“Ketofol” for Procedural Sedation and Analgesia in the Emergency Department: Is the Juice Worth the Squeeze?

Amanda Fowler, PharmD
PGY2 Emergency Medicine Pharmacy Resident
University Health System, San Antonio, Texas
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center,
University of Texas Health Sciences Center at San Antonio
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Learning objectives:
1. Review goals and principles for safe and effective procedural sedation in the emergency department.
2. Relate those goals and principles to individual properties of ketamine and propofol.
3. Evaluate current literature available for use of combination ketamine and propofol for procedural sedation in the emergency department.
4. Identify the appropriate clinical scenario and patient population for sedation with “ketofol” in the emergency department.
Procedural sedation and analgesia (PSA)

I. Definition\(^1,2\)
   A. Provision of sedation and analgesia to accomplish a therapeutic or diagnostic procedure
      1. Frequent occurrence in the emergency department (ED)\(^2,3\)
      2. Standard of care in the ED\(^1\)
   B. Previously termed “conscious sedation”
      1. Term was a misnomer and has since been abandoned
         a. Patients are not truly conscious if they are sedated

II. Purpose
   A. Humanely complete necessary painful procedures or difficult diagnostic imaging\(^1-4\)
      1. Provide adequate analgesia, anxiolysis, and amnesia
      2. Muscle relaxation often required for procedure completion
   B. Decrease healthcare resource utilization
      1. Operating room patient load
      2. Anesthesiologist personnel
      3. Patient wait and recovery time
      4. Healthcare cost

III. Goals of care (Figure 1)\(^1\)
   A. Alleviate anxiety
   B. Minimize pain and discomfort
   C. Maximize amnesia
   D. Control patient behavior and movement for safe completion of procedures
   E. Minimize risks to ensure safe discharge

Figure 1. Goals of care for PSA

IV. Spectrum of drug-induced sedation (Figure 2)\(^1,2\)
   A. Minimal
      1. For procedures in which pain is controlled by local or regional analgesia (e.g. lumbar puncture, abscess incision and drainage)
      2. Anxiolysis
      3. Normal response to verbal commands
      4. Respiratory and cardiovascular function unaffected
B. Moderate
   1. Best correlates with term “conscious sedation”
   2. For procedures in which muscular relaxation and analgesia are needed (e.g. shoulder dislocation reduction, synchronized cardioversion)
   3. Depressed consciousness
      a. Or a dissociative, trance-like state from ketamine
      b. Slowed, but purposeful response to verbal commands
   4. Spontaneous ventilation adequate without intervention\(^2,5\)
      a. Hypoxia and hypoventilation incidence from 10 – 30%
      b. Ventilatory support required in 5 – 15% of patients
   5. Cardiovascular function remains intact

C. Deep
   1. Used for painful procedures that require muscular relaxation with minimal patient recoil (e.g. hip dislocation reduction, etc.)
   2. Intensely suppressed consciousness, patient not easily aroused
   3. Purposeful response after repeated or painful stimuli
   4. May require intervention to maintain airway
   5. Cardiovascular function usually remains intact

D. General anesthesia
   1. Unarousable
   2. Respiratory intervention required
   3. Cardiovascular function may be impaired

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**Figure 2. Levels of sedation\(^1\)**

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V. Principles for safe and effective PSA\(^2\)
   A. Lightest appropriate level of sedation required for procedure
   B. Plan and prepare for producing and managing deeper levels of sedation (details below)
   C. Administer analgesic before sedative
   D. Observe and monitor until mental status returned to baseline (recovery)

VI. Pitfalls
   A. Over sedation
      1. Over-dosage
         a. Dose miscalculation
         b. Inappropriate bolus strategy
            i. Mini-bolus to desired effect leads to greater overall drug exposure
      2. Duration of sedative exceeds duration of procedure
         a. Pain causes adrenergic stimulus \(\rightarrow\) cardiorespiratory drive\(^6\)
            i. Procedure completion often removes background pain
            ii. Deeper level of sedation attained
            iii. Respiratory adverse effects often occur
3. Vital sign changes due to over sedation can be life-threatening without intervention
   a. Respiratory depression
   b. Hemodynamic depression

B. Other adverse effects may be overcome with supportive care
   1. Nausea and vomiting
   2. Laryngospasm
   3. Hyper-salivation

C. Preparation can prevent or minimize severity of sedation adverse effects
   1. Patient evaluation
      a. American Society of Anesthesiologists (ASA) classification
         (1) Developed to assess degree of pre-operative illness
         (2) Not intended to predict operative risk
         (1) However, ASA class ≥ III was identified as an independent risk factor for complications from general anesthesia
         (2) Common exclusion criterion in PSA studies
      b. Predict potential for difficult airway
         i. Short neck
         ii. Micrognathia (small lower jaw)
         iii. Large tongue
         iv. Trismus (lockjaw)
      c. Predict potential for cardiorespiratory lability
         i. Obstructive or reactive pulmonary disease
         ii. Hypotension, hypovolemia
         iii. Intoxication, altered mental status

2. Preparation
   a. Adjunct airway instruments at bedside
      i. Reversal agents and intubation medications available
   b. Consult anesthesiology for predicted difficult airways
   c. Personnel
      i. At least two providers
         (1) One focused on procedure execution
         (2) One focused on sedation and monitoring
      i. Preferably two physicians and a nurse

VII. Monitoring

A. Objective measurement of sedation
   1. Children’s Hospital of Wisconsin Sedation Scale (CHWSS) (Appendix B1)
   2. Modified Aldrete Recovery Score (Appendix B2)
   3. Colorado Behavioral Numerical Pain Scale (CBNPS) (Appendix B3)
   4. Ramsay Sedation Score (RSS) (Appendix B4)

<table>
<thead>
<tr>
<th>Target Sedation Level</th>
<th>Level of Consciousness</th>
<th>Heart Rate</th>
<th>Respiratory Rate</th>
<th>Blood Pressure</th>
<th>Oxygen Saturation</th>
<th>End-tidal Carbon Dioxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>Q 2-5 min</td>
<td>Q 15 min</td>
<td>Q 15 min</td>
<td>Q 15 min</td>
<td>Continuous</td>
<td>-----</td>
</tr>
<tr>
<td>Moderate/ Dissociative</td>
<td>Continuous</td>
<td>Continuous</td>
<td>Continuous + direct observation</td>
<td>Q 5 min</td>
<td>Continuous</td>
<td>May consider continuous</td>
</tr>
<tr>
<td>Deep</td>
<td>Continuous</td>
<td>Continuous</td>
<td>Continuous + direct observation</td>
<td>Q 5 min</td>
<td>Continuous</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

