Ketamine and Dexmedetomidine: Not Just a Back Up Plan

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Objectives

- Review the PK/PD of ketamine and dexmedetomidine
- Recognize and manage adverse drug reactions from ketamine and dexmedetomidine
- Describe the benefits and risk of continuous infusion of ketamine and dexmedetomidine in critically ill patients
- Analyze the recent literature evaluating the use of ketamine and dexmedetomidine for ICU sedation, acute agitation, and alcohol withdrawal

Analgosedation

- Society of Critical Care Medicine (SCCM) recommends analgesia first sedation with light sedation goals for most critically ill patients (2B recommendation)
- Analgesia first sedation + sedative if needed

Advantages	Disadvantages

• Decrease overall exposure to sedatives
• Associated with shorter durations of
  • Mechanical ventilation
  • ICU LOS and cost
• Avoid potential sedative related ADR:
  • Death (e.g., PRIS)
  • Delirium
  • Metabolic acidosis
  • Hemodynamic derangement
	• Respiratory depression
	• Reduced GI motility
	• Pain recurrence and withdrawal upon analgesic discontinuation
	• Opioid induced hyperalgesia
	• Immunosuppression

Barr et al. Crit Care Med 2013

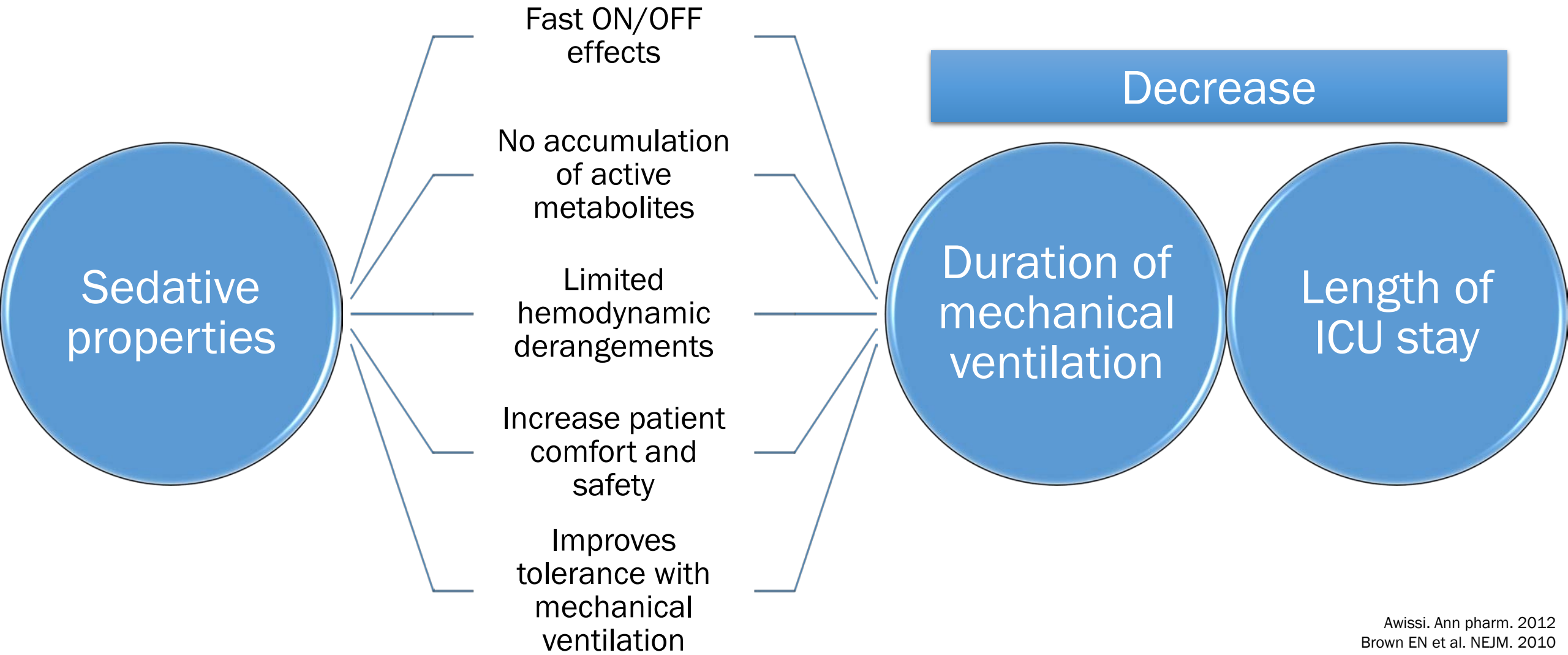
Analgosedation is not for everybody

Many patients will require sedative supplementation (18-70%)

