamine versus Fentanyl for Analgesia during Propofol Procedural Sedation: A Randomized Clinical Trial, *Acad Emerg Med* 2008; 15: 1-10

Objectives: **"To compare the frequency and severity of intrasedation cardiorespiratory events and interventions in ED patients undergoing propofol procedural sedation and analgesia (PSA) for orthopedic reductions or minor surgical procedures, using either low-dose ketamine or fentanyl as the adjunct analgesic agent" and "to compare secondary outcomes of adequacy of sedation and analgesia, frequency of individual hemodynamic and respiratory events and interventions, and recovery times postsedation". (p. 2)**

Methods: **Double-blind, prospective, randomized controlled trial conducted at Queen's University ED (Ontario), a tertiary hospital between Dec 2004 and Feb 2006. During hours when procedural physicians were on call, potential subjects were identified by research nurses, EPs, or ED nurses, if they required procedural sedation for an abscess drainage or orthopedic reduction. Exclusion criteria included age < 14 or > 65; ASA class III or greater; significant cardiac, pulmonary, hepatic, or renal disease; weight > 130 kg; physician diagnosed OSA; chronic opioid use; recent substance abuse or prior opioid dependence; acute intoxication; psychotic disorder; or fentanyl, ketamine, or propofol allergy.**

Two physicians (one for sedation, one for procedure) were present at the bedside for every procedure. $ETCO_2$ supplemented cardiac monitoring and pulse oximetry on every patient, but supplemental oxygen was only initiated if 0_2 <92%. If prior analgesics had been employed, a minimum 30-minute washout period occurred before initiating the study protocol.

Patients were randomized to receive either 0.3mg/kg ketamine or 1.5 µg/kg fentanyl followed 2-minutes later by propofol 0.4mg/kg with 0.1 mg/kg thereafter every 30-seconds as needed. The Modified Observer's Assessment of Alertness/Sedation scale was used to grade adequate sedation (respond only to painful stimuli) and the Modified Post-Anesthesia Discharge Scoring System (*Current Opinions in Anesthesiology* 1997; 10: 445-450) was used to determine readiness for discharge.

Data were collected on a standardized form including a time stamp for adverse events. The 1° outcome was frequency of cardiorespiratory events using a new consensus-derived (not validated) Intrasedation Event Rating Scale (see Table 1).

Table 1
Intrasedation Event Rating Scale for Procedural Sedation and Analgesia

None
Mild
SaO2 < 92% at any time
Administration of supplemental O2 by nasal cannula
sBP < 100 mmHg (if baseline ‡ 110 mm Hg)
Rise in ETCO2 > 10 mm Hg above baseline
Moderate
SaO2 < 80% at any time
SaO2 < 90% for ‡ 1 minute despite supplemental oxygen
Administration of supplemental O2 by nonrebreather mask
Jaw thrust or chin lift required
Loss of ETCO2 waveform for ‡ 30 seconds or recurrent loss
sBP < 90 mm Hg
Cardiac dysrhythmia* with sBP > 100 mm Hg
Severe
SaO2 < 70% at any time
SaO2 < 85% for ‡ 1 minute despite supplemental oxygen
Assisted ventilations provided with bag valve mask
Artificial airway required
Vomiting prior to recovery of verbal response
Cardiac dysrhythmia* with sBP < 100 mm Hg
Vasoactive agent administered
Naloxone administered
ETCO2 = oral–nasal sampled end-tidal carbon dioxide; SaO2 = arterial oxygen saturation; sBP = systolic blood pressure.
*Does not include sinus tachycardia < 150⁄min or premature beats.

Secondary outcomes included the frequency of prespecified intrasedation events (from the above scale), the propofol dosing required for induction and maintenance, procedural and recovery times, sedating and operating physician sedation adequacy assessment, patient analgesic and sedation adequacy assessment, and the frequency and severity of emergence phenomena.