Table 1. Recommended frequency for monitoring parameters in PSA
B. Ventilation: end-tidal carbon dioxide (ETCO₂) (Table 1)
   1. Carbon dioxide (CO₂) partial pressure upon exhalation completion
   2. Normal range: 35 – 45 mm Hg CO₂
   3. Greater sensitivity compared to pulse oximetry
      a. Particularly in patients on supplemental oxygen (O₂)
      b. O₂ desaturation is a delayed outcome of hypoventilation or obstruction
C. Oxygenation: pulse oximetry (SaO₂) (Table 1)
   1. Measures the O₂ saturation of peripheral blood
   2. Surrogate marker for O₂ delivery to tissues
D. Cardiovascular stability: blood pressure and heart rate monitoring (Table 1)

VIII. Adverse event (AE) reporting
A. Study-specific, numeric thresholds frequently used
   1. Some define specific durations of vital sign divergence
   2. May report clinically insignificant AEs or miss significant AEs
B. Quebec Criteria¹⁰
   1. Consensus statement from the Pediatric Emergency Research Canada (PERC) and Pediatric Emergency Care Applied Research Network (PECARN)
   2. Uniform definition of AEs observed in pediatric PSA in the ED
      a. Standardization in PSA research
      b. Intervention-based, not “numeric threshold and duration”
   3. Has been extrapolated to adult populations¹¹,¹²

Medications for PSA

I. The ideal agent¹³
   A. Rapid onset of action
   B. Adequate duration of action for procedure
   C. Predictable dose response
   D. Analgesia
   E. Rapid patient recovery
   F. Minimal side effects
II. Propofol¹³⁻¹⁵
   A. Non-barbiturate hypnotic sedative
      1. Global central nervous system (CNS) depression¹⁶⁻¹⁸
         a. γ-aminobutyric acid A (GABAₐ) receptor agonism (Figure 3)
         b. N-methyl-D-aspartate (NMDA) receptor antagonism
         c. Leads to amnestic effects

Figure 3. Propofol GABAₐ receptor activity
B. Dosing for PSA (single-agent)
   1. Initial bolus: 1 – 1.5 mg/kg intravenous (IV)
   2. Repeat bolus: 0.5 mg/kg IV Q3 – 5 minutes as needed
C. Ideal qualities
   1. Rapid onset of action
      a. 10 – 50 seconds
   2. Rapid recovery
      a. Time to recovery (first drug to patient ability to obey verbal commands) from doses of 1, 2, and 3 mg/kg was 3, 6, and 8 minutes, respectively
      b. Time to recovery (first drug to eye opening, extubation, and ability to state name) in morbidly obese patients (body mass index > 35 kg/m^2) from doses of 1, 2, and 3 mg/kg was 10.7, 13.2, and 14.6 minutes, respectively
   3. Amnestic (mechanism described above)
   4. Antiemetic
      a. Reduces concentrations of serotonin and 5-hydroxyindolacetic acid (primary serotonin metabolite) in the area postrema of the brain stem
   5. Global CNS depression leads to overall muscle relaxation
      a. Often required for successful procedure completion
D. Adverse effects
   1. Hypotension
      a. General anesthesia induction doses (2 – 2.5 mg/kg)^15,20
         i. Up to 30% reduction from baseline in mean arterial blood pressure (MAP)
         ii. Incidence: 3-26% adults, 17% pediatrics
      b. Moderate sedation for ED PSA (0.5 – 1mg/kg)^20
         i. 3.5 – 17.1% reduction in MAP reported in ED PSA literature
      c. More likely in patients ASA class III – IV
   2. Respiratory depression
      a. General anesthesia induction doses (2 – 2.5 mg/kg)^20
         i. Incidence of apnea lasting > 30 sec: 40%
      b. Moderate sedation for ED PSA (0.5 – 1mg/kg)^20
         i. Incidence of apnea requiring bag mask ventilation: < 5%
III. Ketamine^13,14
   A. Phencyclidine derivative
      1. Dissociative anesthetic^7,18,22,23
         a. Noncompetitive NMDA antagonism at the phencyclidine receptor site (Figure 4)
         b. Disrupts communication between thalamic and limbic brain regions
            i. Prevents brain from processing external stimuli (e.g. pain)
            ii. Leads to amnestic effects
   
**Figure 4. Ketamine NMDA receptor activity**

[Diagram of Ketamine NMDA receptor activity]
2. Analgesic$^{22-26}$
   a. Multiple studies demonstrate efficacy; mechanism not fully understood
   b. NMDA antagonism prevents opiate tolerance and hyperalgesic states ("windup phenomenon")
   c. Some studies suggest $mu$ receptor activity and naloxone reversal
      i. Results not reproducible in subsequent studies
3. Muscle tone (and airway reflexes) preserved$^{18,22,27}$
4. Sympathomimetic$^{22,28}$
   a. Direct noradrenergic neuron stimulation
   b. Neuronal catecholamine reuptake inhibition
   c. Resultant central and peripheral increase in circulating catecholamines

B. Bolus dose-response curve
1. Dissociative vs. sub-dissociative dosing$^{23,25,27}$
   a. Sub-dissociative (analgesia only)
      i. IV: $\leq 0.5$ mg/kg
   b. Dissociative (sedation and analgesia)
      i. Adult
         (1) IV: 1 – 2 mg/kg; IM: 3 – 4 mg/kg
      ii. Pediatric
         (1) IV: 1.5 – 2 mg/kg; IM 4 – 5 mg/kg
   c. Doses between 0.5 and 1 mg/kg IV are less predictable

C. Dosing for PSA (single agent)$^{27,29}$
1. Initial bolus:
   a. Adults: 1 mg/kg IV or 4 – 5 mg/kg IM
      i. IM administration not preferred in adults
   b. Children: 1.5 – 2 mg/kg IV or 4 – 5 mg/kg IM
      i. IM may be preferred in children who do not have or require IV access
2. Repeat bolus:
   a. Adults: 0.5 mg/kg IV as needed to maintain sedation
   b. Children: 0.5 – 1 mg/kg IV or 2 – 4 mg/kg IM as needed

D. Ideal qualities$^{22,27,30}$
1. Rapid onset of action$^{7,23}$
   i. IV: 30 – 40 seconds
   ii. IM: 3 – 4 minutes
2. Fast recovery$^{7,23}$
   a. IV: 5 – 10 minutes
   b. IM: 12 – 25 minutes
3. Amnestic
4. Analgesic
5. Spontaneous respiration and airway reflexes maintained
   a. All reflexes (not only respiratory) are maintained in dissociative sedation
      i. Patients may still reflex to pain
      ii. Extremity movements may interefere with procedures