- Alcohol/drug withdrawal & drug intoxication
- Neuromuscular blockade
- Elevated intracranial pressure
- Status epilepticus
- ECMO

Barr et al. Crit Care Med. 2013
Awissi. Ann pharm. 2012

What is the ideal sedative agent



Awissi. Ann pharm. 2012
Brown EN et al. NEJM. 2010

Current non-benzodiazepine options available

Propofol

Dexmedetomidine

Ketamine

Ketamine: Mechanism of Action

CNS

- Noncompetitive antagonist of NMDA receptors in the brain + spinal cord
  - Reduces the frequency and mean opening time of the Ca_2 channel + prevents Ca_2 influx
  - Anti-inflammatory properties: Inhibits NF-kB, TNF-alpha, + IL-6
- Very weak agonist for the delta + mu opioid receptors
  - Naloxone has no effect in reversing ketamine effects

Cardiovascular

- Directly stimulates the CNS to release catecholaamines
- Inhibits neuronal and extra-neuronal uptake of catecholamines
  - Results in a 10-30% increase in SBP and HR
  - Response attenuated with dexmedetomidine
- Negative inotrope

Pulmonary

- Does not suppress normal upper airway protective reflexes (coughing, sneezing and swallowing)
- Inhibits effect on muscarinic receptors → increase in bronchial secretion and mucus formation
- Preserves pulmonary hypoxic vasoconstriction and has minimal effects on PVR
- Stimulates Beta 2 receptors → bronchodilation (dose dependent)

Green SM et al. Ann Emerg Med. 2009
Erstad BL et al. J Crit Care. 2016

Ketamine: Pharmacokinetics

Absorption

- Oral: 17-24%
  Onset: 30min
- IM: 93%
  Onset: 3-4 min
- Intranasal: 45%
  Onset: 10 min

Distribution

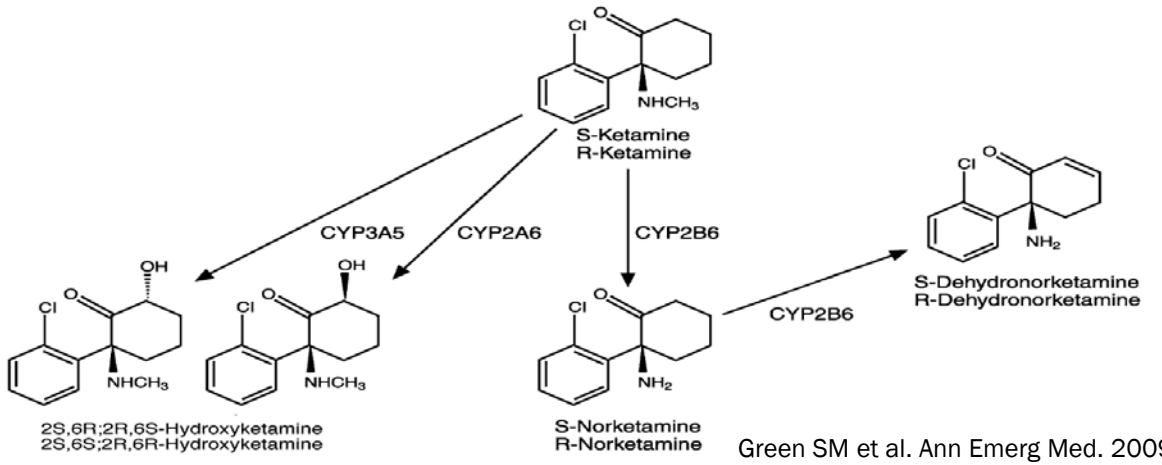
- VD: 2-3L/kg
- Alpha half life: 2-4 min
- Beta half life: 2-4 h
- Protein binding: 10-30%

Metabolism

- 80% is N-demethylated to norketamine
- CYP 3A, 2B6 and 2C9 responsible for N-demethylation

Elimination

- Metabolites are excreted in bile and urine after glucuronidation
- Renal excretion: 4% as unchanged drug



