Brigham and Women's Hospital
Founding Member, Mass General Brigham

Dexmedetomidine and common analgesic /sedatives medications used for procedural sedation and analgesia (PSAA)

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October 2024

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosure: Presenter has no financial or intellectual relationships relevant to this activity.

Objectives

- Evaluate the most current literature on the use of dexmedetomidine for dental PSAA

- Discuss other medication commonly used in PSAA, including patient-specific variables that have potential to impact the safety and efficacy of the various pharmacotherapy options used in PSAA

Goals of PSAA in dental surgery: General principals we can all agree on in no particular order

- Facilitate the procedure
- Minimize pain
- Minimize anxiety/agitation
- Minimize unpleasant memories of the procedure
- Minimize over-sedation/prolonged sedation
- Minimize adverse effects of medications
- Minimize LOS/time in recovery/office chair time/hospital time
- Minimize delirium
- Minimize long-term consequences of operative/procedural pain
- Minimize mortality

Questions:

1. **What therapy is best to optimized these outcome?**
    - **Likely depends on many factors/variables**

Ito T, et al. J Pers Med. 2023 Mar 1;13(3):461. doi: 10.3390/jpm13030461.

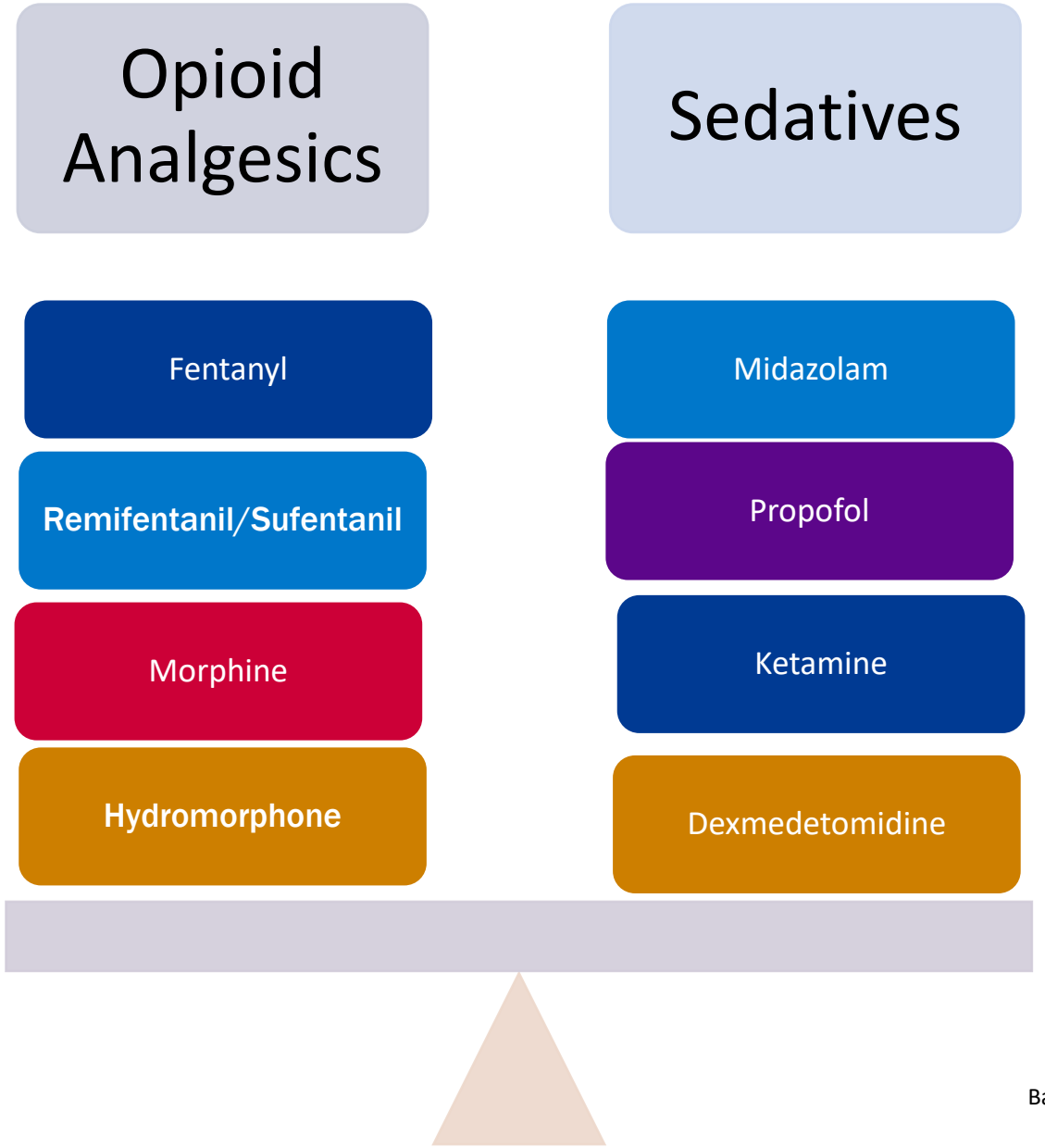
Patient Case 1

A 10-year-old female presents for a painful but short procedure. The patient does not currently have an IV.

- Very anxious
- HR: 130 bpm
- RR: 20 breaths/min

You consider using IN dexmedetomidine for the procedure. What are the potential advantages and disadvantages of IN dexmedetomidine in this patient.

Pharmacotherapy Options



Baker SN, et al. *J Pharm Pract*. 2011;24(2):189-195.

Average wholesale cost of select medication used for PSAA

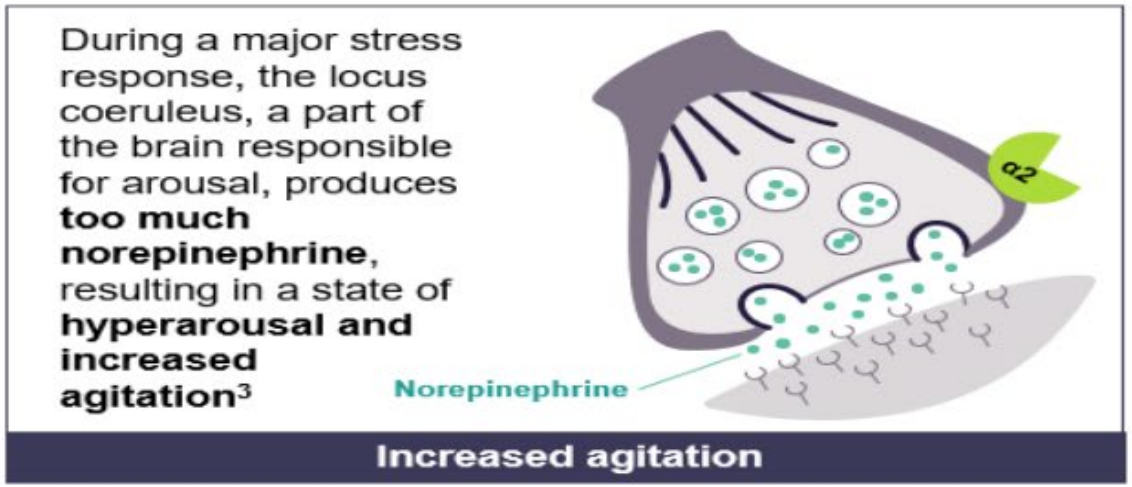
- Opioids
  - Fent 100 mcg ~ $1.54
  - Morphine 2 mg ~ $2.87
  - Hydromorphone 1 mg ~ $4.32
  - Sufentanil – 50 mcg/1mL ~ $8.58
  - Remifentanil – 1 mg ~ $61.29

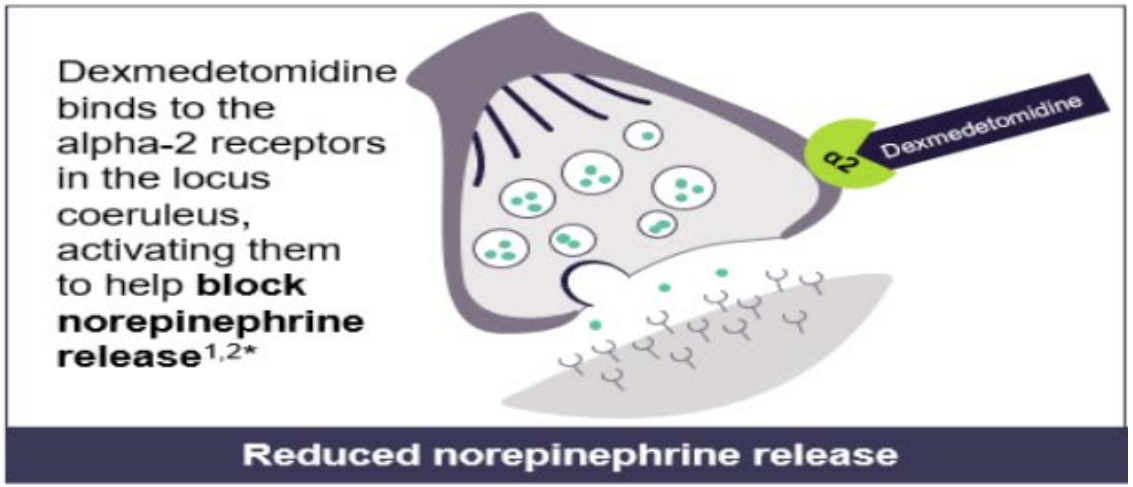
- Sedatives
  - Midaz 2mg ~ $0.65
  - Midaz 5mg ~ $1.16
  - Propofol 20 mg ~ $4.32
  - Dexmedetomidine 200 mcg vial ~ $5.25
  - Ketamine 10 mg/mL (20 mL) ~ $19.78

- Dexmedetomidine – alternative dosage forms
  - IV 80 mcg/20 mL (4 mcg/mL) vial ~ $32
  - IV 200 mcg/50 mL (4 mcg/mL) bag~ $18
  - Buccal film 120 mcg or 180 mcg~ $125

Dexmedetomidine overview

- Pharmacology and Pharmacokinetics
  - Mechanism of action: Centrally acting selective alpha$_2$-adrenoreceptor agonist
    - Very similar to clonidine, however dexmedetomidine is 8-times more selective than clonidine to the alpha-2 receptor
    - Presumed to reduce release of norepinephrine, a key mediator of agitation





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Sim JH, Yu HJ, Kim ST. Korean J Anesthesiol. 2014;67(1):8-12.
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Whalen LD, et al. Pediatr Crit Care Med. 2014;15(8):706-714.
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Miller CWT et al. West J Emerg Med. 2020;21(4):841-848.

