Special K and Milk of Amnesia: A Balanced Breakfast?

Ketamine plus Propofol ("Ketofol") for Adult Procedural Sedation in the Emergency Department

by Ricky Turgeon

Procedural Sedation

- 4 main emergency department procedures
  1. Orthopedic manipulations
  2. Cardioversion
  3. Incision & drainage (I&D)
  4. Foreign-body removal/insertion (e.g. chest tube)
- Can be distressing ± painful
- Procedural sedation is:
  - Provision of sedation ± analgesia to enable tolerability of unpleasant procedures
  - without compromising cardiorespiratory function

Procedural Sedation: Our Options

Sedatives

- Propofol
- Midazolam
- Ketamine
- Etomidate

Combinations:

- Ketamine + propofol ("Ketofol")

± Analgesic (controversial)

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Why consider Ketofol?

Ketamine vs Propofol

	Propofol	**Ketamine**
Sedative quality	• GABAergic sedation ✓ Sedation ✓ Amnesia	• Dissociative sedation ✓ Sedation ✓ Analgesia ✓ Amnesia
VITALS	↓ BP, HR ↓ RR/apnea, SpO_2	↑ BP, ↑ HR
CNS		Recovery agitation/hallucinations
HEENNT	• Dose-dependent loss of airway patency	• Horizontal nystagmus • Hypersalivation/excessive secretions • Airway protection preserved
RESP	↑ $ETCO_2$/ $PaCO_2$	
GI/ABDO/ LIVER/HEME	Not emetogenic (can treat ketamine-induced vomiting)	Recovery emesis
MSK/EXTREM/ DERM	• Loss of muscle tone • Pain on injection	Muscle toned preserved, enhanced

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Our Clinical Question

P	In adult presenting to the emergency department who require sedation for a procedural intervention,
I	does the combination of ketamine + propofol
C	vs • Propofol • Midazolam ± fentanyl • Ketamine • Or any permutation of the above or other agents
O	Improve or worsen: • Mortality, serious adverse events • Overall satisfaction with regimen (patient, physician, nurse) • Sedation efficacy (onset, duration, need for repeat dosing) • Agitation & other acute psychiatric outcomes • Hemodynamic stability • Ventilation • GI distress • Muscular rigidity
T	During & immediately following procedure (as applicable)

Search Strategy

Databases	• PubMed • EMBASE • CENTRAL • Cochrane Database of Systematic Reviews • International Pharmaceutical Abstracts
Search Terms	• (procedur* OR conscious) AND sedation • (ketamine AND propofol) OR ketofol
Further considered if	• Adults (at least 50% of included patients) • Set in emergency department
Results	• 5 systematic reviews • No meta-analysis • **5 RCTs** • 1 prospective case series

Ketofol Dosing Strategies in RCTs

1. **Single-syringe 1:1 K+P**
   - **N=3**

2. Single dose of K, followed by P induction & PRN
   - N=1, not discussed further due to significant risk of bias

3. Single dose of sub-sedative K, followed by P induction & PRN
   - N=1, not discussed further (compared ketamine analgesic properties)

RCT 1: Phillips 2010

D	• Single-centre, "single-blind" RCT
P	• n = 28 • ≥21 y, procedure requiring sedation
I	1. K + P 12.5 mg (each) IV initially, then 5 mg q10-20 sec until sedated 2. Propofol 0.5-1.5 mg/kg IV initially, then 5 mg q10-20 sec until sedated
O	• Safety: o Hemodynamic: Initial SBP, SBP change from baseline, SBP nadir o Respiratory: Proportion experiencing respiratory depression (SpO2 <90% or airway intervention) o Presence/absence of emergency phenomena o Other negative event • Sedation o Length of sedation after lase dose o Total dosage of medication required during procedure

J Pain Pallial Care Pharmacother 2010;24:349-55.