Green SM et al. Ann Emerg Med. 2009
Erstad BL et al. J Crit Care. 2016

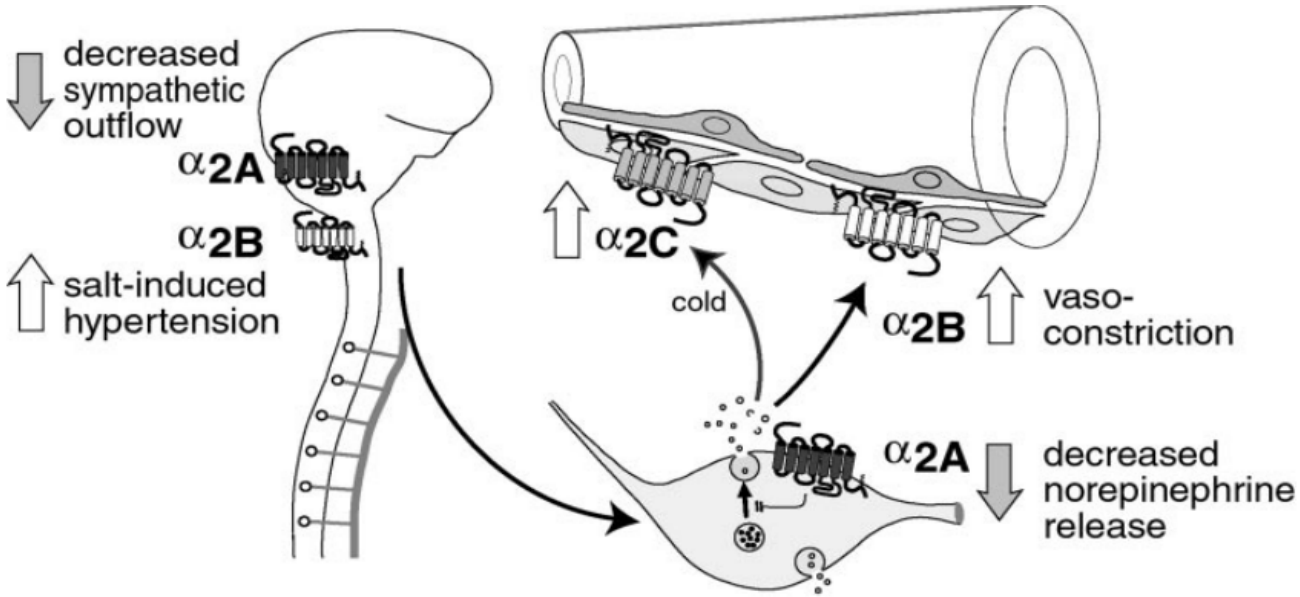
Ketamine dosing by indication and route of administration

Indication	Route	Dose
Dissociative sedation	IV	1.5–2 mg/kg
	IM	4–5 mg/kg
Brief sedation—rapid administration <5 s	IV	0.5–0.8 mg/kg
Analgesia	IV	0.2–0.75 mg/kg
	IM	1–3 mg/kg
	IN	0.5–1 mg/kg
Induction of rapid sequence intubation	IV	2 mg/kg
Moderate to severe asthma	IV	2 mg/kg
Pharmacologic restraint	IM	4–5 mg/kg

Green SM et al. Ann Emerg Med. 2009
Erstad BL et al. J Crit Care. 2016

Dexmedetomidine: Mechanism of Action

CNS	• Hypnotic effect of DEX ↓ neuronal firing in the locus ceruleus + activity in the ascending noradrenergic pathway (via alpha-2A)
	  • ↓ noradrenergic output from the locus ceruleus allows for increased firing of inhibitory neurons which further inhibit the locus ceruleus
	• Analgesic effect:
	  • Activation of both α2-C and α2-A, in the neurons of the superficial dorsal horn directly ↓ pain transmission
	  • Reduce the release of substance P, and glutamate

Cardiovascular	 DEX can significantly↑ SBP when plasma conc. ↑ from 0.5 to 3.2 ng/ml. • Correlate with the rate of IV infusion and plasma concentration • At serum conc. greater than 1 mcg/l, the BP changes from a mild decrease from baseline to an elevation

Keating GM et al. Drugs. 2015
Tomassoni AJ. Crit Care toxicology. 2017

Dexmedetomidine: Pharmacokinetics

Absorption

IV: 100%
Onset: 15-20 min

Intranasal: 82%
Onset: 30-45 min

Distribution

VD: 109-223 L

Distribution half life: 6 min

Elimination half life: 2.2-3.7 h

Protein binding: 94%

Metabolism

34% Direct N-glucuronidation by UGT2B10 + UGT1A4

Hydroxylation of CYP2A6

No active metabolites

Elimination

Metabolites excreted renally (95%) and fecally (4%)

Less than 1% is excreted unchanged

Keating GM et al. Drugs. 2015
Tomassoni AJ. Crit Care toxicology. 2017

Comparison of Adverse Effects of Sedatives

Dexmedetomidine	Ketamine

• Bradycardia: up to 30% decrease from baseline
  • Incidence: 1-42%
  • Increase risk with AVN blockers, hypovolemia
• Hypotension: 13-68%
• Hypertension
  • Increase risk: larger doses + rapid IV push
• Dry mouth
• Fever: up to 10%
	• Emergence reactions: 5-25%
	  • Crying, Agitation, delirium, dysphoria, nightmares, and hallucinations
	• Vomiting 5-15%
	  • Increased when given IM, IV at doses >2.5mg/kg
	  • Can be treated with BDZ or ondansetron
	• Laryngospasm
	  • Appears to be idiosyncratic
	• Increase in ICP
	  • Only in patients with structural barriers to normal CSF flow (ex: hydrocephalus)
	• Hyper-salivation
	• Hypertonicity and Random movements
	  • involuntary, rhythmic muscle contractions involving the arms and legs