Dexmedetomidine overview

Table 2. Advantages of each sedative.

	Short-Acting	Antagonist	Less Respiratory Depression
Propofol [43,44]	✔✔	-	✔
Midazolam [1,70,71]	✔	✔	✔
Dexmedetomidine [85–87]	-	-	✔✔
Remimazolam [96,97,100]	✔✔	✔	✔

- Pharmacology and Pharmacokinetics
  - Onset of action ~ 5-10 minutes
  - Peak effect ~ 15-30 minutes
  - Duration of effect ~ 60-120 min after bolus
  - Highly lipophilic
  - Highly protein bound
  - Metabolized by phase 1 and phase 2 metabolism
    - Phase 1 - CYP450 - 2A6
    - Phase 2 - Hepatic N-glucuronidation, N-methylation

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Dexmedetomidine overview

- Advantages
  - Enhanced analgesic effects of other analgesics (intraop/postop)
    - Mild analgesic properties
      - Reduces opioid consumption in some surgery patients
      - However, opioid consumption has not been reduced in mix med/surg trials
  - Light sedative
    - Hard to reach deep sedation
  - Minimum to no respiratory depression at doses used in clinical practice
  - In ICU/immediate postoperative patients MAY reduce time on mechanical ventilation compared to midazolam infusion (SEDCOM) (MIDEX) in the ICU
  - ?Produce protective sleep compared to alternative medications?
  - Several routes of administration

Szumita PM, et al. Am J Health Syst Pharm. 2007 Jan 1;64(1):37-44.
Reardon DP, Szumita PM, et al. Am J Health Syst Pharm. 2013 May 1;70(9):767-77.
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Whalen LD, et al. Pediatr Crit Care Med. 2014;15(8):706-714.
Precedex (dexmedetomidine) [prescribing information]. Lake Forest, IL: Hospira Inc; December 2023.
Patel MK, Szumita PM, et al. Am J Health Syst Pharm. 2024 Aug 9:zxae224. Epub ahead of print.

Dexmedetomidine overview

- Disadvantages
  - ADE (details in next slide)
  - Hard to deeply sedate (if that is the goal)
  - Must be diluted before IV administration
    - 100 mcg/mL (2 mL vial), recommended to 4 mcg/mL
    - Typically, 1 vial in 50 mL bag = 200 mcg/50 mL
  - Administration techniques (IV bolus, continuous infusion)
    - IV bolus over 10 minutes (at least)
    - Continuous infusion, easier said than done
  - Most evidence in the ICU or intraop with continuous infusion
  - Increased ADEs with certain clinical variables (younger patients, older patients, higher doses, concomitant use with propofol)
  - No reversal agent
  - Lack of high-quality literature for dental procedures

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Ebert TJ, et al. Anesthesiology. 2000;93(2):382-394.
Sim JH, Yu HJ, Kim ST. Korean J Anesthesiol. 2014;67(1):8-12.
McLaughlin K, Szumita PM. Am J Ther. 2022 Nov-Dec 01;29(6):e669-e671.
Schurr JW, Szumita PM. J Clin Pharmacol. 2021 Jul;61(7):848-856.
Pathan S, et al. J Crit Care. 2021;62:19-24.
Whalen LD, et al. Pediatr Crit Care Med. 2014;15(8):706-714.

Dexmedetomidine overview

- Risks
  - Common
    - Braydycardia and Hypotension
      - Alpha-2 adrenergic receptor subtypes: Alpha-2A
  - Effects specific to dental treatment
    - Xerostomia (normal salivary flow resumes upon discontinuation)
  - Clinically relevant, but less common
    - Cardiac arrest/asystole/sinus arrest
    - Transient tachycardia/hypertension
      - Typically associated with higher peak plasma concentration
      - Alpha-2 adrenergic receptor subtypes: Alpha-2B
    - Respiratory depression (yes, this can happen, typically with other risk factors)
    - Fever
    - Withdrawal
      - Typically seen with longer duration of use(>24 hours, up to 30% patients)
        - Hypertension, tachycardia, delirium, agitation
        - Can be mitigated with clonidine
      - Has been seen with short term (pediatric)
        - Anxiety and delirium

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Reardon DP, Szumita PM, et al. Am J Health Syst Pharm. 2013 May 1;70(9):767-77.
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Whalen LD, et al. Pediatr Crit Care Med. 2014;15(8):706-714.
Precedex (dexmedetomidine) [prescribing information]. Lake Forest, IL: Hospira Inc; December 2023.
Terry K, Blum R, Szumita P. SAGE Open Med. 2015 Dec 15;3:2050312115621767.

Dexmedetomidine overview

- Bolus
  - Adult: 0.5 - 1 mcg/kg IV over 10 minutes (can be longer to reduce ADE)
  - Pediatric: up to 2 mcg/kg IV
- Continuous infusion
  - Typically, 0.2-0.7 mcg/kg/hr (ranges up to 2.5 mcg/kg/hr, but use caution with higher dosing)
- Techniques used to lower risk of CV and hemodynamic risks of IV dexmedetomidine
  - Lower dosing (bolus and/or infusion)
  - Extend the duration of the bolus
    - Package insert recommended to give bolus over 10 min
    - Studies suggest less ADE with longer 20 or 30 minutes
  - Eliminate the bolus (likely not practical in many cases of dental surgery, but has been studied)
  - Space out titration intervals of continuous infusion (titrate every 30 minutes, peak effect is delayed!)
  - Different routes of administration
    - Nasal
    - Local/regional
    - Buccal? (for acute agitation in bipolar and mania, not PSAA… yet)

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Ebert TJ, et al. Anesthesiology. 2000;93(2):382-394.
Sim JH, Yu HJ, Kim ST. Korean J Anesthesiol. 2014;67(1):8-12.
Gerlach AT, et al. J Crit Care. 2009 Dec;24(4):568-74.
Chrysostomou C et, al. J Pediatr. 2014;164(2):276-282.

Dexmedetomidine – Brief history

Dexmedetomidine in the ICU

- May well conducted RCT in ICU setting
- IV bolus plus Continuous infusion, predominantly utilized post-cardiac surgery
  - Decrease use of opioids compared to benzo
- IV bolus associated with ADE (cardiac) falls out of favor
  - Most give continuous infusion without bolus
- IV continuous infusion more widespread ICU usage
  - Improved outcome vs. benzo infusions
    - Reduced time on MV
    - ?reduced delirium?
- 2018 SCCM PADIS guideline support propofol/dexmedetomidine over benzodiazepines in ICU

Dexmedetomidine anesthesia and PSAA

- Sparse, heterogeneous, generally poor-quality literature on PSAA for dental surgery
- Often given with other sedatives (midaz or ketamine) and an opioid
- IV dosing practices differ depending on literature
  - IV bolus only
    - Wide variety of dosing scheme
  - IV bolus plus infusion
  - Intranasal
  - Added to standard Spinal/regional/peripheral

Baumgartner K, et al. *Acad Emerg Med*. 2023 Mar;30(3):196-208. Szumita PM, et al. Am J Health Syst Pharm. 2007 Jan 1;64(1):37-44.
Reardon DP, Szumita PM, et al. Am J Health Syst Pharm. 2013 May 1;70(9):767-77.
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Pathan S, et al. J Crit Care. 2021;62:19-24.
Whalen LD, et al. Pediatr Crit Care Med. 2014;15(8):706-714.
Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Alternative routes of dexmedetomidine

- Intranasal
  - May mitigate emotional distress associated with an invasive or unpleasant exam or procedure
  - Avoid intravenous access
  - Primarily in pediatric, although some adult data
  - Typically given in conjunction with an analgesic
  - Typically, not as monotherapy for the entire procedural sedation
    - Consider the duration of the procedure
    - Prolonged pharmacokinetic or pharmacodynamic effects
  - Atomizers can be expensive: range ~ $7-$15 per
- Buccal
  - Not ready for primetime in PSAA until literature supports
  - Currently utilize for acute agitation for specific disease states
  - Very expensive
- Local or regional
  - Has been combined with local or regional anesthesia
    - Increase onset of local, improve quality, and prolong length of action
- Enteral??
  - Sparse literature for PSAA