Internal Validity: Phillips 2010

Selection bias	• Sequence generation	Computer-generated
	• Allocation concealment	?
Performance & detection bias	• Blinding of anyone?	?
Attrition bias	• Addressed incomplete outcome data	No LTFU; ITT analysis
Reporting bias	• Free from selective outcome reporting?	?

Results: Phillips 2010

Outcome	Ketofol wins? (KP vs P)
Safety	
• Initial SBP	139.9 mm Hg overall
• SBP change from baseline	-1.6% vs -12.5%
• SBP nadir	139.5 mm Hg vs 118.3 mm Hg
• Proportion experiencing respiratory depression	No difference
• Presence of emergency phenomena	0% vs 0%
• Other negative event	None reported
Efficacy outcomes	
• Length of sedation after last dose	No difference
• Total propofol dose required	~1 mg/kg vs 1.9 mg/kg

Bottom Line for Phillips 2010

- High risk of bias
- Better hemodynamic stability?

RCT 2: Nejati 2011

D	• Single-centre, "double-blind" RCT
P	• n = 62 • ≥18 y (median 25 y) • ASA class I-II • Procedure requiring sedation
I	<u>Both administered as single vials to desired sedation level:</u> 1. Ketamine + propofol • Median received: 1.125 mg/kg of each 2. Midazolam + fentanyl • Median received: M 0.04 mg/kg + F 2 mcg/kg
O	1. Time to sedation, patient pain severity (VAS), practitioner satisfaction 2. Sedation level (Ramsay Sedation Scale), change in SpO_2 & vital signs, AE rates

Acad Emerg Med 2011;18:800-6.

Internal Validity: Nejati 2011

Selection bias	• Sequence generation • Allocation concealment	Computer-generated Anesthesiologist not involved in trial prepared study pack
Performance & detection bias	• Blinding of patient	Identical vials, then sedated
	• Blinding of clinician, data collector, & outcome adjudicator	• Syringes covered in aluminum foil • No attempt to blind to AEs
Attrition bias	• Addressed incomplete outcome data	No LTFU; ITT analysis
Reporting bias	• Free from selective outcome reporting?	?

Results: Nejati 2011

Outcome	Ketofol wins? (KP vs MF)
Safety	
• HR change from baseline	No difference
• SBP change from baseline	+4 mm Hg vs 0 mm Hg
• Proportion of patients experiencing SpO_2 <90%	3% vs 35%
• Proportion needing bag mask ventilation	3% vs 3%
• Proportion experiencing emergence reaction	29% vs “less”
Efficacy	
• Time to sedation (1^o)	No difference
• Change in patient pain severity (1^o)	0 vs +3
• Sedation level	Not clearly reported
Physician satisfaction (1^o)	No difference

Bottom Line for Nejati 2011

- High risk of bias
- Ketofol benefit/risk uncertain
  - Less SpO_2 <90%
    - but no difference in bag-mask ventilation
    - Clinical significance uncertain
  - More emergence reactions
  - ?Less pain
    - Can't rule out performance bias
      - Issue with practitioner rather than sedative

RCT 3: Andolfatto 2012

S	• Lions Gate Hospital Emergency Department (single centre)
P	• n = 284 • ≥14 y (median 48-54 y) • ASA class I-III (97% ASA I or II) • Procedure requiring sedation ○ 60% orthopedic, 15-20% incision & drainage, 15% cardioversion
I	1. Single-vial ketamine/propofol 0.375 mg/kg IV (of each) initially, then 0.188 mg/kg IV (of each) q1 min PRN 2. Propofol 0.75 mg/kg IV initially, then 0. 375 mg/kg IV q1 min PRN • Both to target deep sedation (Ramsay Sedation Score [RSS] ≥5)
C	• No pre-/procedural oxygenation unless O_2 desaturation • No analgesia <30 min prior to procedural sedation

Ann Emerg Med 2012;59:504–12.