E. Adverse effects
1. Sympathomimetic reactions$^7$
   a. Transient hypertension$^{20,31}$
      i. 10 – 50% increase from baseline
      ii. 5 - 10% incidence
b. Transient tachycardia
   i. Frequent\textsuperscript{7,27}
   ii. Bradycardia has also been reported\textsuperscript{7}

c. Tachyarrhythmia
   i. Typically avoided in patients with cardiovascular disease\textsuperscript{27}
      (1) Coronary artery disease, heart failure, uncontrolled hypertension
   ii. Literature inconclusive on hyperdynamic state increasing myocardial O\textsubscript{2} demand\textsuperscript{32}
   iii. 2.2 mg/kg IV associated with a 1% incidence\textsuperscript{33}

2. Emergence phenomena\textsuperscript{7}
   a. Vivid, possibly frightening, hallucinations during emergence from anesthesia
   b. Adults > children\textsuperscript{20,22,27,34}
      i. Reported incidence of emergence reactions in adults ranges from 0-30%
      ii. Reported incidence of emergence reactions in children are 1.4%
   c. Uncommon with doses used for PSA
      i. Risk increases with\textsuperscript{27,34}
         (1) Single dose ≥ 2.5 mg/kg IV
         (2) Total dose ≥ 5 mg/kg IV

d. Treatment/prevention
   i. Midazolam 0.05 mg/kg IV, max 2 mg
   ii. Propofol may also treat or prevent\textsuperscript{20}
      (1) GABA receptor agonist, like benzodiazepines
      (2) No comparative studies in current literature

3. Paradoxical respiratory depression and laryngospasm\textsuperscript{20,35}
   a. Associated with rapid IV push infusions and high doses\textsuperscript{36}
      i. Uncommon with doses used for PSA
      ii. Risk increases with\textsuperscript{27,36}
         (1) Single dose ≥ 2.5 mg/kg IV
         (2) Total dose ≥ 5 mg/kg IV
      iii. Administer IV push over > 60 seconds to avoid respiratory depression\textsuperscript{7,27}

4. Nausea and/or vomiting
   a. Generally occurs after emergence from dissociative state
   b. Adult incidence: 5 – 15%\textsuperscript{31}
   c. Pediatric incidence: 8.4%\textsuperscript{27,34}
      i. Predictors include
         (1) Dose ≥ 2.5 mg/kg
         (2) Intramuscular route of administration
         (3) Increasing age up to 12 years
            (a) Linear increase in incidence of emesis with increasing age (peaked at 12 years of age in patients between 0 and 21)

IV. “Ketofol”
A. What is “ketofol”?
   1. Lack of consensus in the literature
      a. Ratio of ketamine to propofol per dose
         i. ED literature reports a 1:1 ratio in single-syringe “ketofol”
      b. Weight-based dosing
   2. Mixing to produce a 1:1 “ketofol” solution\textsuperscript{11,37}
      a. All currently available formulations of propofol are 10 mg/mL
      b. Consider concentration of ketamine available
         i. 10 mg/mL, 50 mg/mL, or 100 mg/mL
c. Dilute concentrated ketamine to 10 mg/mL with normal saline (NS)
   i. 50 mg/mL: mix 2 mL of ketamine 50 mg/mL with 8 mL of NS
   ii. 100 mg/mL: mix 1 mL of ketamine 100 mg/mL with 9 mL of NS

d. Combine 10 mL of ketamine 10 mg/mL with 10 mL of propofol 10 mg/mL to produce 20 mL of “ketofol” 10 mg/mL
   i. “Ketofol” 10 mg/mL = ketamine 5 mg/mL + propofol 5 mg/mL

B. Theoretical benefits
   1. Lower doses of each sedative results in decreased dose-related side effects
   2. Opposing actions may moderate each effect (Table 2)

Table 2. Opposing actions of ketamine and propofol

<table>
<thead>
<tr>
<th>Effect</th>
<th>Ketamine</th>
<th>Propofol</th>
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<tbody>
<tr>
<td>Blood pressure</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>Respiratory drive</td>
<td>↔ *</td>
<td>↓</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Emergence reaction</td>
<td>↑</td>
<td>↔ **</td>
</tr>
<tr>
<td>Analgesia</td>
<td>↑</td>
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* Airway muscle tone maintained, however large doses and rapid infusions associated with respiratory depression and laryngospasm
** GABA receptor activity is hypothesized to prevent emergence reactions

C. Compatibility
   1. Little data available
   2. Two studies demonstrate compatibility with 10 mg/mL propofol and 10 mg/mL ketamine for one hour and three hours

“Ketofol” for ED PSA - Literature Review

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<td>Objective</td>
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<td>Trial design</td>
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<tr>
<td>Patients</td>
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<td>Outcomes</td>
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<td>Methods</td>
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### Results

**Baseline characteristics**

- **N** = 114
- Median age, yr (IQR): 36 (20 – 58)
- Most common indication: orthopedic, n (%): 79 (69.3)
- Supplemental O₂, n (%): 110 (97)
- Pre-procedural analgesia, n (%): 43 (38)

**Primary outcome: Sedation effectiveness and safety**

- Median total dose administered: 0.75 mg/kg each of propofol and ketamine
  - Range: 0.2 to 2.05 mg/kg; IQR: 0.6 to 1.0 mg/kg
- Procedure completion without adjunctive medications, n (%): 110 (96.5)

**Vital sign changes**

- Pulse, beats/min, median change (IQR): +6 (0 to 16)
- MAP, mm Hg, median change (IQR): +13.2 (4 to 19)
- O₂ saturation, n (%): 33 (29)
  - Decrease in O₂ saturation, median (IQR): -2 (1 to 3)

**Total minor AEs, n (%):** 8 (7)
- Airway malalignment, n (%): 3 (3) – resolved after airway repositioning

**Total significant AEs, n (%):** 4 (4)
- Apnea or hypoxia, n (%): 3 (3) – resolved with stimulation, airway repositioning and 100% O₂, one patient required bag-valve-mask bagging x 2 min
- Unpleasant recovery, n (%): 1 (1) – resolved with 0.025 mg/kg midazolam IV

**Secondary outcomes:**

- Recovery time, min, median (IQR): 15 (12 to 19)
- Physician and patient satisfaction scores, median (IQR): 10 (10 to 10) [nurse, 10 (9 to 10)]