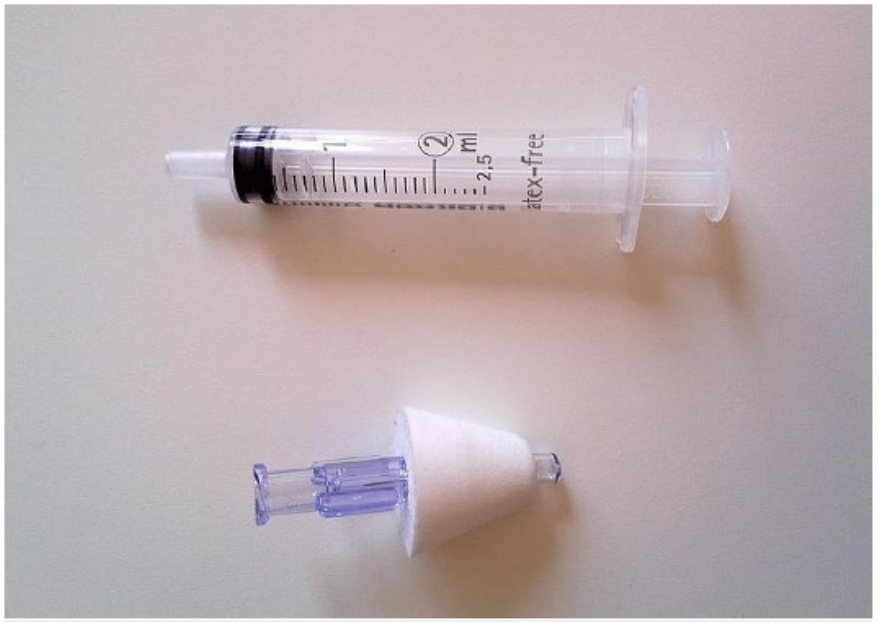


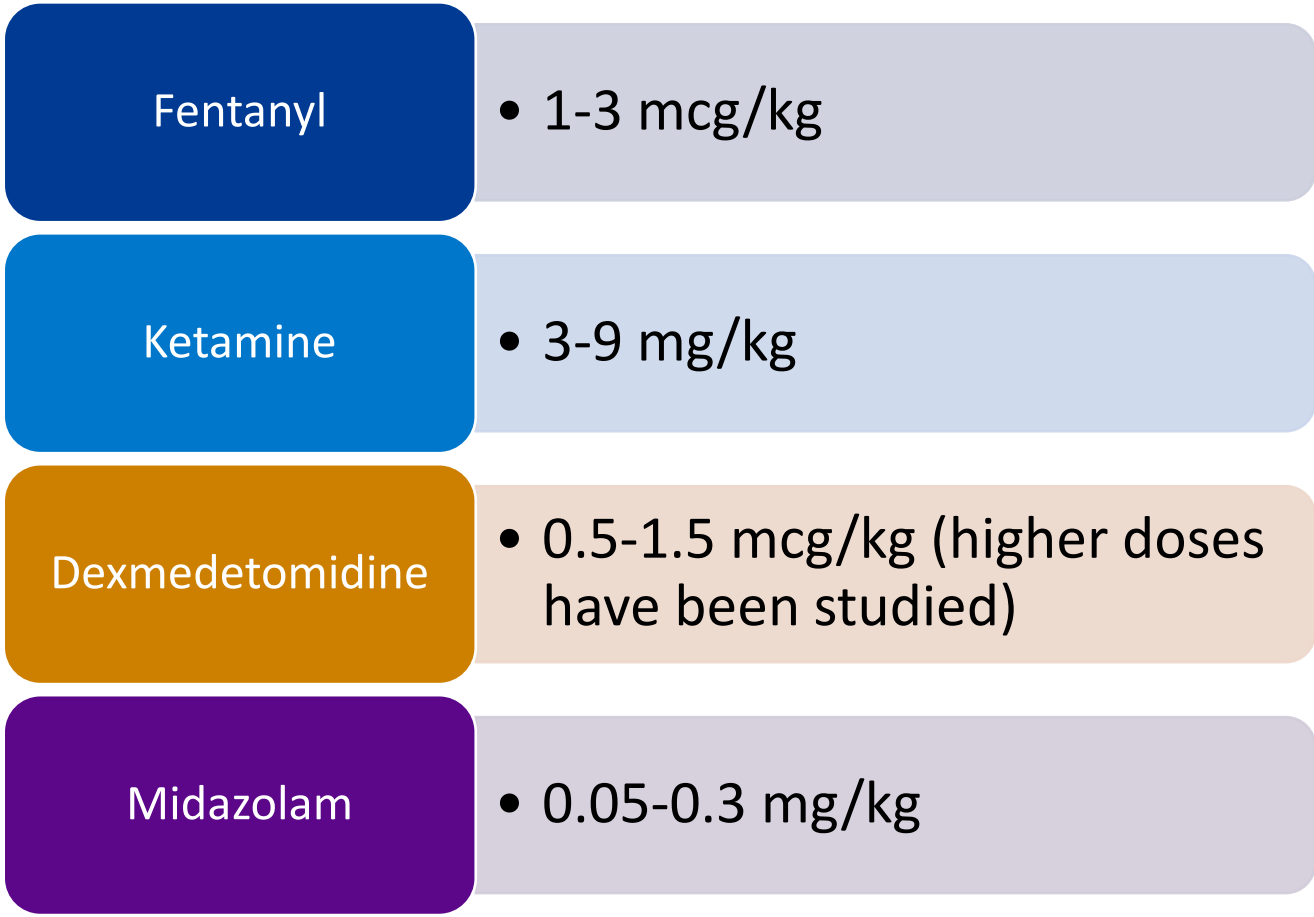
FIGURE 3: MAD Nasal Intranasal Atomization Device

MAD: mucosal atomization device

Bhargavi M, et al. Cureus. 2023 Mar 26;15(3):e36721.
Keles Set al. Drug Des Devel Ther. 2018 Mar 28;12:647-653.
Chen Z, et al. 2023 May 17;17:1463-1484.

Alternative routes: Intranasal (IN) options with general dosing range

- Medication
  - Fentanyl
  - Ketamine
  - Dexmedetomidine
  - Midazolam
- Patient type
  - Adult or pediatric
  - Analgesic or sedative/anxiolytic
- Administration nuances



Kern J, et al. *Emerg Med Pract*. 2022;24(6):1-24.; Green SM, et al. *Ann Emerg Med*. 2011;57(5):449-61.; Miller KA, et al. *Ann Emerg Med*. 2019;73(5):470-480. Sahyoun C, et al. *Eur J Pediatr*. 2021;180(6):1799-1813.

Oral and Sublingual (SL) Options

- Considerations
  - ?place in therapy?
    - Patient population
  - Timing relative to procedure

Dexmedetomidine	• Sublingual 60-180 mcg • Oral ~2 mcg/kg in apple juice X1 ~1 hour before surgery
Ketamine	• Oral: 0.5 mg/kg/day (in 3 or 4 divided doses)
Midazolam	• Oral: 0.25-0.5 mg/kg (max 20 mg/dose) • Sublingual: 0.2 mg/kg
Sufentanil	• Sublingual: 30 mcg (adult)

Tobias et al. *Saudi J Anaesth*. 2011;5(4):395-410.; Green SM, et al. *Ann Emerg Med*. 2011;57(5):449-461.
Shanmugaavel AK, et al. *Pediatr Dent*. 2016;38(2):106-111.; Shaat MA, et al. *Int J Paediatr Dent*. 2022;32(2):232-239. ; Reardon CE, et al. *Ann Pharmacother*. 2019;53(12):1220-1226.

Sublingual or buccal: Dexmedetomidine film

- Indication
  - Acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults
- Limitations
  - Safety concerns (requires specific monitoring)
  - Not available in outpatient setting
  - Expensive
- Future use in PSAA???

– Initial Dose

AGITATION	ADULTS	HEPATIC IMPAIRMENT		ELDERLY
		MILD/MODERATE	SEVERE	
MILD	120 mcg	90 mcg	60 mcg	120 mcg
MODERATE	120 mcg	90 mcg	60 mcg	120 mcg
SEVERE	180 mcg	120 mcg	90 mcg	120 mcg

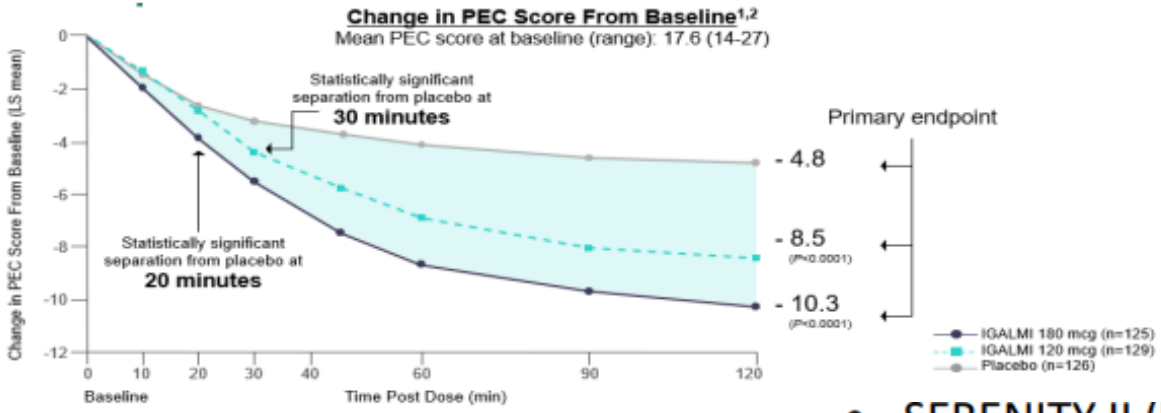
– Optional 2nd or 3rd doses
  - Check if hemodynamically stable: SBP ≥90 mm Hg, DBP ≥60 mm Hg, and HR ≥60 beats per minute
  - May give half of the initial dose at intervals of at least 2 hr for up to 3 total doses (unless starting at 90 mcg or 60 mcg, then repeat doses will be 60 mcg).
  - Cut the strip in half to get the desired repeat doses

Data on file. BXCL501-301 CSR (SERENITY I). BioXcel Therapeutics, Inc. January 2021): Igalmi (dexmedetomidine sublingual film) prescribing information. BioXcel Therapeutics, Inc.; 2022[17].

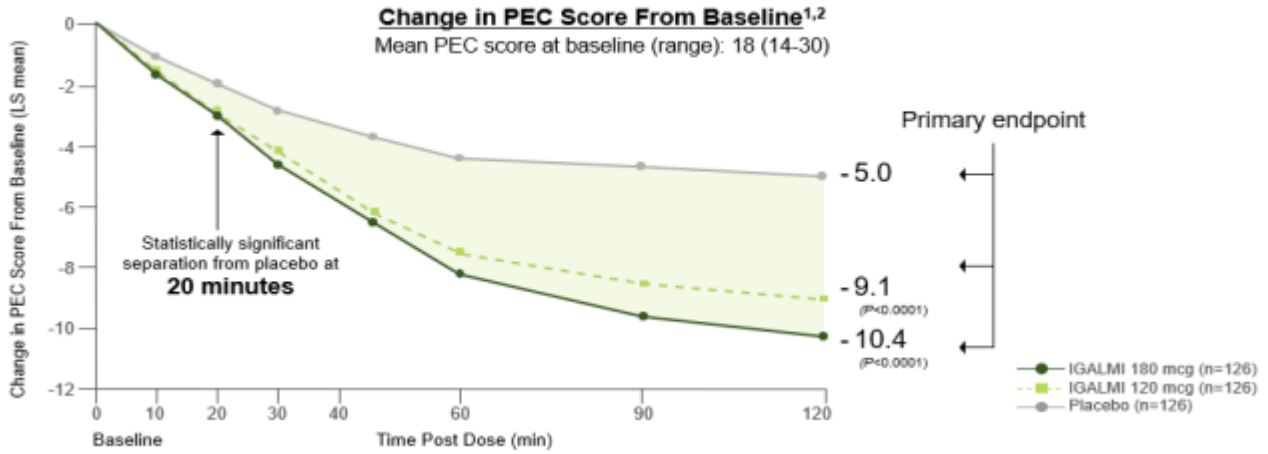
Miller CWT et al. West J Emerg Med. 2020;21(4):841-848.