Keating GM et al. Drugs. 2015
Tomassoni AJ. Crit Care toxicology. 2017
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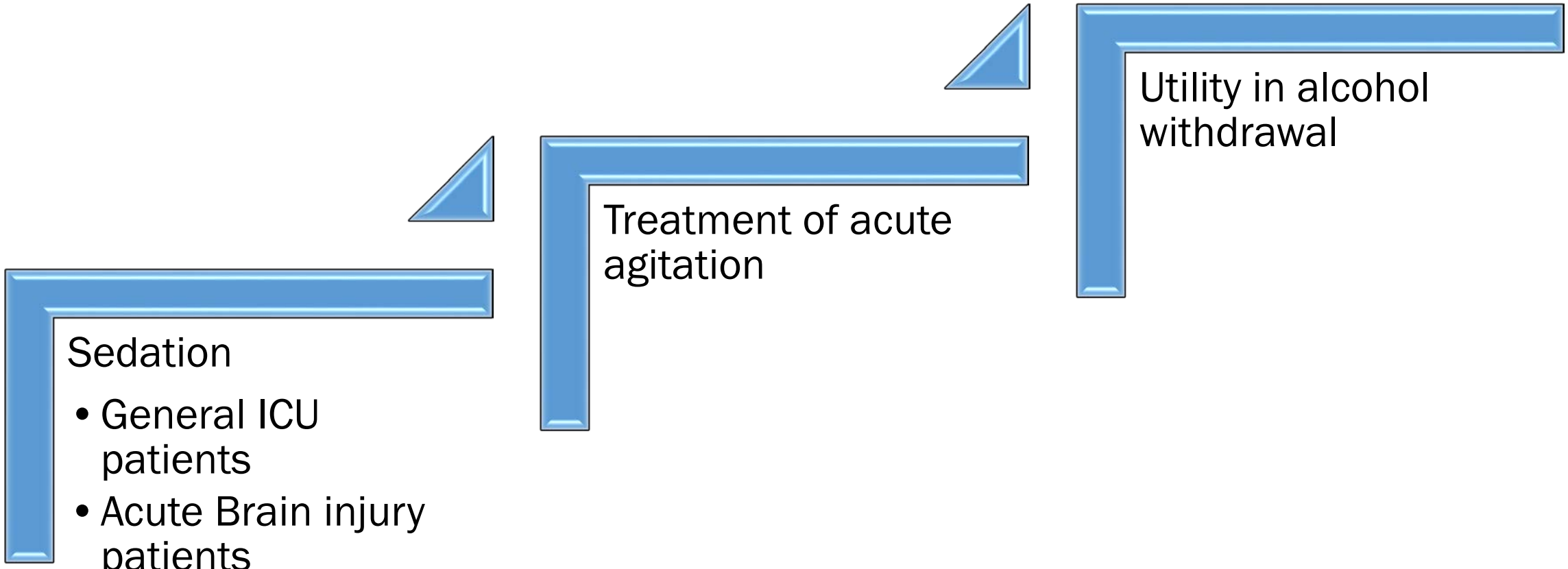
Question 1

For ketamine which dose would be classified as sub-dissociative

A. 2 mg/kg IM
B. 0.5 mg/kg IV
C. 1.2 mg/kg IV
D. 1.5 mg/kg IM
E. Both A and B

Clinical application of ketamine + dexmedetomidine



Evidence for dexmedetomidine in ICU sedation

Study Name + Comparator	N	% Time at target sedation range	Dex median (IQR) dose (mcg/kg/h) + duration	Main outcomes
MIDEX (2012) DEX: 0.2-1.4 mcg/kg/h MID: 0.03-0.2 mg/kg/h	249 251	60.7 56.6	NO LD MD: 0.45 (0.27-0.76) Duration: 42h	Median time to extubation 101h v 147h*
				Median duration of ICU stay 211h v 243h
PRODEX (2012) DEX: 0.2-1.4 mcg/kg/h PRO: 0.3-4.0 mg/kg/h	251 247	64.6 64.7	NO LD MD: 0.93 (0.67-1.2) Duration: 42h	Median time to extubation 69h vs 93h*
				Median duration of ICU stay 164h v 185h
SEDCOM (2009) DEX: 0.2-1.4 mcg/kg/h MID: 0.02-.01 mg/kg/h	244 122	77.3 75.1	LD: 1 mcg/kg (only in 8%) MD: 0.83 (0.46–1.20) Duration: 84h	Median time to extubation 3.7 days v 5.6 days*
				Median duration of ICU stay 5.9 days v 7.6 days