With 62 subjects per arm, the study was powered at 90% with two-sided alpha 0.05 to detect a three-fold reduction in frequency of observed cardiorespiratory clinical events. An interim data safety analysis was planned *a priori* at 50% of target enrollment.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Randomized in consecutive, computer-generated, randomly permuted blocks of six". (p. 2)
2.	Was randomization concealed (blinded)?	Yes. "Patients, physicians, nurses, and data entry personnel were blinded to the contents of the syringes and the randomization schedule. The statistician performing data analysis and the drug-monitoring committee were also blinded to the drug assignment of each arm of the study". (p. 2)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All patients enrolled were included in the final analysis according to the intention-to-treat principle". (p. 6)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	See Table 2 (p. 4). The ketamine group was more frequently male and had more orthopedic procedures compared with abscess I&D. The fentanyl group started with a higher pain score (4.6 vs. 5.9).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No – see above.
2.	Were clinicians aware of group allocation?	No – see above, although they guessed allocation arm in 78% of cases.
3.	Were outcome assessors aware of group allocation?	Uncertain – not specifically stated.
4.	Was follow-up complete?	No loss to follow-up is reported.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• By *a priori* criteria, enrollment was stopped by the interim safety analysis after 63 subjects were enrolled. • 83.9% of fentanyl group had at least one event compared with 46.9% of the ketamine group. All 5 severe events occurred in the fentanyl group. • After adjustment for age, gender, weight, pre-procedure pain, and procedure type, fentanyl subjects were more likely to have a higher intrasedation event rating (OR 4.6; 95% CI 1.4 – 15.3, p=0.012). • Every observed component of the intrasedation event rating was encountered more frequently in the fentanyl group (Table 4, p.5) but the majority of events were oxygen desaturations with a "number needed to harm" of 2.8 (95% CI 1.9 – 5.7) for fentanyl to produce one desaturation below 80% that otherwise would not have occurred. • 9.7% of fentanyl group required an airway repositioning intervention though none required prolonged observation or hospitalization for a PSA related adverse event. • NNT = 2.5 (95% CI 1.6 – 5.7) for ketamine to avoid one desaturation < 92% with fentanyl. • To maintain sedation, propofol dose was higher in the ketamine group (mean difference 0.4mg/kg). • Ketamine had shorter recovery time (28° vs. 37° minutes). • Patients, operating physicians, and sedating physicians found no difference between fentanyl and ketamine for sedation or analgesia, although sedating physicians overall satisfaction on 1 – 10 scale favored ketamine (difference -1.6, 95% CI -2.3 – -0.9).

		• Sedation physicians were able to guess the treatment arm in 78% of cases (p. 6). • No emergence phenomena were identified!

2.	How precise was the estimate of the treatment effect?	The significant results above have sufficiently narrow CI to assure reasonable precision.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes, ED patients at Level I teaching hospital requiring PSA for orthopedic reduction or abscess drainage.
2.	Were all clinically important outcomes considered?	Yes.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes, ketamine is cheap and readily available with excellent safety profile.

Limitations

1) **Premature study closure based upon *a priori* data safety monitoring criteria. Although patient safety in research is paramount, many examples of contrary findings exist when fully powered studies are carried to completion.**

2) **Selection bias – investigators could have evaluated the demographic characteristics of subjects presenting during off-hours for investigators to ensure such patients do not systematically differ from those successfully recruited.**

3) **No details provided on excluded patients. Given extensive list of exclusion criteria, knowing which most often remove patients from consideration would be helpful.**

4) **Non-validated intrasedation event rating scale, though the scale has face validity and construct validity based upon the correlation of the scale with sedating physicians' event perspectives.**

5) **Insufficient blinding of clinicians – probably unavoidable for this research question.**

6) **No inter-rater reliability assessment of the subjective rating tools.**

7) **No validated tool to measure emergence phenomena.**

Bottom Line

Well-designed, single-center, multiply blinded RCT demonstrating that ketamine (0.3mg/kg) is safer than fentanyl (1.5mg/μg/kg) when used as an adjunct to titrated propofol for ED procedural sedation of orthopedic injuries in young healthy adults. Quantitatively, the ketamine NNT = 2.5 to avoid one desaturation < 92% while the fentanyl NNH = 2.8 to cause one desaturation < 80%. The lack of any observed emergence phenomena likely resulted from the protective effect of propofol and the low dose of ketamine in a very select patient population.