Sublingual or buccal: Dexmedetomidine film onset and duration

- SERENITY I (schizophrenia)



- SERENITY II (bipolar I or II disorder)



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Preskorn SH et al. JAMA. 2022;327(8):727-736.
Preskorn SH et al. JAMA. 2022;327(8):727-736.

Procedural sedation - variables

Preoperative

- Presedation assessment
  - ASA Physical Classification System (I-VI)
  - Mallampati score
- Patient factors
  - Obstructive sleep apnea
  - On respiratory depressants
  - Conditions influencing drug metabolism
- Depth of sedation
  - Anticipated duration
  - Anticipated degree of discomfort or pain
- Monitoring restrictions

Procedural Sedation and Analgesia

Technique of administering sedatives or dissociative agents with or without analgesics to:

- Induce an altered state of consciousness
- Allow the patient to tolerate painful and unpleasant procedures
- Preserve cardiorespiratory function

The intent of the sedation, not necessarily the agent itself, determines whether it is procedural sedation

Goodwin SA, et al. *Ann Emerg Med*. 2014; 63(2):247-258.

Sedation Depths

Minimal sedation
- Near-baseline level of alertness with normal responses to verbal commands

Moderate sedation
- Respond purposefully to verbal commands, either alone or accompanied by light tactile simulation

Dissociative sedation
- Trance-like cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability

Deep sedation
- Cannot be easily aroused but responds purposefully after repeated or painful stimulation

General anesthesia
- Unresponsiveness to all stimuli and the absence of airway protective reflexes

Goodwin SA, et al. *Ann Emerg Med*. 2014; 63(2):247-258.

Same mechanism of action

A bottle of tequila or a glass of wine?

Monitoring/rescue

Capnography- when applicable

- Accurate predictor of respiratory depression
- Early detection of apnea
- Detects decreases in respiratory rate AND tidal volume

Supplemental oxygen

- Absolute reduction of 10% in rates of hypoxemia/apneic
- Required or optional depending on agents used

Rescue equipment

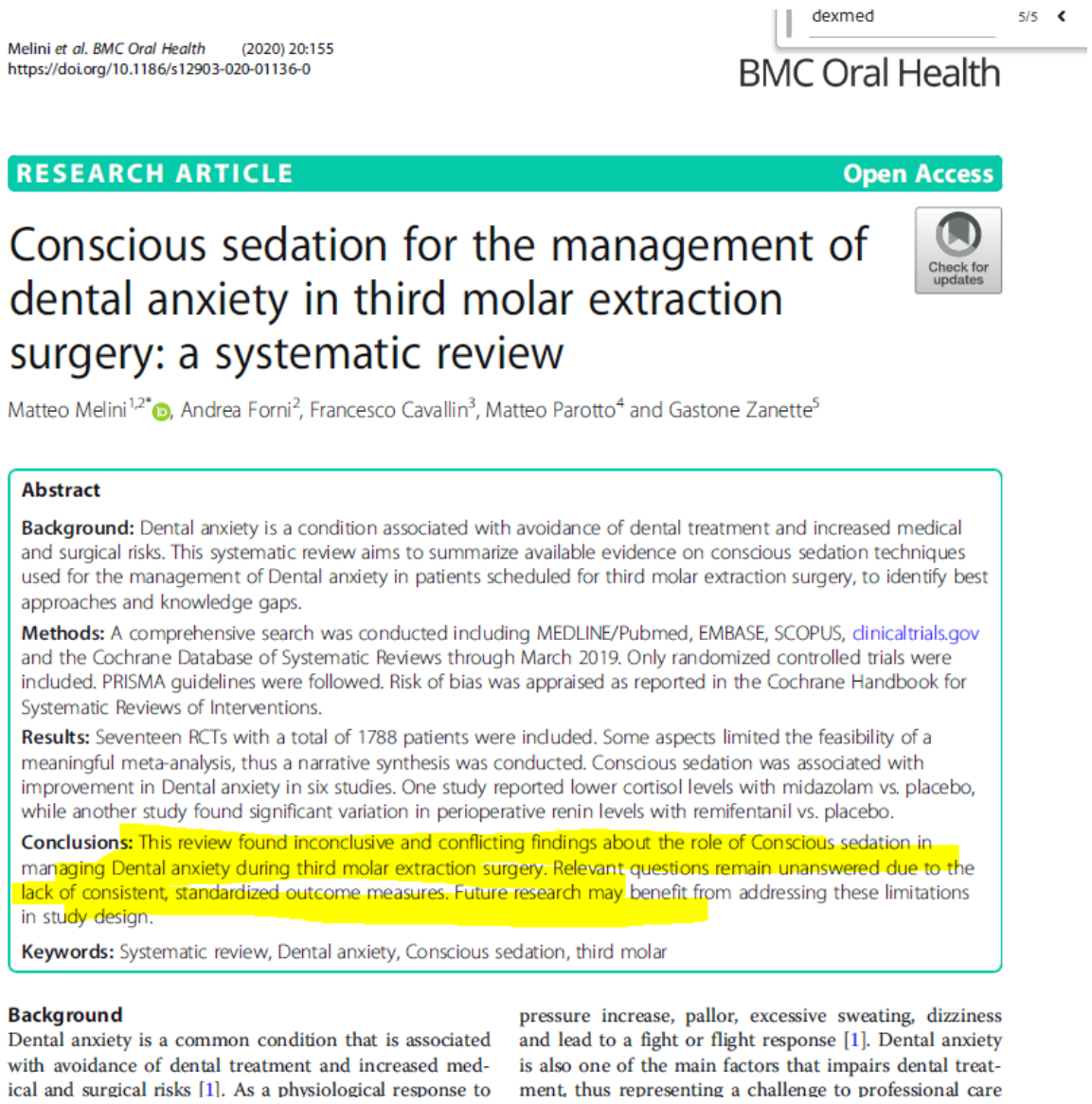
- Be ready to perform advanced airway manipulations or intubate/secure the airway
- Suction
- Intravenous fluids
- Reversal agents, if available
- Resuscitation supplies

Kern J, et al. *Emerg Med Pract*. 2022;24(6):1-24.
Lamond DW. *Emerg Med Australas*. 2010;22:265-286.

Dexmedetomidine for PSAA – literature in dental surgery

- Extensive literature search
  - Limited RCT
  - Limited published real-world literature

- Get ready for a roller coaster ride!
  - Heterogeneity
  - Mostly small studies
  - Very few in USA
  - Different setting
    - Office based
    - OR/hospital based
  - All different types
    - Patients
    - Interventions
    - Comparison
    - Outcomes



dexmed 5/5

Melini et al. BMC Oral Health (2020) 20:155
https://doi.org/10.1186/s12903-020-01136-0

BMC Oral Health

RESEARCH ARTICLE Open Access

Conscious sedation for the management of dental anxiety in third molar extraction surgery: a systematic review

Matteo Melini[1,2*], Andrea Forni[2], Francesco Cavallin[3], Matteo Parotto[4] and Gastone Zanette[5]

Abstract

Background: Dental anxiety is a condition associated with avoidance of dental treatment and increased medical and surgical risks. This systematic review aims to summarize available evidence on conscious sedation techniques used for the management of Dental anxiety in patients scheduled for third molar extraction surgery, to identify best approaches and knowledge gaps.

Methods: A comprehensive search was conducted including MEDLINE/Pubmed, EMBASE, SCOPUS, clinicaltrials.gov and the Cochrane Database of Systematic Reviews through March 2019. Only randomized controlled trials were included. PRISMA guidelines were followed. Risk of bias was appraised as reported in the Cochrane Handbook for Systematic Reviews of Interventions.

Results: Seventeen RCTs with a total of 1788 patients were included. Some aspects limited the feasibility of a meaningful meta-analysis, thus a narrative synthesis was conducted. Conscious sedation was associated with improvement in Dental anxiety in six studies. One study reported lower cortisol levels with midazolam vs. placebo, while another study found significant variation in perioperative renin levels with remifentanil vs. placebo.

Conclusions: This review found inconclusive and conflicting findings about the role of Conscious sedation in managing Dental anxiety during third molar extraction surgery. Relevant questions remain unanswered due to the lack of consistent, standardized outcome measures. Future research may benefit from addressing these limitations in study design.

Keywords: Systematic review, Dental anxiety, Conscious sedation, third molar

Background

Dental anxiety is a common condition that is associated with avoidance of dental treatment and increased medical and surgical risks [1]. As a physiological response to pressure increase, pallor, excessive sweating, dizziness and lead to a fight or flight response [1]. Dental anxiety is also one of the main factors that impairs dental treatment, thus representing a challenge to professional care

RCT of Dex for pre/intraop for orthognathic surgery: Dexmed IV bolus followed by CI vs placebo

- Single-center, Iran
- 60 mostly young adults
- Dex 1 mcg/kg over 10 min bolus followed by 0.2 mcg/kg/hr

- Results
  - PONV
    - Nausea
      - P 46.7%, Dex 3.3% - p<0.001
    - Vomiting
      - 0% in either group

ANESTHESIA / TEMPOROMANDIBULAR DISORDERS / FACIAL PAIN

The Beneficial Effect of Preoperative Dexmedetomidine in Controlling Postoperative Pain, Nausea, and Vomiting After Orthognathic Surgery: A Triple-blind Randomized Clinical Trial

Ali Labafchi, DMD, * *Zahra Shooshtari, DMD,* * *Ricardo Grillo, MSc,*† *Alireza Sharifian Attar, MD, MS,*‡ *Majid Eshghpour, DMD, DDS,*§ *and Sahand Samieirad, DMD, DDS*§‖

Purpose: Controlling postoperative pain and nausea (PONV) following orthognathic surgery can be challenging. The aim of the study was to assess the efficacy of dexmedetomidine (DEX) in reducing pain and preventing nausea and vomiting in subjects undergoing orthognathic surgery.