Dex: dexmedetomidine, PRO: propofol, MID: midazolam
*Significant difference

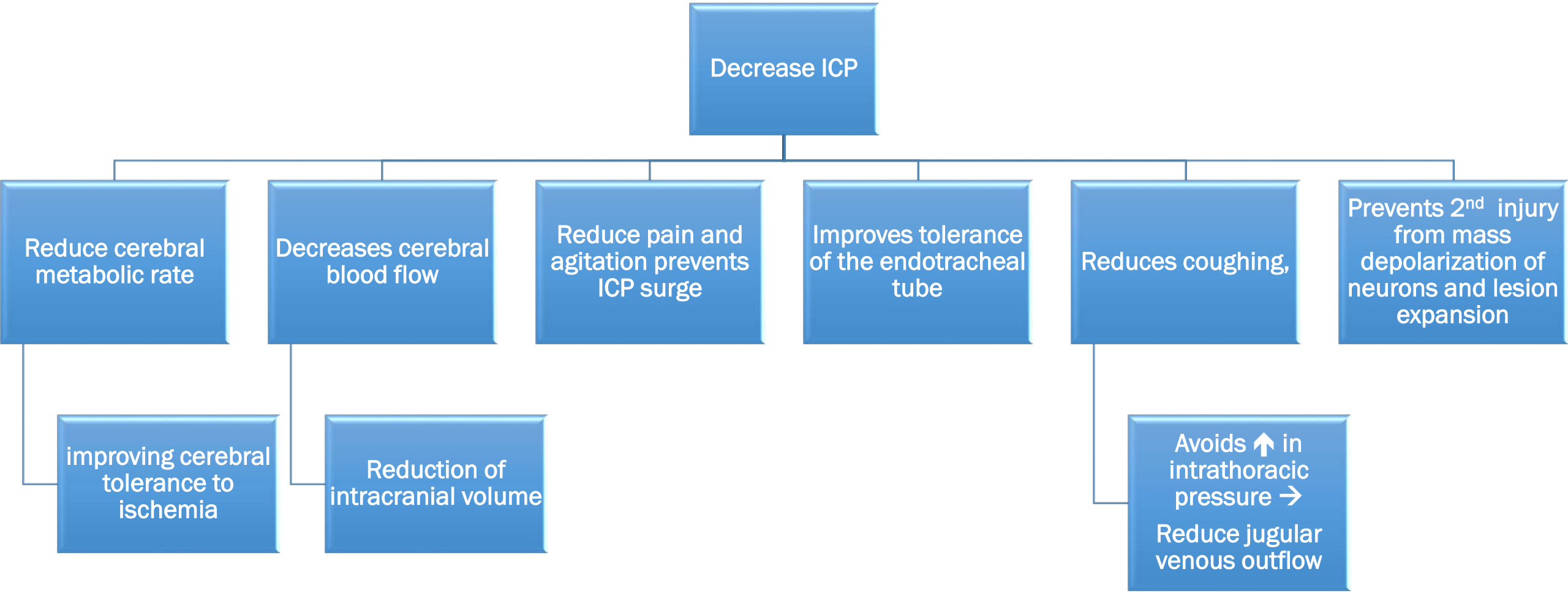
Jakob SM et al. JAMA. 2012
Riker RR et al. JAMA 2009

Does literature support the use of ketamine in ICU

Author (year) and study design	Patients	Ketamine dosing (mg/kg/h) Regimen	Comparator regimen	Primary Outcomes	Significant findings
Guillou et al. (2003) Prospective, single center, double-blind RCT (n=93)	Major abdominal surgery and mechanically ventilated in SICU	Ketamine + Morpine PCA Bolus: 0.5 mg/kg Initial: 0.12 for 24 h, then 0.06 mg/kg/hr for the following 24 h	Morphine via PCA + placebo LD: 2mg MD: 1mg q7min	Morphine Consumption at 48 h 80 (+/-37) v 58 (+/-35) mg (P < 0.05)	No difference • Hallucinations • Pain scores • Ramsay sedation scores
Umunna et al (2015) Single center retrospective (n=30)	Mechanically intubated > 24 h	No bolus given Initial: 0.5 Median: 2 Range: 0.5-4 Duration: 59.6 h	None	Incidence of ADR 4/30 switched agents due to ADR • 2/4: Afib • 2/4: Agitation	Average MAAS: 1.9 • 50% also on fentanyl infusions
Groetzinger et al (2015) Single center retrospective (n=43)	Mechanically intubated > 6 h	Used as an adjunct Initial: 0.16 Median: 0.44 Range: 0.05-2 Duration: 86.4 h	None	Goal SAS score achieved in 69% of pts	Once initiated • 60% of pts had 1 sedative ↓ or DC
Buchheit et al (2017) Single center retrospective (n=40)	Mechanically ventilated in SICU	No bolus Initial: 0.3 Median: 0.3 Range: 0.06-0.3 Duration: 46 h	Morphine:6.6 mg/h Propofol:150 mg/h	The Morphine infusion rate at 24 h after ketamine initiation 0 (0-3.3) v. 6.6 (3.3-10) mg/h (P < .001	Once initiated • 55% of pts had opioid infusions DC within 24 h • No difference in RASS