### Author’s conclusions

- “Ketofol” is an effective sedation agent, with high completion rates and satisfaction scores
- Adverse effects were uncommon and responded to intervention

### Take home points

- “Ketofol” provides adequate sedation and analgesia for most adult procedures in the ED
- Study design created selection bias (only included physicians who chose to use “ketofol”)
- Wide dosing range reflects spectrum of sedation and analgesia requirements
- Median dose of 0.75 mg/kg IV falls in the unpredictable dosing range for ketamine
  - Definite analgesia with possible anesthesia
- Difficult to generalize low adverse event rate due to low sample size
  - Events were manageable

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<table>
<thead>
<tr>
<th>Objective</th>
<th>Determine if a 10 minute sedation time difference exists between “ketofol” and ketamine</th>
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<tbody>
<tr>
<td>Trial design</td>
<td>Randomized, double-blind, controlled trial at an urban, academic, pediatric ED</td>
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<table>
<thead>
<tr>
<th>Patients</th>
<th><strong>Inclusion criteria</strong></th>
</tr>
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<tbody>
<tr>
<td>ASA class I and II</td>
<td>Age 2 to 17</td>
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<tr>
<td>Isolated orthopedic injury</td>
<td>Requirement of PSA</td>
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<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>Hemodynamically unstable</td>
</tr>
<tr>
<td>Significant heart or lung disease</td>
</tr>
<tr>
<td>Intoxication</td>
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<table>
<thead>
<tr>
<th>Outcomes</th>
<th><strong>Primary</strong></th>
</tr>
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<tbody>
<tr>
<td>Decrease in total sedation time comparing “ketofol” sedation to ketamine alone</td>
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<table>
<thead>
<tr>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to sedation recovery</td>
</tr>
<tr>
<td>AE incidence</td>
</tr>
</tbody>
</table>
### Methods
- Clinical trial pharmacist prepared study medications in separate, identical syringes
- Procedure initiated after sedation score < 3 achieved on the CHWSS (Appendix B1)
- Pre-procedural analgesia administered based on clinical judgment of physician
  - Administered “well before” initiation of procedural sedation
- Prophylactic O₂ administered based on clinical judgment of physician
- Recovery defined as a score of 8 on the Aldrete Recovery Score (Appendix B2)
- AEs defined by Quebec Criteria
- Total sedation time = first study drug injection to Aldrete score ≥ 8
- Time to recovery = last study drug injection to Aldrete score ≥ 8
- Sedation efficacy = CHWSS score < 3 without requirement for non-study drugs
- Staff and patient satisfaction scores recorded using a 7 point scale
  - 1 = “not satisfied” and 7 = “extremely satisfied”

### Intervention
- Initial bolus
  - “Ketofol” group: 0.5 mg/kg ketamine and 0.5 mg/kg propofol IV
  - Ketamine group: 1 mg/kg ketamine and 0.05 mL/kg 20% lipid emulsion IV
- Repeat bolus: every 2 minutes as needed for sedation score ≥ 3
  - “Ketofol” group: 0.5 mg/kg propofol IV
  - Ketamine group: 0.25 mg/kg ketamine IV

### Baseline characteristics
- “Ketofol” n = 67; ketamine n = 69
- Median age of both groups was 11 years
- Pre-procedural opiates: “ketofol” n = 31 (46%); ketamine n = 27 (39%)
- Prophylactic O₂: “ketofol” n = 51 (76%); ketamine n = 43 (62%)

#### Primary outcome:
<table>
<thead>
<tr>
<th>Outcome</th>
<th>“Ketofol”, n = 67</th>
<th>Ketamine, n = 69</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median total sedation time, min (IQR)</td>
<td>13 (9 to 19)^</td>
<td>16 (12 to 22)</td>
<td>-3 (-5 to -2)</td>
</tr>
</tbody>
</table>

^ 3 “Ketofol” cases were technically challenging reductions and required supplemental sedation

#### Secondary outcomes:
<table>
<thead>
<tr>
<th>Outcome</th>
<th>“Ketofol”, n = 67</th>
<th>Ketamine, n = 69</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to recovery, min (IQR)</td>
<td>10 (8 to 14)</td>
<td>12 (9 to 18)</td>
<td>-2 (-4 to -1)</td>
</tr>
<tr>
<td>Sedation efficacy, n (%)</td>
<td>64 (96)</td>
<td>69 (100)</td>
<td>-4 (-9 to 1)</td>
</tr>
<tr>
<td>Number of AEs, n (%)</td>
<td>17 (25)</td>
<td>34 (49)</td>
<td>-24 (-39 to -8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2)</td>
<td>8 (12)</td>
<td>-10 (-18 to -2)</td>
</tr>
<tr>
<td>Airway obstruction</td>
<td>5 (8)</td>
<td>4 (6)</td>
<td>2 (5 to 8)</td>
</tr>
<tr>
<td>O₂ desaturation</td>
<td>3 (5)</td>
<td>2 (3)</td>
<td>2 (5 to 8)</td>
</tr>
<tr>
<td>Unpleasant recovery</td>
<td>5 (8)</td>
<td>9 (13)</td>
<td>-5 (-15 to 5)</td>
</tr>
<tr>
<td>Patient absolute recall, n (%)</td>
<td>5 (8)</td>
<td>12 (17)</td>
<td>9 (1 to 21)</td>
</tr>
</tbody>
</table>

Less common AEs included muscle rigidity, nausea, diplopia, hypersalivation, rash, and pain on injection were not statistically different (not listed here)

- Airway repositioning was the only intervention required for respiratory AEs
- Patient, nurse, & physician more likely to be “extremely satisfied” with “ketofol” group

### Author’s conclusions
- “Ketofol” in separate syringes is an effective combination for pediatric PSA
  - Shortened total sedation time by 3 minutes and recovery time by 2 minutes
  - Produced fewer AEs (especially less vomiting) compared to ketamine alone
- Both regimens had similar efficacy and incidence of airway complications

### Take home points
- “Ketofol” separate syringe strategy (dosed ketamine, then propofol) was effective for PSA
- Statistics not reported for baseline characteristics
- Statistically, not clinically, significant change in total sedation and recovery time
- Dose used in ketamine only arm less than that typically used
- Significant difference in vomiting between groups
- Very low incidence of respiratory adverse effects, responded to intervention
Appendix B3