Methods: The authors implemented a triple-blinded, randomized clinical trial. Healthy adults with class III jaw deformity scheduled for bimaxillary orthognathic surgery were included. Subjects were randomized to the DEX or placebo groups. The DEX group received premedication with DEX 1 μg/kg IV over 10 minutes followed by a maintenance dose (0.2 μg/kg/hour) while the placebo group received normal saline. The primary outcome variables were postoperative pain, postoperative nausea, and postoperative vomiting . Pain was assessed using a visual analog scale at 1, 3, 6, 12, 18, and 24 hours, postoperatively). Nausea and vomiting were recorded throughout the postoperative period. Statistical analysis was performed using χ^2, *t* test, and repeated measures ANOVA with a *P* value < .05 considered significant.

Results: A total of 60 consecutive subjects with a mean age of 24.6 ± 3.5 years completed the study. There were 38 females (63.33%) and 22 males (36.66%). The mean visual analog scale was significantly lower in the DEX group at all time-points ($P < .05$). There was a significantly greater demand for rescue analgesics in the placebo group compared to the DEX group ($P = .01$). Fourteen subjects (46.7%) in the placebo group and one subject (3.3%) in the DEX group reported nausea ($P < .001$). Postoperative vomiting was not observed in any of the subjects.

Conclusion: Premedication with DEX can be considered a viable treatment option for reducing postoperative pain and postoperative nausea after bimaxillary orthognathic surgery.

Labafchi A, et al. J Oral Maxillofac Surg. 2023 Aug;81(8):941-949.

RCT of Dex for pre/intraop for orthognathic surgery: Dexmed IV bolus followed by CI vs placebo

Table 2. COMPARING STUDY GROUPS WITH RESPECT TO POSTOPERATIVE VAS VALUES (MEAN ± SD)

Pain Group	1 hours	3 hours	6 hours	12 hours	18 hours	24 hours	*P*-Value* (Between Different Time Intervals)
Placebo	4.2 ± 0.9	4.8 ± 0.9	5.7 ± 0.9	6.6 ± 1.4	5.1 ± 1.1	3.8 ± 0.8	<.001
DEX	3.2 ± 0.8	4.0 ± 1.0	4.8 ± 0.9	5.3 ± 0.9	4.0 ± 0.9	2.8 ± 0.9	<.001
P-Value* (intergroup comparison)	<.001	.002	<.001	<.001	<.001	<.001	

Labafchi A, et al. J Oral Maxillofac Surg. 2023 Aug;81(8):941-949.

RCT of Dex for intraop for mandibular surgery: CI vs Bolus

- Single center in Iran
- 40 Patients
- CI vs bolus: total of "0.5 mg/kg" – must be a typo as this 1000-fold dosing error)
- Outcome:
  - Primary: pain intensity in recovery
  - Secondary: hemodynamics

Oral and Maxillofacial Surgery (2024) 28:569–575
https://doi.org/10.1007/s10006-023-01169-z

RESEARCH

Opioid requirement and pain intensity after mandibular surgeries with dexmedetomidine administration in two ways: intraoperative infusion versus bolus injection

Saeed Nezafati[1] · Abbas Ali Dehghani[2] · Reza Khorshidi Khiavi[1] · Ali Mortazavi[1] · Loghman Ebrahimi[1]

Received: 17 March 2023 / Accepted: 8 June 2023 / Published online: 19 June 2023

Abstract

Purpose The purpose of this study is to compare the opioid requirement and pain intensity after surgeries of mandibular fractures with administration of dexmedetomidine by two approaches of infusion and single bolus.

Methods In this double-blind clinical trial, the participants were randomized and matched in terms of age and gender in two groups (infusion and bolus). In both groups, the amount of narcotic used, hemodynamic indices, oxygen saturation, and pain intensity were collected based on the ten-point Visual Analogue Scale (VAS) at 7 time points for 24 h. SPSS version 24 software was used for data analysis. A significance level of less than 5% was considered.

Results A total of 40 patients were included in the study. There was no significant difference between the two groups in terms of gender, age, ASA class, and duration of surgery ($P>0.05$). There was no significant difference between the two groups in terms of nausea and vomiting and subsequently receiving anti-nausea medication ($P>0.05$). The need for opioid consumption after surgery was not different in two groups ($P>0.05$). Infusion of dexmedetomidine reduced postoperative pain more rapidly than its single bolus dose ($P<0.05$). However, over time, there was no significant difference between the two groups in terms of changes in oxygen saturation variables ($P>0.05$). Homodynamic indices including heart rate, systolic blood pressure, and diastolic blood pressure in the bolus group were significantly lower than the infusion group ($P<0.05$).

Conclusion Administration of dexmedetomidine in the form of infusion can reduce postoperative pain better than bolus injection, with less probability of hypotension and bradycardia.

Keywords Postoperative pain · Open reduction · Dexmedetomidine

Nezafati S, et al. Oral Maxillofac Surg. 2024 Jun;28(2):569-575.

RCT of Dex for intraop for mandibular surgery: CI vs Bolus

- CI associated with
  - “better pain control”
  - less probability of hypotension and bradycardia

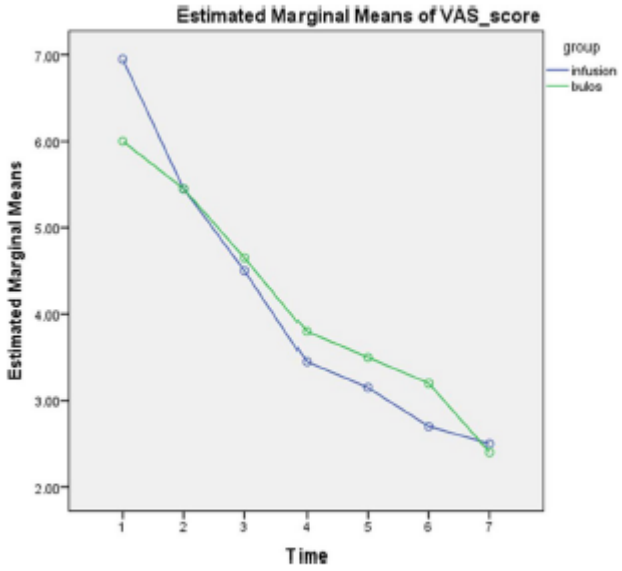
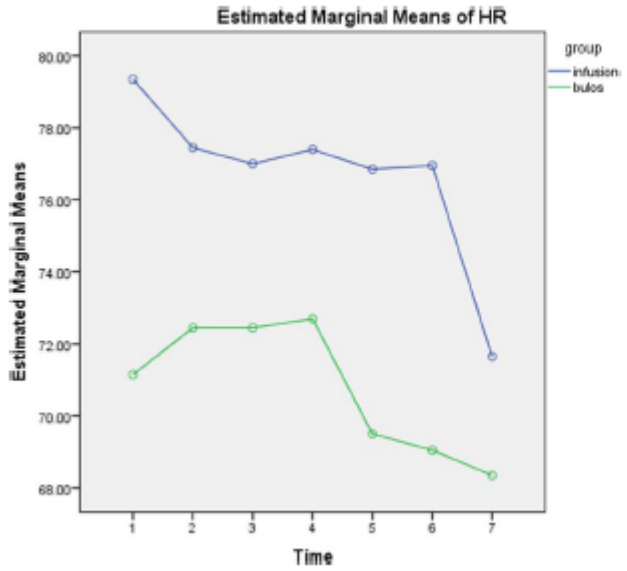
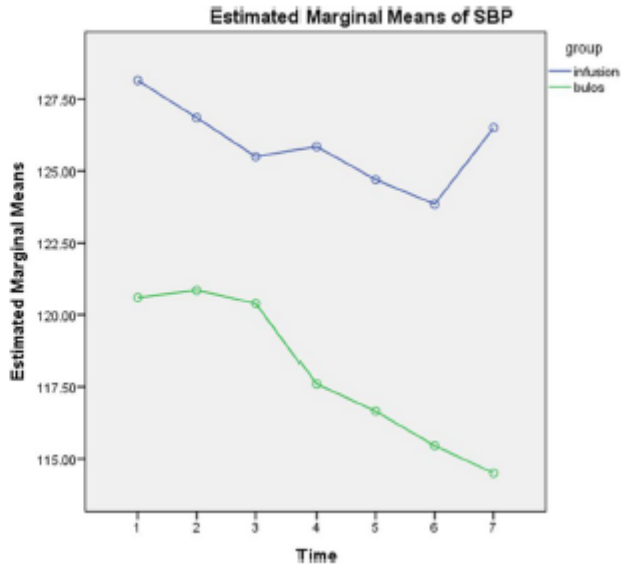


Fig. 1 VAS score changes during the first 24 h after surgery in two groups





Nezafati S, et al. Oral Maxillofac Surg. 2024 Jun;28(2):569-575.