Primary Outcome: Andolfatto 2012

- **Respiratory event requiring intervention (as per Quebec criteria)**

Table 1. Quebec Criteria adverse respiratory events.[33]

Oxygen desaturation	A decrease in oxygen saturation resulting in any of the following: vigorous tactile stimulation, airway repositioning, suctioning, supplemental oxygen delivery, any airway placement, bag-valve-mask ventilation
Central apnea	Cessation of ventilatory effort* resulting in any of the following: vigorous tactile stimulation, bag-valve-mask ventilation, any airway placement
Partial upper airway obstruction	The occurrence of stridor or snoring responding to airway repositioning, airway placement, or suctioning
Complete upper airway obstruction	Ventilatory effort with no air exchange† resulting in any of the following: airway repositioning, suctioning, bag-valve-mask ventilation, any airway placement
Laryngospasm	Partial or complete upper airway obstruction, with oxygen desaturation caused by involuntary and sustained closure of the vocal cord not relieved by airway repositioning, suctioning, or oral/nasal airway insertion
Clinically apparent pulmonary aspiration	The presence before the end of the recovery phase of new physical symptoms (cough, crackles/rales, decreased breath sounds, tachypnea, wheeze, rhonchi, respiratory distress), or requirement for supplemental oxygen to maintain baseline oxygenation, or chest radiograph findings of focal infiltrate, consolidation, or atelectasis

Ann Emerg Med 2012;59:504–12.

Secondary Outcomes: Andolfatto 2012

O

ADRs (requiring intervention or interfering with procedure)

- VITALS: Hypotension, bradycardia
- CNS: Recovery agitation
- GI: Vomiting
- MSK/DERM: Muscular rigidity, rash
- Unexpected sedation-related hospitalization
- Use of reversal agents for opioids/BZDs

Sedation parameters

- Induction time
- Sedation efficacy
- Sedation consistency (RSS <5 during procedure or need for repeat dosing)
- Total medication dosage
- Sedation time
- Recovery time
- Procedural sedation

Physician, nurse & patient satisfaction (VAS 1-10, 10 = very satisfied)

Internal Validity: Andolfatto 2012

Selection bias	• Sequence generation • Allocation concealment	Computer-generated RN not involved in recruitment or care of study subjects
Performance & detection bias	• Blinding of patient	Identical vials, then sedated
	• Blinding of clinician, data collector, & outcome adjudicator	Sunglasses to blind nystagmus, nothing for muscle tone
Attrition bias	• Addressed incomplete outcome data	No LTFU; ITT analysis
Reporting bias	• Free from selective outcome reporting?	Inconsistencies between ClinicalTrials.gov protocol, methods & reported results

Results

Outcome	Ketofol	Propofol	NNT/NNH	RR (95% CI)
Death	0%	0%		-
Unplanned hospital admission	0%	0%		
ADRs				
• Respiratory events (1º outcome)	30%	32%	-	0.93 (0.66-1.32)
• Recovery agitation	7%	0%	NNH 14	
• Hypotension	0%	0.7%	-	-
• Muscular rigidity	0%	1%	-	-
• Bradycardia, vomiting, use of opioid/BZD reversal agent	Not reported			

Results

Outcome	Ketofol	Propofol	NNT/NNH	RR (95% CI)
Sedation parameters				
• Consistent (RSS ≥5 for procedure + no need for re-dose)	54%	35%	5	1.57 (1.20-2.06)
• Procedural agitation	3.5%	11%	14	0.33 (0.12-0.89)
• Total medication dose	0.7 mg/kg each	1.5 mg/kg		
• Induction time, efficacy, sedation time, recovery time	No difference			

External Validity: Andolfatto 2012

Setting	• Lions Gate Hospital, North Vancouver	• Local!