Event | “Ketofol”, n (%) | Propofol, n (%) | Difference, % (95% CI)
--- | --- | --- | ---
Overall respiratory depression | 21 (22) | 27 (28) | 6 (-6 to 18)
ETCO₂ ↑ > 5 mm Hg | 11 (11) | 20 (21) | 10 (-1 to 20)
Respiratory rate < 8 bpm | 3 (3) | 5 (5) | 2 (-4 to 8)
SaO₂ < 90% | 7 (7) | 11 (12) | 5 (-4 to 13)
Apnea > 15 s | 2 (2) | 4 (4) | 2 (-3 to 7)
Airway manipulation | 10 (10) | 14 (15) | 5 (-5 to 14)
Bag-valve-mask | 2 (2) | 5 (5) | ---
Jaw thrust | 8 (8) | 9 (9) | ---

Several patients experienced more than one marker of respiratory distress

"Ketofol" n = 97; Propofol n = 96

Baseline characteristics are as follows:

- **Ketofol** (93% class I, 7% class II): 80% of class I and 20% of class II
- Propofol (91% class I, 9% class II): 80% of class I and 20% of class II

**Conclusions:**The intervention did not result in a statistically significant difference in provider satisfaction between ketofol and propofol.

**Interim analysis:**
- **Primary outcome:** No difference in provider satisfaction.
- **Secondary outcome:** No significant difference in incidence of respiratory depression.
- **Tertiary outcome:** No significant difference in sedation efficacy.

**Conclusion:** The study did not find a significant difference in provider satisfaction or incidence of respiratory depression between ketofol and propofol.

**References:**
- Fowler A. 2014

---

**Table 1:**

<table>
<thead>
<tr>
<th>Event</th>
<th>“Ketofol”, n (%)</th>
<th>Propofol, n (%)</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall respiratory depression</td>
<td>21 (22)</td>
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<td>6 (-6 to 18)</td>
</tr>
<tr>
<td>ETCO₂ ↑ &gt; 5 mm Hg</td>
<td>11 (11)</td>
<td>20 (21)</td>
<td>10 (-1 to 20)</td>
</tr>
<tr>
<td>Respiratory rate &lt; 8 bpm</td>
<td>3 (3)</td>
<td>5 (5)</td>
<td>2 (-4 to 8)</td>
</tr>
<tr>
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<td>7 (7)</td>
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<td>5 (-4 to 13)</td>
</tr>
<tr>
<td>Apnea &gt; 15 s</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>2 (-3 to 7)</td>
</tr>
<tr>
<td>Airway manipulation</td>
<td>10 (10)</td>
<td>14 (15)</td>
<td>5 (-5 to 14)</td>
</tr>
<tr>
<td>Bag-valve-mask</td>
<td>2 (2)</td>
<td>5 (5)</td>
<td>---</td>
</tr>
<tr>
<td>Jaw thrust</td>
<td>8 (8)</td>
<td>9 (9)</td>
<td>---</td>
</tr>
</tbody>
</table>

---

**Objective:** Compare respiratory depression between "ketofol" and propofol alone for ED PSA

**Trial design:** Randomized, double-blinded, placebo controlled trial at a university teaching hospital ED

**Outcomes:**

**Primary**
- Incidence of respiratory depression

**Secondary**
- Sedation efficacy
- Total propofol dose
- Provider satisfaction

**Methods**

- Pharmacy prepared syringes of either ketamine 0.5 mg/kg or identical volume of saline
- All patients received 0.5 or 1 mcg/kg fentanyl IV at the physician’s discretion
- All patients received supplemental O₂ (2 L/min)
- All patients wore sunglasses to hide nystagmus or lack thereof to maintain blinding
- Respiratory AEs defined by:
  - Increase in ETCO₂ by 5 mm Hg x ≥ 10 seconds
  - Respiratory rate < 8 breaths/min x ≥ 10 seconds
  - SaO₂ < 90% x ≥ 10 seconds
  - Apnea ≥ 15 seconds
  - Airway manipulation (jaw repositioning or bag valve mask device)
- Goal sedation level = CBNPS score 0 to 1 (Appendix B3)
- Sedation efficacy = CBNPS 0 to 1 maintained through procedure
- Physician and nurse recorded satisfaction with quality of sedation using a 5 point scale
  - 1 = “not satisfied” and 5 = “excellent”

**Intervention**

- Study drug administered over one minute (ketamine 0.5 mg/kg or saline placebo)
- Immediately followed by propofol loading dose 1 mg/kg over two minutes
  - Repeat boluses of propofol 0.5 mg/kg as needed to maintain goal sedation level

**Results**

- “Ketofol” n = 97; Propofol n = 96
- Median age: “ketofol” 20 years (2 – 83); propofol 22 years (2 – 75)
- ASA class: “ketofol” [94% class I, 6% class II]; propofol [91% class I, 9% class II]
- Fentanyl dose:
  - “Ketofol”: 0.5 mcg/kg – 76%; 1 mcg/kg – 24%
  - Propofol: 0.5 mcg/kg – 72%; 1 mcg/kg – 28%
- Most common indication: fracture or dislocation reduction – 87% “ketofol”; 89% propofol

**Event**

<table>
<thead>
<tr>
<th>Event</th>
<th>“Ketofol”, n (%)</th>
<th>Propofol, n (%)</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall respiratory depression</td>
<td>21 (22)</td>
<td>27 (28)</td>
<td>6 (-6 to 18)</td>
</tr>
<tr>
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<td>11 (11)</td>
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</tr>
<tr>
<td>Respiratory rate &lt; 8 bpm</td>
<td>3 (3)</td>
<td>5 (5)</td>
<td>2 (-4 to 8)</td>
</tr>
<tr>
<td>SaO₂ &lt; 90%</td>
<td>7 (7)</td>
<td>11 (12)</td>
<td>5 (-4 to 13)</td>
</tr>
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<td>2 (2)</td>
<td>4 (4)</td>
<td>2 (-3 to 7)</td>
</tr>
<tr>
<td>Airway manipulation</td>
<td>10 (10)</td>
<td>14 (15)</td>
<td>5 (-5 to 14)</td>
</tr>
<tr>
<td>Bag-valve-mask</td>
<td>2 (2)</td>
<td>5 (5)</td>
<td>---</td>
</tr>
<tr>
<td>Jaw thrust</td>
<td>8 (8)</td>
<td>9 (9)</td>
<td>---</td>
</tr>
</tbody>
</table>