IV Midaz vs IV dexmed in dental implant

- Single center RCT in Wuhan, China
  - M – 0.05 mg/kg bolus followed by CI 0.04-0.2 mg/kg/hr
  - D – 1 mcg/kg bolus followed by CI 0.2-0.7 mcg/kg/hr
- All patients had local
- 30 patient in each arm
  - OAAS score
  - VAS
  - Satisfaction

Hindawi
BioMed Research International
Volume 2020, Article ID 6130162, 7 pages
https://doi.org/10.1155/2020/6130162

Hindawi

Clinical Study

Comparison in Sedative Effects between Dexmedetomidine and Midazolam in Dental Implantation: A Randomized Clinical Trial

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Received 28 February 2020; Revised 3 May 2020; Accepted 5 May 2020; Published 2 June 2020

Academic Editor: Stavros Baloyannis

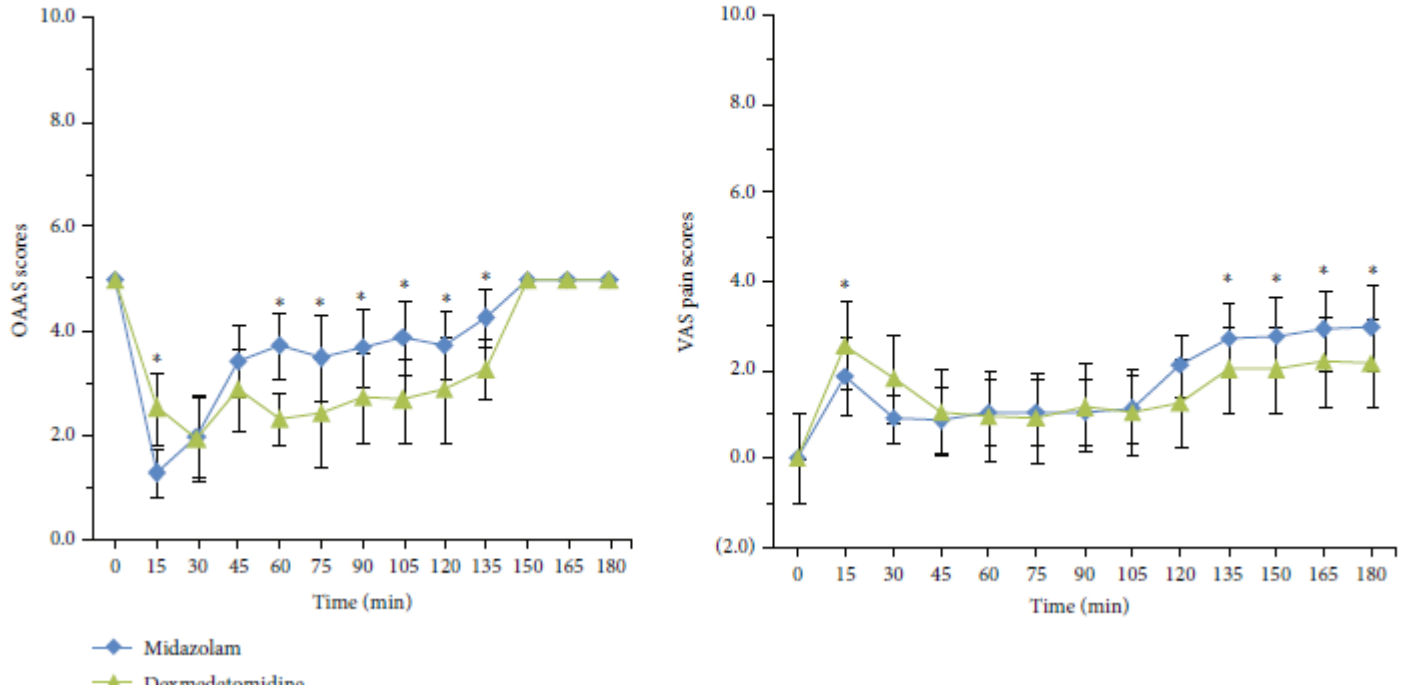
Dexmedetomidine refers to an α_2-adrenergic receptor agonist causing potent sedative, analgesic, and minimal respiratory depression compared with alternative drugs. The present study was aimed at comparing the efficaciousness and safety of midazolam and dexmedetomidine as sedatives for dental implantation. We recruited 60 patients belonging to group I or II of the American Society of Anesthesiologists (ASA) and treated them with either midazolam or dexmedetomidine in a random manner. Patients' duration of analgesia after surgery, surgeon and patient degrees of satisfaction, Observer's Assessment of Alertness/Sedation Scale (OAAS) scores after drug administration, visual analogue scale (VAS) pain scores, and vital signs were recorded variables. Patients administered dexmedetomidine had significantly lower OAAS scores than those administered midazolam ($p < 0.05$). Patients administrated dexmedetomidine had a significantly longer analgesia duration after the surgical procedure than those administered midazolam, and the difference was statistically significant ($p < 0.05$). Dexmedetomidine had a significantly larger number of surgeons satisfied with the level of sedation/analgesia than midazolam ($p < 0.05$). Accordingly, it is considered that dexmedetomidine can achieve better postoperative analgesia, surgeon satisfaction, and sedation than midazolam.

Table 1: Observer's assessment of alertness and sedation using the Observer's Assessment of Alertness/Sedation Scale.

Responsiveness	Speech	Facial expression	Eyes	Score
Responds readily to normal tone of voice	Normal	Normal	Clear, no ptosis	5
Responds slowly to normal tone of voice	Mild slurring	Mild relaxation	Mild ptosis, less than half the eye	4
Responds only after loud or repeated calling	Slurring	Pronounced relaxation	Glazed, obvious ptosis	3
Responds after mild prodding or shaking	Few recognised words	Pronounced relaxation	Glazed, obvious ptosis	2
No response to mild prodding or shaking	No words	Pronounced relaxation	Glazed, obvious ptosis	1

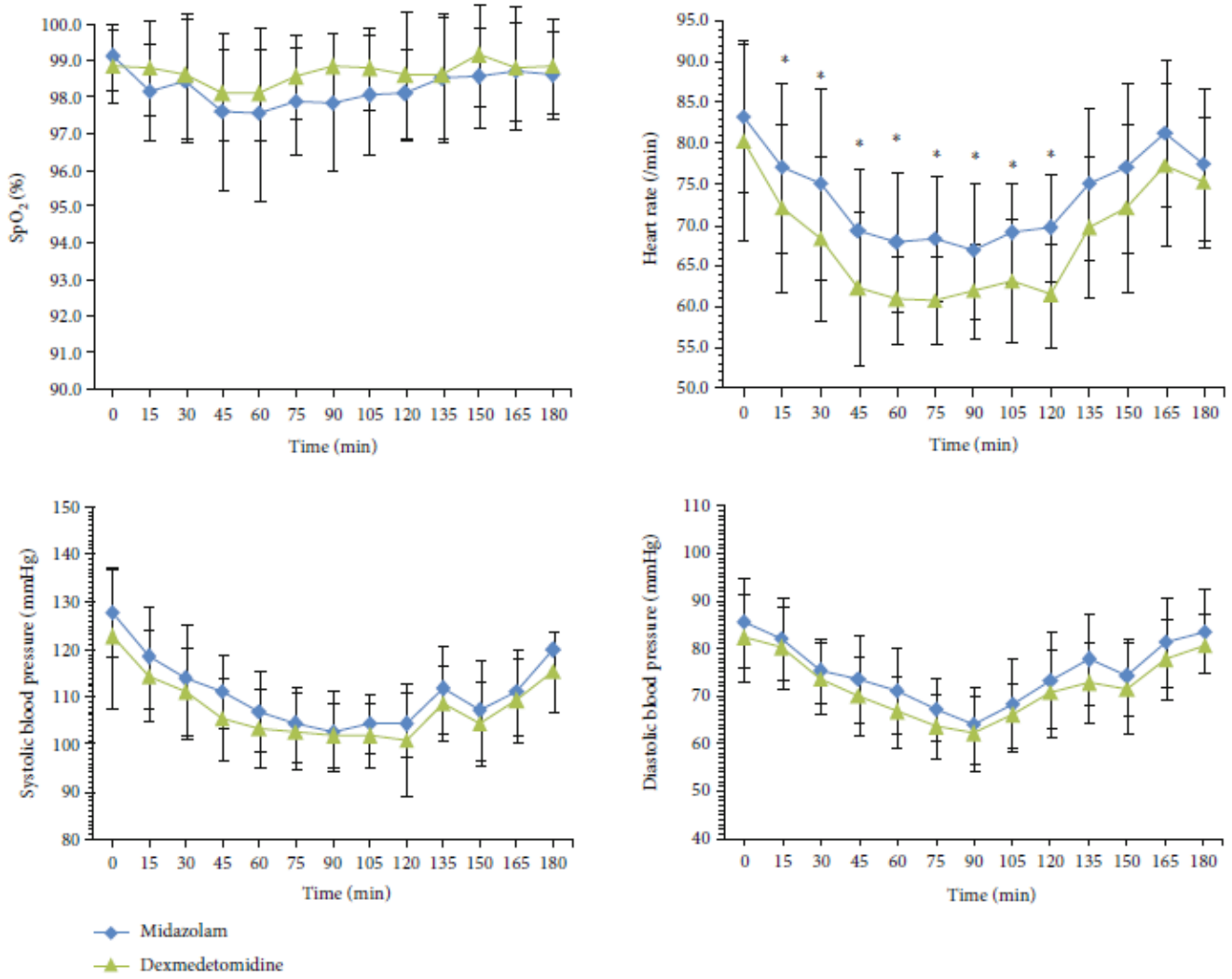
Wang L, et al. Biomed Res Int. 2020 Jun 2;2020:6130162.

IV Midaz vs IV dexmed in dental implant



Wang L, et al. Biomed Res Int. 2020 Jun 2;2020:6130162.

IV Midaz vs IV dexmed in dental implant



Wang L, et al. Biomed Res Int. 2020 Jun 2;2020:6130162.

IV Midaz vs IV dexmed in dental implant

Table 2: Comparison of demographic information, clinical characteristics, and postoperative data of patients for the two groups.

Variables	Group D ($n = 30$)	Group M ($n = 30$)	p value
Age (year)	41.61 ± 9.82	43.34 ± 8.43	0.316
Body weight (kg)	61.12 ± 8.63	59.20 ± 7.73	0.168
Males/females	19/11	18/12	0.070
Duration of surgery (min)	117.40 ± 15.18	115.75 ± 13.57	0.719
Number of dental implants	2.35 ± 0.88	2.00 ± 0.73	0.177
Total volume of local anesthetic used (mL)	7.33 ± 0.67	7.48 ± 0.99	0.579
Surgeon satisfaction score	7.45 ± 1.15	7.60 ± 1.05	0.668
Patient satisfaction score	9.40 ± 0.59	9.25 ± 0.55	0.414
Time elapsed before taking the paracetamol tablet (h)	3.92 ± 0.49	5.18 ± 0.65*	≤0.001

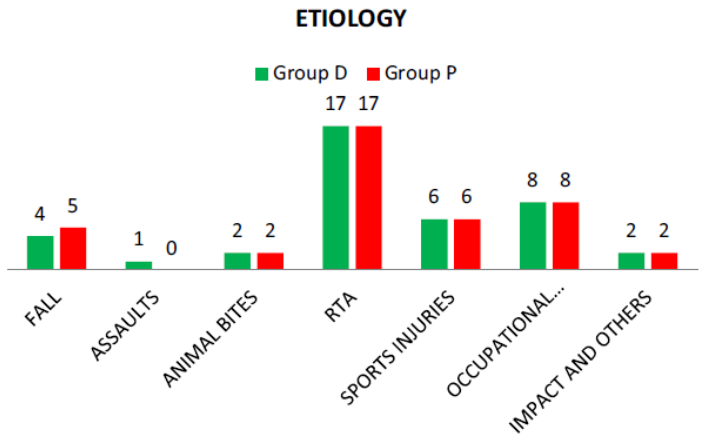
M: midazolam; D: dexmedetomidine. Data shown are the number or mean ± standard deviation. *$p < 0.05$.