Sedation in Acute Brain Injuries

Rationale for using sedation in patients with acute brain injury



Oddo et al. Critical Care. 2016

Fundamental problems associated with sedation in acute brain injury

- Continued benzodiazepine use
  - Leads to tolerance and tachyphylaxis
  - Increased incidence of delirium

- Propofol at higher doses or longer duration increases risk of
  - Arterial hypotension
  - Hypertriglyceridemia
  - Propofol infusion syndrome (PRIS)

- Daily sedation breaks are not sufficiently safe in this patient group

Oddo et al. Critical Care. 2016

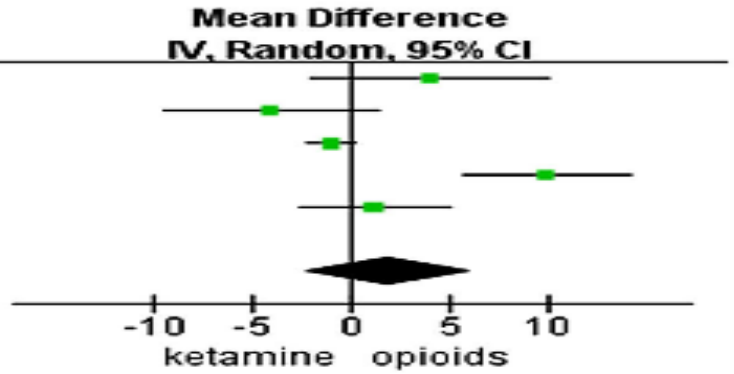
Ketamine does not increase intracranial pressure compared with opioids

Variable	Continuous infusion	Bolus dosing
Total patients	104	63
Study design	Four prospective RCTs	2 prospective single arm trials 1 prospective case control
Pt description	All patients were classified as severe TBI, with GCS of 8 or less, and all being ventilated + sedated with midazolam	
Dosing range	2.5-6.2 mg/kg/h	1-5 mg/kg
Duration range	1 – 6 days	N/A
Outcomes	No difference in ICP control No ICP fluctuations	Reduction in ICP with ketamine bolus Sustained effect when used preemptively for stimulating procedures

A ICP

Study or Subgroup	ketamine Mean	SD	Total	opioids Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bourgoin 2003	19	8.4	12	15	6.8	13	16.8%	4.00 [-2.02, 10.02]
Bourgoin 2005	14.6	8.3	15	18.7	6.8	15	17.9%	-4.10 [-9.53, 1.33]
Kolenda 1996	12	2.2	17	13	1.2	18	24.5%	-1.00 [-2.18, 0.18]
Michalczyk 2013	27	7	39	17	6	10	20.0%	10.00 [5.68, 14.32]
Schmittner 2007	15.9	5.8	12	14.7	3.4	12	20.9%	1.20 [-2.60, 5.00]
Total (95% CI)			**95**			**68**	**100.0%**	**1.94 [-2.35, 6.23]**

Heterogeneity: $Tau^2 = 19.15$; $Chi^2 = 27.54$, $df = 4$ ($P < 0.0001$); $I^2 = 85\%$
Test for overall effect: $Z = 0.89$ ($P = 0.38$)



Gillman LM et al. Neurocrit Care. 2014

Dexmedetomidine use in acute brain injury

Effect on ICP

- 3 studies (2 RCTs + 1 prospective control trial)
- 54 patients 85% of patients with TBI
- All patients had a baseline ICP < 20
- No difference in ICP as compared to placebo or propofol

Effect on CPP

- When compared to propofol
  - No difference in brain tissue oxygenation or lactate-to-pyruvate ratio
  - No difference in mean CPP during active drug infusion, during breaks in sedation for neurological examination

ADRs

- Total of 13 studies and 425 patients
- Hypotension: 6-46%
- Bradycardia: 5-41%
- No significant differences in adverse events between dexmedetomidine and propofol or midazolam