**Baseline characteristics**

- “Ketofol” n = 97; Propofol n = 96
- Median age: “ketofol” 20 years (2 – 83); propofol 22 years (2 – 75)
- ASA class: “ketofol” [94% class I, 6% class II]; propofol [91% class I, 9% class II]
- Fentanyl dose:
  - “Ketofol”: 0.5 mcg/kg – 76%; 1 mcg/kg – 24%
  - Propofol: 0.5 mcg/kg – 72%; 1 mcg/kg – 28%
- Most common indication: fracture or dislocation reduction – 87% “ketofol”; 89% propofol

**Interim analysis**

**Primary outcome:** No significant difference in provider satisfaction between ketofol and propofol.
Results continued

<table>
<thead>
<tr>
<th>Secondary outcomes:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Event</strong></td>
</tr>
<tr>
<td>Sedation efficacy, n (%)</td>
</tr>
<tr>
<td>Median total propofol dose, mg</td>
</tr>
</tbody>
</table>

- Physician and nurse satisfaction significantly higher in “ketofol” group, p < 0.001
- No episodes of hypersalivation, emergence reactions, or any other serious AE
- Study halted after interim analysis showed no significant difference in primary outcome
- Post hoc: “ketofol” patients spent more sedation time at a CBNPS score of 0 (93% vs. 84%) (Figure 5)

Author’s conclusions
- Similar respiratory safety profile for both regimens
- No emergence reactions or hypersalivation likely due to sub-dissociative dose ketamine
- A more consistent level of sedation is achieved with “ketofol”

Take home points
- “Ketofol” separate syringe strategy (dosed ketamine, then propofol) was effective for PSA
- No difference in respiratory AEs; ~ 10% episodes required intervention in “ketofol” group
- No statistical difference in sedation efficacy
  - Post hoc analysis demonstrated a trend toward more effective sedation
    - Likely due to additive analgesia provided by ketamine

---


**Objective**
- Determine whether a ≥ 13% absolute reduction in respiratory AEs occurs comparing single-syringe “ketofol” to propofol for ED PSA

**Trial design**
- Randomized, double-blind, controlled trial at a trauma, community, teaching hospital ED

**Patients**
- Inclusion criteria
  - Requirement of PSA
  - ASA class I - III
  - 14 years or older
- Exclusion criteria
  - Unable to consent
  - Pregnancy

**Outcomes**
- **Primary**
  - Number and proportion of patients with a respiratory AE (Quebec Criteria)
- **Secondary**
  - Sedation inconsistency
  - Sedation efficacy (lack of recall, procedure abandonment, unplanned observation/ admit)
  - Induction time (first dose to RSS of 5/procedure initiation)
  - Procedure time
  - Sedation time (first dose to procedure completion)
  - Recovery time (last dose to discharge criteria met)
Methods

- Respiratory AEs defined by the Quebec Criteria
- Pre-procedural analgesia was allowed at the physician’s discretion, 30 minute washout
- All medications were prepared in identical 20 mL syringes by a trained nurse
  - Propofol 10 mg/mL or “ketofol” 1:1 (ketamine 5 mg + propofol 5 mg)/mL
- Sedation inconsistency = failure to maintain RSS of ≥ 5 (Appendix B4) and/or repeat dose
- All patients wore sunglasses to hide nystagmus or lack thereof to maintain blinding
- Patient recovery assessed using the Modified Aldrete Recovery Score (Appendix B2)
- Physician, nurse, and patient satisfaction were recorded using a 10 point scale
  - 1 = “not at all effective/satisfied” and 10 = “extremely effective/satisfied”

Intervention

- Initial bolus dose: 0.075 mL/kg study medication IV over 15 – 30 seconds
  - “Ketofol” group: 0.375 mg/kg ketamine + 0.375 mg/kg propofol
  - Propofol group: 0.75 mg/kg
- Repeat bolus dose: 0.0375 mL/kg study medication IV over 15 – 30 seconds (for RSS < 5)
  - “Ketofol” group: 0.188 mg/kg ketamine + 0.188 mg/kg propofol
  - Propofol group: 0.375 mg/kg

Results

Baseline characteristics

- “Ketofol” n = 142; propofol n = 142
- Ages 14 to 95; median 48 years “ketofol”; 54 years propofol
- ASA classes I and II: 97% in both groups
- Most common indication in both groups: fracture reduction, 43% “ketofol”; 46% propofol

Primary outcome: No significant difference

<table>
<thead>
<tr>
<th>Event</th>
<th>“Ketofol”, n (%); [95% CI]</th>
<th>Propofol, n (%); [95% CI]</th>
<th>Difference, %; [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory AE</td>
<td>43 (30) [23 to 38]</td>
<td>46 (32) [25 to 41]</td>
<td>2 [-9 to 13]</td>
</tr>
<tr>
<td>O₂ desaturation</td>
<td>38 (27) [20 to 35]</td>
<td>36 (25) [19 to 33]</td>
<td>2 [-9 to 12]</td>
</tr>
<tr>
<td>Central apnea</td>
<td>15 (11) [7 to 17]</td>
<td>13 (9) [6 to 15]</td>
<td>2 [-5 to 9]</td>
</tr>
<tr>
<td>Complete obstruction</td>
<td>6 (4) [2 to 9]</td>
<td>4 (3) [1 to 7]</td>
<td>1 [-3 to 6]</td>
</tr>
</tbody>
</table>

No difference in partial airway obstruction (n=11 both groups), laryngospasm, or aspiration (n=0 both groups)

Secondary outcomes:

- Sedation inconsistency (composite RSS < 5 & repeat dose) [negative outcome] (Figure 6)
  - 46% “ketofol”; 65% propofol; difference 19% [95% CI, 8 to 31%]

Figure 6. Sedation consistency measured by RSS

- Total medication dosage: “ketofol”: 0.7 mg/kg each; propofol: 1.5 mg/kg
- Sedation efficacy
  - “Ketofol”: 129 (91%); propofol: 126 (89%); difference 2 [95% CI, -5 to 9]
  - Propofol: 14 procedural agitation, 1 rigidity, 1 procedural agitation & rigidity
### Results continued

- “Ketofol”: 8 recovery agitation, 3 procedural agitation, 2 agitation during both
  - Induction and sedation time: 2 minutes and 7 minutes, respectively, for both groups
  - Recovery time: “ketofol” 8 minutes; propofol 6 minutes
  - Physician and nurse median satisfaction score: “ketofol” 10; propofol 9
  - Patient median satisfaction score: “ketofol” 10; propofol 10

### Author's conclusions

- Single-syringe “ketofol” did not decrease respiratory AEs when targeting deep sedation
  - Quebec Criteria reliance on clinician judgment for necessity of intervention
  - “Ketofol” provides a more consistent depth of sedation
  - Antiemetic effects of propofol blunted the ketamine nausea and vomiting response