Wang L, et al. Biomed Res Int. 2020 Jun 2;2020:6130162.

IV Dex vs placebo in maxillofacial soft tissue injuries

- **Single center emergency department in India**

- 80 Patients
  - D IV bolus of 1 mcg/kg dexmed over 20 min followed by CI of 0.2 mcg/kg/min
  - P Participants in the placebo group received 0.9%



J. Maxillofac. Oral Surg.
https://doi.org/10.1007/s12663-024-02122-7

ORIGINAL ARTICLE

Evaluation of Analgesic Efficacy of Dexmedetomidine as an Adjuvant to Local Anaesthesia in Maxillofacial Soft Tissue Injuries: A Prospective Randomised Clinical Trial

U. Hemavathi[1] · C. Sreekanth[2] · Akshay Shetty[1] · Aparna Melethu Krishnakumari[1] · Shreyans Sanaki Jain[1] · Aditya Iyengar[1]

Received: 1 June 2023 / Accepted: 19 January 2024

Abstract

Aims and Objectives Dexmedetomidine is a relatively new, potent, and highly selective α2-adrenergic receptor agonist used for perioperative sympatholytic, analgesia, and sedation. We conducted this study to evaluate the effects of dexmedetomidine as an adjunct to local anaesthesia for maxillofacial soft tissue injuries as day care in the emergency department on patient hemodynamics and analgesic efficacy.

Materials and Methods Eighty patients gave informed consent to participate in the study. They were divided into Groups P and D, each of which consisted of 40 participants. Patients received saline injections in Group P, and Group D received dexmedetomidine (DEX) with local anaesthesia infiltration to both groups. Hemodynamic parameters, duration of surgery, pain of first rescue analgesia, Pain score, patient satisfaction, and surgeons satisfaction were recorded and quantified using unpaired t tests or Mann–Whitney and ANOVA tests. Data and qualitative data parameters were compared using Chi-square test. A P value < 0.05 was considered significant.

Results Our study showed statistically significant reduced heart rate, systolic, and diastolic blood pressures in DEX compared to the placebo group where none had hypotension or bradycardia in clinical settings. The dexmedetomidine group had shorter operative time and decreased need for analgesia due to lower VAS scores. Patient and surgeon satisfaction were superior in the DEX group compared to the other groups.

Conclusion Dexmedetomidine effectively suppresses the hemodynamic stress response during minor surgical procedures. We conclude that dexmedetomidine is an effective medication to be used in the emergency room for day-care procedures, as a potent analgesic, anxiolytic providing hemodynamically stable patients, with minimal side effects. We summarise that considering the above properties of dexmedetomidine can be incorporated into ERAS (early return after surgery) protocol, making it an optimal drug of choice as an alternative to moderate sedative drugs, in managing soft tissue injuries of maxillofacial region.

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Keywords Maxillofacial soft tissue injuries · Dexmedetomidine · Local anaesthesia · Outpatient sedative · Day-care procedures

Hemavathi, U., et al. *J. Maxillofac. Oral Surg.* (2024). https://doi.org/10.1007/s12663-024-02122-7

Dex vs placebo in maxillofacial soft tissue injuries

Table 1 Demographic variables

	Group D	Group P	*P*
Group statistics			
Age			
Mean age	34.925 ± 9.4852	35.300 ± 9.6668	0.861
Gender			
Male	31 (77.5%)	31 (77.5%)	1.000
Female	9 (22.5%)	9 (22.5%)	
Frequency of analgesia			
0	34 (85.0%)	0 (0%)	< 0.001*
1	6 (15.0%)	18 (45.0%)	
2	0 (0%)	22 (55.0%)	
Time to first use of rescue analgesia (min)			
Time to first use of rescue analgesia (min)	173.75 ± 19.799	78.58 ± 5.931	< 0.001*

*Indicates statistically significant results

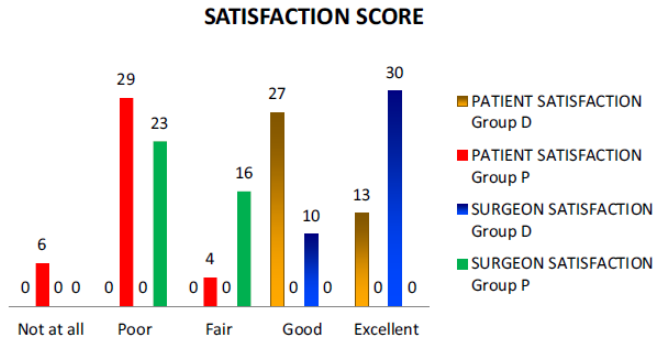
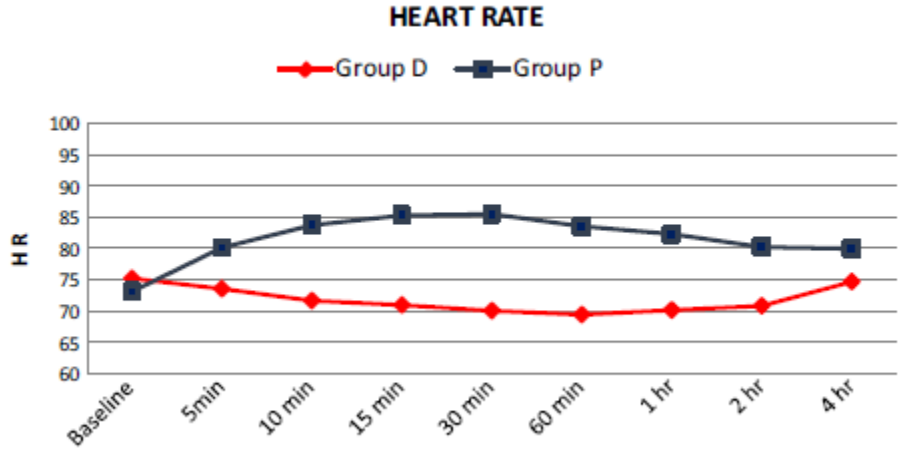


Fig. 6 Surgeons and patient satisfaction in both groups



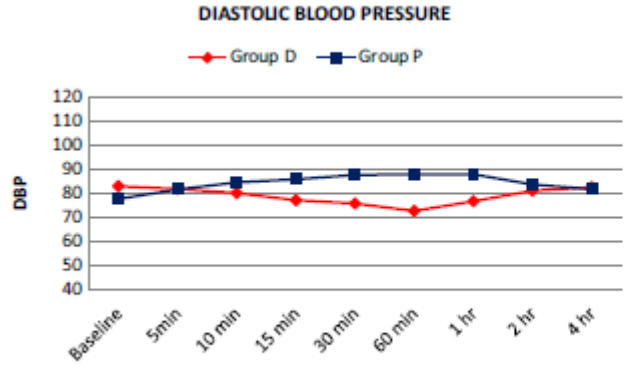


Fig. 4 Variables of diastolic BP in both groups

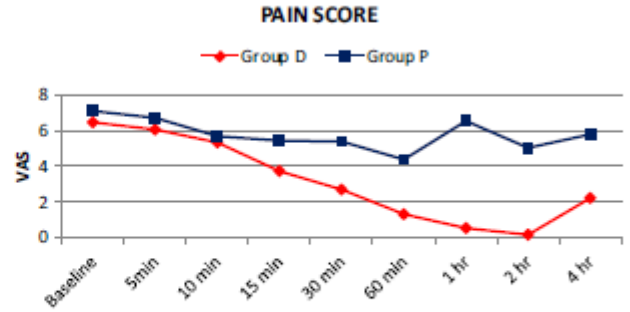


Fig. 5 VAS score in both groups

Hemavathi, U., et al. *J. Maxillofac. Oral Surg.* (2024). https://doi.org/10.1007/s12663-024-02122-7

IV Dex target-controlled infusion during dental surgery- Case series from Brazil

Case Report

Sedation with dexmedetomidine target controlled infusion during dental surgery: a retrospective case report

Marina Ayres Delgado[1^], Rodrigo Tavares de Lanna Rocha[1^], André dos Santos Mendonça[1^], Bruno Pessoa Chacon[1^], Bruna de Carvalho Oliveira[1^], Lais Mendes Viana[1^], Davi Ribeiro Nascimento[1^], Bruno Pereira Campanha[2^]

[1]Division of Anesthesiology, Department of Surgery, Hospital das Clínicas de Belo Horizonte, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [2]Maxillofacial Surgery, Military Police Hospital, Belo Horizonte, Brazil

Contributions: (I) Conception and design: MA Delgado, RT de Lanna Rocha; (II) Administrative support: B de Carvalho Oliveira, BP Campanha; (III) Provision of study materials or patients: A dos Santos Mendonça; (IV) Collection and assembly of data: BP Chacon; (V) Data analysis and interpretation: MA Delgado, LM Viana; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Marina Ayres Delgado, MD, PhD. Division of Anesthesiology, Department of Surgery, Hospital das Clínicas de Belo Horizonte, Universidade Federal de Minas Gerais, Av Alfredo Balena 110, Santa Efigênia, Belo Horizonte 30130-100, Brazil. Email: marina.ayres.delgado@gmail.com.

Background: Dexmedetomidine has emerged as a valuable sedation approach in the context of dental surgery. In the Hannivoort target-controlled infusion (TCI) model is possible to correlate the plasma-site concentration with the sedative effects of dexmedetomidine.