Patients	• Procedures
	  ○ 60% orthopedic reductions
	  ○ 20% I&D
	• Comorbidities
	  ○ 97% ASA class I-II
		• Mostly very painful, moderate-duration procedures
		• Relatively healthy individuals (in practice, ASA ≥3 typically sent to OR)

Interventions	• Ketofol 1:1 0.375 mg/kg IV, then 0.188 mg/kg IV PRN • Propofol 0.75 mg/kg IV, then 0.375 mg/kg IV	• Doses previously demonstrating good sedation • Wide variation in inter-institutional practice ○ e.g. some sites use propofol 1-1.5 mg/kg, then 0.5 mg/kg

Bottom Line of Andolfatto 2012

- Moderate level of bias
- Did not show that Ketofol is safer from a respiratory perspective
- Any other Ketofol benefits/risks?
  - Possibly lower risk of procedural agitation & dipping below target sedation level
    - Can easily be influenced by clinician performance bias
  - Higher rate of recovery agitation

Conclusion & Application

- Greater acquisition cost
- Ketofol offers no clear advantage versus propofol or other studied comparators
- Additional consideration:
  - No commercially-available "Ketofol" – risk of preparation errors
    - 2 different ketamine vial sizes (10 mg/mL, 50 mg/mL)
- Sedation regimen should be selected based on patient characteristics
  - Ketamine (alone) good option for:
    - Patient has history of substance abuse (higher/unpredictable propofol dose requirements)
    - Longer procedures, such as I&D
      - Ketamine duration of sedation: 10-15 min
      - Propofol duration of sedation: 3-5 min

Questions?

Re-Cap of Major Trial Limitations

PICO

Interventions

- Variation in doses used
- Variation in dosing strategies

Outcomes

- Wide variation in outcome definitions
  - e.g. Different SpO_2 & $ETCO_2$ cutoffs
- Significant subjectivity in certain outcome definitions
  - e.g. When to perform an intervention for a respiratory event
- No consistency in results between trials

Re-Cap of Major Trial Limitations

Internal validity	• Overall inadequate description of trial design • Blinding – questionable ○ Is it even possible to blind for ketamine's distinct pharmacologic profile?
Results	• Many outcomes assessed & statistical tests conducted (multiplicity) • Questionable clinical importance of statistically significant results ○ Clinically important adverse outcomes (e.g. intubation, death) too infrequent to assess intervention effect
External validity	• Applicable ○ Most emergency departments follow similar selection

Fun Youtube Videos!

- Ketamine sedation in a pediatric patient: http://www.youtube.com/watch?v=ERb5OT__bvE

Adult Ketofol Observational Evidence

D	Prospective consecutive case series	
P	• 728 adults receiving procedural sedation in single-centre ED • Lions Gate Hospital (Jul 2005 to Dec 2009)	
I	Ketamine + propofol single syringe 1:1 mixture (median dose 0.7 mg/kg of each)	
O	Successful sedation: **98%** Median recovery time: **14 min** Median staff satisfaction: **10/10**	Recovery agitation: **3.6%** New hypotension: **0.1%** Need for bag-mask ventilation: **2.9%** Vomiting: **0.1%**

Acad Emerg Med 2011;18:237–45.

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Background information

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2. Alletag MJ, Auerbach MA, Baum CR. Ketamine, propofol, and ketofol use for pediatric sedation. Pediatr Emerg Care. 2012;28:1391–5–quiz1396–8.

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Case series

- Andolfatto G, Willman E. A Prospective Case Series of Single-syringe Ketamine-Propofol (Ketofol) for Emergency Department Procedural Sedation and Analgesia in Adults. Academic Emergency Medicine. 2011;18:237–45.

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RCTs

Asynchronous ketamine/propofol dosing (not discussed in this seminar)

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Ketofol 1:1 dosing

3. Phillips W, Anderson A, Rosengreen M, et al. Propofol Versus Propofol/Ketamine for Brief Painful Procedures in the Emergency Department: Clinical and Bispectral Index Scale Comparison. J Pain Palliat Care Pharmacother. 2010;24:349–55.
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3. Thomas MC, Jennett-Reznek AM, Patanwala AE. Combination of ketamine and propofol versus either agent alone for procedural sedation in the emergency department. American Journal of Health-System Pharmacy. 2011 Nov 17;68(23):2248–56.
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