### Take home points

- Single-syringe strategy mixed 1:1 as (ketamine 5 mg + propofol 5 mg)/mL
- Trained nurse prepared all study drugs
- Drug, dose, and incidence of pre-procedural analgesia not reported
- Propofol bolus dose (0.75 mg/kg IV) was lower than dosing range typically used for PSA
  - May contribute to requirement of more repeat boluses to complete procedure
- Procedural agitation in propofol group likely due to painful procedures without analgesics
- Respiratory AEs were not decreased using a 1:1 single-syringe ketofol mixture

---

### I. Summary of literature

#### A. Efficacy

1. “Ketofol” achieves adequate and consistent sedation for ED procedures
   a. Studied dose range: 0.375 – 0.75 mg/kg of ketamine and propofol each
   b. Literature supports both a single-syringe and two-syringe strategy
2. “Ketofol” statistically decreases sedation and recovery time vs. ketamine
   a. 3 minutes and 2 minutes, respectively, are not clinically significant

#### B. Safety

1. “Ketofol” does not significantly decrease dose-related adverse effects
   a. Exception: vomiting when compared to ketamine alone in children
      i. Median age of 11 years close to age in which the effect peaks
      ii. Vomiting incidence on “ketofol” was 10% less than on ketamine
   b. Hypotension: no difference between “ketofol” and propofol
   c. Respiratory AEs: no difference between “ketofol” and propofol or ketamine
   d. Emergence reactions: no difference between “ketofol” and ketamine
2. Sample sizes not large enough to conclusively rule out rare, but serious AEs

---

### “Ketofol” Considerations for Use

#### I. Safety of mixing in a single syringe

- Lack of standardization
  1. Ratio of ketamine: propofol
     a. Single-syringe “ketofol” literature in the ED support a 1:1 ratio
        i. 10 mg/mL “ketofol” as (5 mg ketamine + 5 mg propofol)/mL
     b. Single-syringe “ketofol” literature outside of the ED have reported mixing ratios from
        1:1 to 1:10 (ketamine:propofol)\(^1\)

- Institute for Safe Medication Practice (ISMP) warns unlabeled syringes may be confused for propofol alone\(^3\)

- Multiple concentrations available for IV ketamine
  1. 10 mg/mL, 50 mg/mL, and 100 mg/mL
  2. Wide variety of stocking patterns in EDs across the nation (Table 3)
     a. It is important to know which concentrations your ED stocks
Table 3. Ketamine Concentrations Stocked in ED Automated Medication Dispensing Systems

<table>
<thead>
<tr>
<th>Available Ketamine Preparation</th>
<th>Responding Hospitals, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilute Concentration Only (10 mg/ml)</td>
<td>7</td>
</tr>
<tr>
<td>Concentrated Only</td>
<td>4</td>
</tr>
<tr>
<td>500 mg/10 ml (50 mg/ml)</td>
<td>2</td>
</tr>
<tr>
<td>100 mg/1 ml (100 mg/ml)</td>
<td>2</td>
</tr>
<tr>
<td>Two Concentrations</td>
<td>10</td>
</tr>
<tr>
<td>10 mg/ml and 50 mg/ml</td>
<td>9</td>
</tr>
<tr>
<td>10 mg/ml and 100 mg/ml</td>
<td>1</td>
</tr>
<tr>
<td>Total Responses</td>
<td>21</td>
</tr>
</tbody>
</table>

Responses collected by Mason H. Bucklin, PharmD, University of Tennessee Medical Center

D. Dilution step
   1. Ketamine must be diluted to 10 mg/mL
   2. Opportunity for mathematical and mechanical errors

II. Practical considerations for use of “ketofol” in the ED
   A. Confusion among providers regarding necessary dilutions and mixing
      1. Informal survey assessing competence in dilution and dosing of “ketofol” (Figures 7 and 8) (Appendix C)

Figure 7. Respondents to “ketofol” survey

![Figure 7](image_url)

Figure 8. “Ketofol” dilution and dosing competence

![Figure 8](image_url)

B. Total sedation time gained with “ketofol” will be lost in preparation time
   1. Three minutes is not clinically significant
   2. Single-syringe “ketofol” will take longer to prepare at bedside or obtain from pharmacy than the three minutes gained in total sedation time

C. Increased resource utilization
   1. Using two vials of product instead of one
      a. Ketamine vial waste: ~8 mL of the 50 mg/mL concentration
      b. Propofol vial waste: ~10 mL of the 10 mg/mL, 20 mL vial
   2. Increased workload prior to the procedure to prepare “ketofol”
      a. Nurse or pharmacist time away from other patients
      b. If pharmacy prepares:
         i. Additional IV lab workload
         ii. Additional wait time for transport from pharmacy to bedside
Conclusions

I. “Ketofol” provides adequate sedation and analgesia for ED procedures
   A. However, it is not uniformly appropriate for every patient
II. Lack of consensus on appropriate dosing regimen and ratio of ketamine to propofol
III. No statistically significant difference in AE rate compared to ketamine or propofol alone
   A. Exception: vomiting
IV. Time added to preparation process exceeds time gained in sedation recovery
   A. When comparing “ketofol” to ketamine alone
V. Potential for dosing errors is high

Appendices

Appendix A. American Society of Anesthesiologists (ASA) classification of physical status

<table>
<thead>
<tr>
<th>ASA Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal, healthy patient without organic, physiologic, or psychiatric disturbance</td>
</tr>
<tr>
<td></td>
<td>The pathologic process that requires the procedure is localized and does not entail a systemic disturbance</td>
</tr>
<tr>
<td>II</td>
<td>Mild systemic disease without functional limitation</td>
</tr>
<tr>
<td></td>
<td>The systemic disturbance may or may not be caused by the pathologic process requiring the procedure</td>
</tr>
<tr>
<td>III</td>
<td>Severe systemic disease with functional limitation</td>
</tr>
<tr>
<td>IV</td>
<td>Severe systemic disease that poses a constant threat to life</td>
</tr>
<tr>
<td>V</td>
<td>Moribund patient unlikely to survive the operation</td>
</tr>
</tbody>
</table>