Oddo et al. Critical Care. 2016
Tran A et al. Neurocrit Care. 2017

Question 2

Which of the following patients should avoid the use of ketamine

A. TBI patient with ICP: 25 on fentanyl 300mcg/hr and propofol a 80 mcg/kg/min
B. TBI patient with a known history of hydrocephalus and ICP 15
C. TBI patient in which an EGD will be performed
D. All of the above

Summary of sedative effects on CNS

Sedative	ICP	CPP	CBF	MAP	Seizure threshold
Dexmedetomidine	Decreased or unchanged	Increased or unchanged	Decreased	Decreased	?
Ketamine	Decreased or unchanged	Increased or unchanged	Increased or unchanged	Increased or unchanged	Decreased

Oddo et al. Critical Care. 2016
Tran A et al. Neurocrit Care. 2017
Gillman LM et al. Neurocrit Care. 2014

Role Of Sedatives In Acute Agitation

Management of acute agitation in non-intubated patients

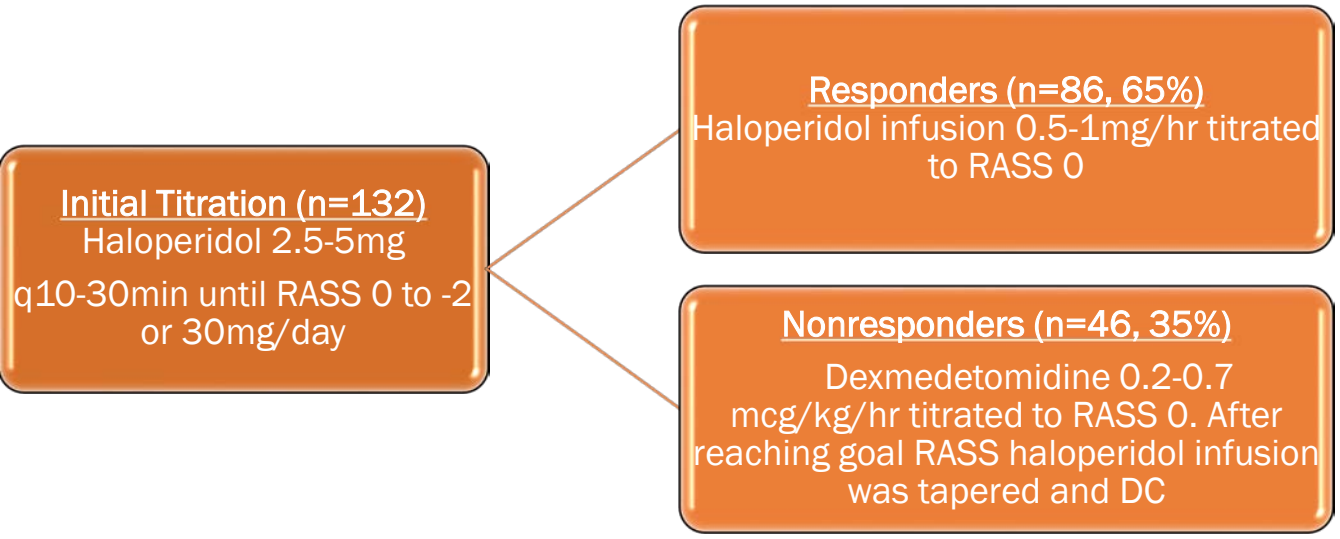
- Prevalence of acute agitated delirium = 25%
- Current problems with commonly utilized agents
  - Doses of haloperidol necessary to relieve agitation can be high
    - IV daily doses can range from 20 to 1540mg
    - Increases concerns for QTc prolongation, extrapyramidal symptoms, and NMS
    - Haloperidol failure rates range from 30-43%
  - Propofol and benzodiazepines utility is limited
    - Due to high risk of respiratory depression and possible intubation

Carrasco et al. Crit Care Med. 2016

Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients

Study design

- Nonrandomized controlled single center trial
- Nonintubated ICU patients with RASS 1-4, CAM-ICU + and ICDSC ≥ 4



Dexmedetomidine group

- Mean RASS of 3.9
- Mean Dose of DEX: 0.47 (0.43-0.50) mcg/k/h
- More time at sedation goal (RASS 0 to -2)
  - (93 v 59%, p=0.0001
- Lower rate of excessive sedation
  - (0 v 11.6%), p=0.01
- Less morphine administered
  - (0.1 v 0.6mg/kg/day p=0.0001
- Decrease in ICU length of stay
  - (3.1 v 6.4 days) p=0.0001
- No difference in bradycardia + hypotension

Carrasco et al. Crit Care Med. 2016

Ketamine: acute agitation

Author (year)	Riddell et al (2017)	Parsch (2017)
Study design	Single center, prospective observational study (n=98)	Single center, retrospective, observational study (n=78)
Patient population	Acutely agitated adult pts in the ED Baseline agitation score: 4.2-4.8 (highly aroused + violent)	Acutely agitated mental health pts transported by critical care retrieval team Retrieval duration range: 175-187 min
Ketamine	N=24 18 pts: 0.87 mg/kg IV 6 pts: 2.97 mg/kg IM	N=28 Ketamine monotherapy: 63% Ketamine + propofol (15%) or BDZ (19%) Antipsychotic combinations: 8%
Comparator	Midazolam (n=19) 3mg IV (12), 2.3mg IM (4) Lorazepam (n=33) 1.9mg (28), 2.4mg IM (5) Haloperidol (n=14) 5.7mg IM (14) Combo: (n=10) 5mg IM haloperidol + Lorazepam 2mg	N=50 Propofol monotherapy: 26% Combo: 26% propofol + BDZ Ketamine monotherapy: 19% Antipsychotic combinations: 16%
Primary outcome	Agitation score $\leq$ 2 2: mildly aroused and pacing,1: settled and 0: asleep)	Compared intubation rates pre- and post ketamine protocol

Ketamine group results	• More pts were no longer agitated at 5, 10, + 15 mins vs other medications ($p = 0.001$, $p \leq 0.001$, $p = 0.032$)
	• No difference in time to control agitation:
	  • (K:6.5 v M:15v L:17.7 v H:13.4v Combo:23.3, p=0.1)
	• Median SBP changes from +5 to +17 mm Hg + HR changes from 0 to +8 beats per minute
	• 8.7% of ketamine pts were intubated
		• Dose: 0.25 - 0.5 mg/kg IV slow push or infusion of 1-2mg/kg/hour titrated to effect
		• 36.00% of pts intubated before v 7.14% after ketamine protocol
		  • OR: 0.14, 95% CI (0.02–0.71, $P < 0.01$)
		• Receiving psychiatric services did not report any adverse findings related to ketamine

Potential Adjunctive Agents Utilized in Alcohol Withdrawal

Options for Benzodiazepine-Refractory Alcohol Withdrawal?

- Refractory alcohol withdrawal
  - Received > 40 mg diazepam or equivalent in one hour
  - Received > 200 mg of diazepam or 40 mg of lorazepam during the first 3h without achieving sedation goals
- Down regulation of GABAA receptors and increase in excitatory neurotransmitters
- Multimodal Approach
  - Identify benzodiazepine failure
  - Adjunctive agents
    - Propofol
    - Dexmedetomidine
    - Phenobarbital
    - Ketamine

Long D et al. Am J Emerg Med. 2017

Dexmedetomidine and Ketamine for AWS

Author (year) and study design	Patients	Prior BDZ requirements (diazepam eq)	Intervention dosing regimen and duration	Comparator regimen	Change in BDZ requirement (diazepam eq)	Significant findings
Wong et al (2015) Retrospective single center N=23	ICU pts + 75% had DTs	170mg	Ketamine Time to start: 33.6 h Median dose: 0.2mg/kg/h Duration: 56 h	N/A	Change in 12 h •Median: −40.0 (−106.7, +21.7) Change in 24 h • Median: −13.3 (−86.7, +50.0)	•ICU LOS: 6.3 d Median duration of MV: 2.5 (2,4)d
Bielka et al (2015) Single center RCT N=72	ICU pts with RASS: 2 + CIWA: 25	30mg	Dexmedetomidine Time to start: 24 h Median dose: 0.5 mcg/kg/h Duration:36 h	Symptom-triggered diazepam protocol	Change at 24 h •DEX decreased 20 v 40 p=0.001	•ICU LOS: 2.1 d Higher rates of bradycardia (31 v 6%) p=0.03
Mueller et al (2014) prospective double blind RCT N=24	ICU pts req ≥ 16mg of lorazepam + CIWA > 15	82mg in lorazepam equivalnet	Dexmedetomidine Time to start: 24.5 h HD: 1.4 mcg/kg/h LD: 0.4 mcg/kg/hr Duration:61 h	Symptom-triggered CIWA protocol with lorazepam	Change at 24 h Median: −56.4 (−94.5 to −16.8) in lorazepam equivalent	ICU LOS: 4.7 d No difference between HD + LD Dex in lorazepam requirements

Conclusion

- Ketamine and dexmedetomidine are increasingly being utilized in critically ill patients due to their unique advantages over more traditional sedatives
  - These agents have proven to lower opioid + BDZ requirements with minimal adverse effects
  - Should be incorporated into a multimodal analgesic approach to treat pain in critically ill patients requiring mechanical ventilation
- Evidence continues to accumulate but more research is needed in the critically ill population for alcohol withdrawal and acute agitation