Appendix B1. Children’s Hospital of Wisconsin Sedation Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Sedation Classification</th>
<th>Level of Consciousness</th>
<th>Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Adequate</td>
<td>Agitated, anxious, in pain</td>
<td>Spontaneous without stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Minimal – conscious</td>
<td>Awake and calm</td>
<td>Spontaneous without stimulus</td>
</tr>
<tr>
<td>4</td>
<td>Moderate – conscious</td>
<td>Drowsy, with eyes open or closed, easily aroused</td>
<td>With mild to moderate verbal stimulus</td>
</tr>
<tr>
<td>3</td>
<td>Moderate – deep</td>
<td>Drowsy, arousable</td>
<td>Moderate tactile or loud verbal</td>
</tr>
<tr>
<td>2</td>
<td>Deep</td>
<td>Can be aroused to consciousness but slow</td>
<td>Requires sustained painful stimuli</td>
</tr>
<tr>
<td>1</td>
<td>Deep</td>
<td>Can be aroused but not to consciousness</td>
<td>Requires sustained painful stimuli</td>
</tr>
<tr>
<td>0</td>
<td>Anesthesia</td>
<td>Unresponsive</td>
<td>No response to painful stimuli</td>
</tr>
</tbody>
</table>

Developed as a Ramsay Sedation Scale modification with more behavioral queues to successfully assess sedation depth; validated in children; does not measure under-sedation
### Appendix B2. Post-anesthetic Aldrete Recovery Score\textsuperscript{41,45,46}

<table>
<thead>
<tr>
<th>Point Value</th>
<th>Original Criteria</th>
<th>Modified Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Color</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pink</td>
<td>SpO\textsubscript{2} &gt; 92% on room air</td>
</tr>
<tr>
<td>1</td>
<td>Pale or dusky</td>
<td>SpO\textsubscript{2} &gt; 90% on O\textsubscript{2}</td>
</tr>
<tr>
<td>0</td>
<td>Cyanotic</td>
<td>SpO\textsubscript{2} &lt; 90% on O\textsubscript{2}</td>
</tr>
<tr>
<td><strong>Oxygenation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Can breathe deeply and cough</td>
<td>Breaths deeply and coughs freely</td>
</tr>
<tr>
<td>1</td>
<td>Shallow but adequate exchange</td>
<td>Dyspneic, shallow, or limited breathing</td>
</tr>
<tr>
<td>0</td>
<td>Apnea or obstruction</td>
<td>Apnea</td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Blood pressure change &lt; 20% of normal</td>
<td>Blood pressure ± 20 mm Hg of normal</td>
</tr>
<tr>
<td>1</td>
<td>Blood pressure change 20% to 50% of normal</td>
<td>Blood pressure ± 20 – 50 mm Hg of normal</td>
</tr>
<tr>
<td>0</td>
<td>Blood pressure change &gt; 50% from normal</td>
<td>Blood pressure ± 50 mm Hg of normal</td>
</tr>
<tr>
<td><strong>Circulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Awake, alert, and oriented</td>
<td>Fully awake</td>
</tr>
<tr>
<td>1</td>
<td>Arousable but readily drifts back to sleep</td>
<td>Arousable on calling</td>
</tr>
<tr>
<td>0</td>
<td>Non-responsive</td>
<td>Non-responsive</td>
</tr>
<tr>
<td><strong>Consciousness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Moves all extremities</td>
<td>Moves all extremities</td>
</tr>
<tr>
<td>1</td>
<td>Moves two extremities</td>
<td>Moves two extremities</td>
</tr>
<tr>
<td>0</td>
<td>No movement</td>
<td>No movement</td>
</tr>
</tbody>
</table>

Scores from each criterion are totaled.

### Appendix B3. Colorado Behavioral Numerical Pain Scale\textsuperscript{42,47}

<table>
<thead>
<tr>
<th>Score</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Restful, no facial expression</td>
</tr>
<tr>
<td>1</td>
<td>Moaning, frowning, restless</td>
</tr>
<tr>
<td>2</td>
<td>Facial grimacing, protective body positioning</td>
</tr>
<tr>
<td>3</td>
<td>Resistive, crying out</td>
</tr>
<tr>
<td>4</td>
<td>Yelling, tossing about</td>
</tr>
<tr>
<td>5</td>
<td>Combative</td>
</tr>
</tbody>
</table>

Validated in adult patients undergoing gastrointestinal procedures; does not measure over sedation.

### Appendix B4. Ramsay Sedation Score\textsuperscript{11,48,49}

<table>
<thead>
<tr>
<th>Score</th>
<th>Patient Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxious or restless (or both)</td>
</tr>
<tr>
<td>2</td>
<td>Cooperative, oriented, and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Asleep – responds quickly to normal voice commands</td>
</tr>
<tr>
<td>4</td>
<td>Asleep – no response to normal voice – brisk response to loud voice or light forehead tap</td>
</tr>
<tr>
<td>5</td>
<td>Asleep – no response to normal voice – sluggish response to loud voice or light forehead tap</td>
</tr>
<tr>
<td>6</td>
<td>Asleep – no response to loud voice or forehead tap – sluggish, purposeful response to pain only</td>
</tr>
<tr>
<td>7</td>
<td>Reflex withdrawal (non-purposeful) to pain only</td>
</tr>
<tr>
<td>8</td>
<td>No response, even to pain</td>
</tr>
</tbody>
</table>
Appendix C. “Ketofol” Mixing Survey

Check one that best describes your practice level:

___ Medical student ___ EM resident ___ EM attending physician
___ ED nurse ___ ED mid-level provider ___ Pharmacist
___ Other : __________________

23 year old female s/p single vehicle MVC. She was a front seat, unrestrained passenger in a head-on collision with the abutment of an overpass. The driver is believed to have been texting while driving. Vital signs are normal and she is GCS15. There is no reported ejection or deaths on the scene, and your patient was negative for LOC. Physical exam is negative except that her left leg is flexed, abducted, internally rotated and appears shorter than the other. X-ray of the joint confirms posterior dislocation of the hip. You discuss procedural sedation with your attending and decide to use “Ketofol” for the hip reduction because all of the cool kids are doing it.

1. You wish to make a 20 mL syringe of 10 mg/mL “Ketofol” to use for the sedation. Please describe how you would prepare your syringe of “Ketofol” including the volume of ketamine 50 mg/mL (10 mL vial) and propofol 10 mg/mL (20 mL vial) that you would use.

2. How many mL of your prepared “Ketofol” would you administer to your patient for induction of sedation? She weighs 135 lbs.

3. The procedure is prolonged due to complications. How many mL of prepared “Ketofol” would you administer for maintenance of sedation and at what interval? She still weighs 135 lbs.

References

15. Diprivan[R] (propofol) [package insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC.; Revised February 2014.