Case Description: In our case report, we employed a dexmedetomidine TCI protocol, involving a loading dose followed by a maintenance infusion. This approach yielded stable hemodynamics, with minimal fluctuations in blood pressure and heart rate. Remarkably, patients within the case report maintained both cooperation and responsiveness while being adequately sedated during their surgical procedures. Prolonged infusions of dexmedetomidine may lead to delayed sedative effects after discontinuation of the drug because of a longer context-sensitive half-life. The use of TCI modes may also be helpful to prevent these adverse effects.

Conclusions: Utilizing dexmedetomidine in conscious sedation for dental surgery offers a range of benefits. These include its analgesic and anxiolytic properties, reduced risk of respiratory depression, and the capacity to promptly awaken patients as necessary. Furthermore, combining dexmedetomidine with midazolam and fentanyl presents a well-balanced sedation strategy that prioritizes patient comfort and safety. The aim of this study is to assess the efficacy of dexmedetomidine when used as a sedative in the TCI model. This evaluation highlights its potential to significantly enhance the dental practice, contributing to improved patient experiences and outcomes during dental procedures.

Keywords: Case report; conscious sedation; dental surgery; dexmedetomidine; target-controlled infusion (TCI)

3 patients

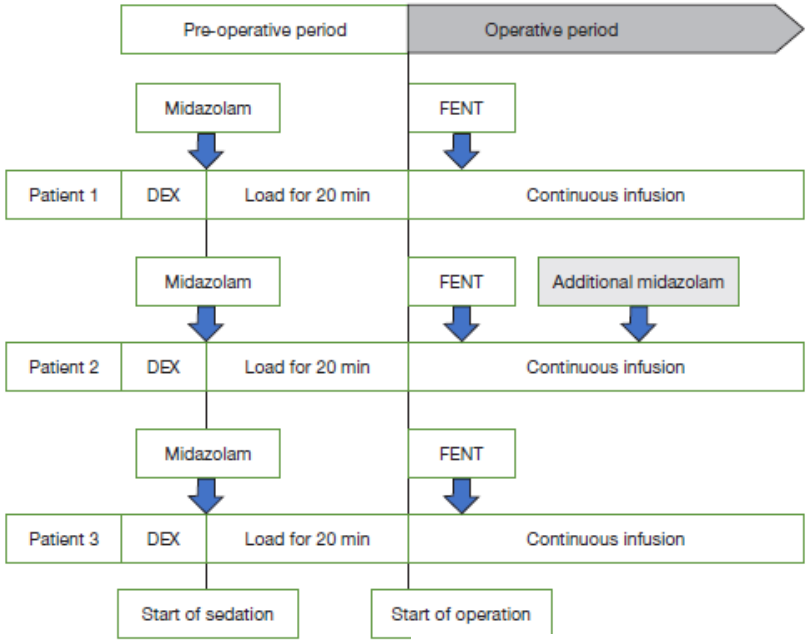


Figure 1 Intravenous sedation protocol in the case report [adapted fro

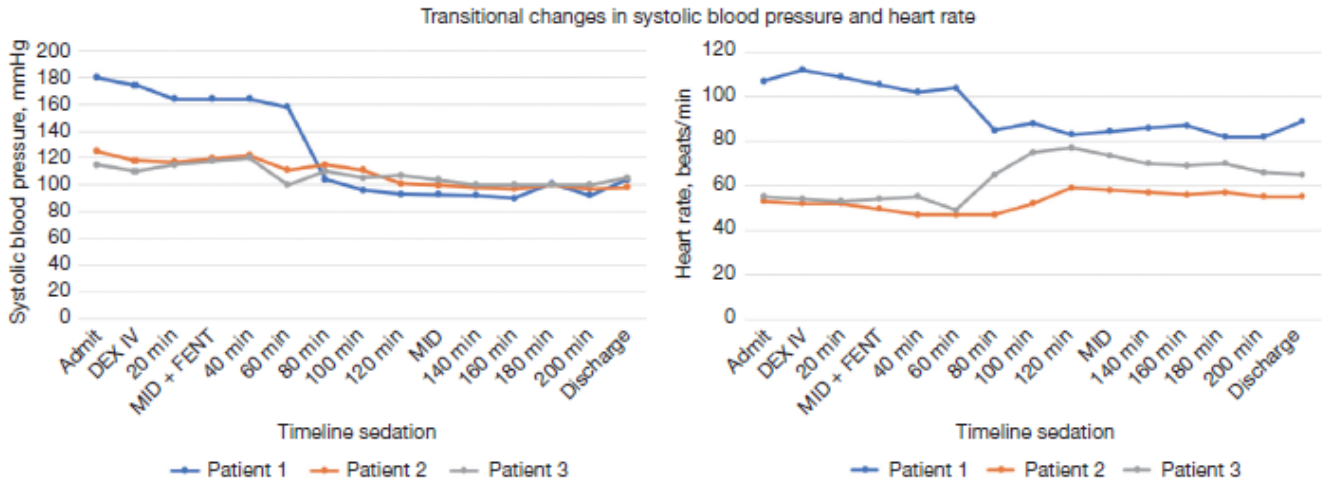
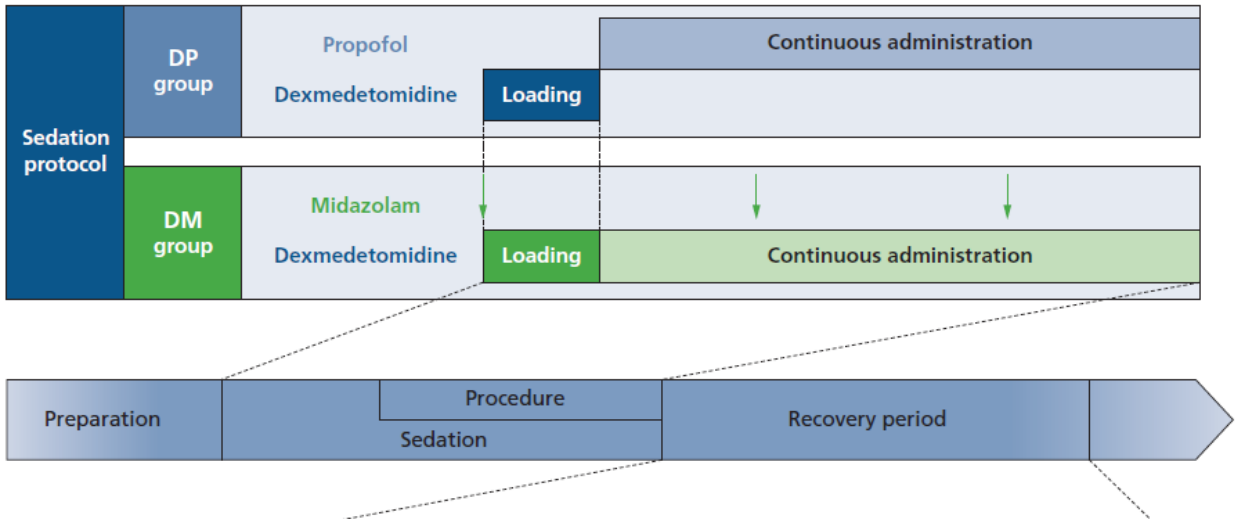


Figure 2 Transitional changes in systolic blood pressure and heart rate, before administration of dexmedetomidine, 10 min after the administration of dexmedetomidine and every 20 min during surgery. DEX, dexmedetomidine; IV, intravenous; MID, midazolam, FENT, fentanyl.

Dex IV load followed by CI propofol vs Midaz load follow by dex infusion

Single center in Japan

- 54 paitents
- DP associated with less recovery time for ambulatory dental practice comparted to DM



Clinical Trial

Check for updates

ADA CE Online

ADA American Dental Association

Supplemental material is available online.

Initial loading of dexmedetomidine and continuous propofol sedation for prevention of delayed recovery

A randomized controlled trial

Hikaru Nakagawa, DDS, PhD; Hiroshi Hanamoto, DDS, PhD; Fumi Kozu, DDS, PhD; Chizuko Yokoe, DDS, PhD; Hiroharu Maegawa, DDS, PhD; Chiho Kudo, DDS, PhD; Hitoshi Niwa, DDS, PhD

ABSTRACT

Background. Sedation with continuous dexmedetomidine and bolus midazolam administration provides a lower incidence of unacceptable patient movement during procedures but requires a longer recovery time. The authors aimed to compare recovery time and unacceptable patient movement during sedation with initial loading of dexmedetomidine followed by continuous propofol infusion with those during sedation with continuous dexmedetomidine and bolus midazolam administration.

Methods. In this prospective randomized controlled trial, 54 patients undergoing dental surgery and requiring intravenous sedation were assigned to either the dexmedetomidine and propofol group (n = 27, dexmedetomidine administered at 6 μg/kg/h for 5 minutes, followed by continuous propofol infusion using a target-controlled infusion) or the dexmedetomidine and midazolam group (n = 27, dexmedetomidine administered at 0.2-0.7 μg/kg/h continuously after the same initial loading dose with bolus midazolam). A bispectral index of 70 through 80 was maintained during the procedure. Patient movement that interfered with the procedure and time from the end of sedation to achieving a negative Romberg sign were assessed.

Results. Times from the end of sedation to achieving a negative Romberg sign in the dexmedetomidine and propofol group (median, 14 minutes [interquartile range, 12-15 minutes]) were significantly shorter ($P < .001$) than in the dexmedetomidine and midazolam group (median, 22 minutes [interquartile range, 17.5-30.5 minutes]). The incidence of unacceptable patient movement was comparable between groups (n = 3 in the dexmedetomidine and propofol group, n = 4 in the dexmedetomidine and midazolam group; $P = .999$).

Conclusions. Sedation with a single loading dose of dexmedetomidine followed by continuous propofol infusion can prevent delayed recovery without increasing unacceptable patient movement.

Practical Implications. The combination of dexmedetomidine and propofol may provide high-quality sedation for ambulatory dental practice. This clinical trial was registered in the University Hospital Medical Information Network Clinical Trials Registry. The registration number is UMIN000039668.

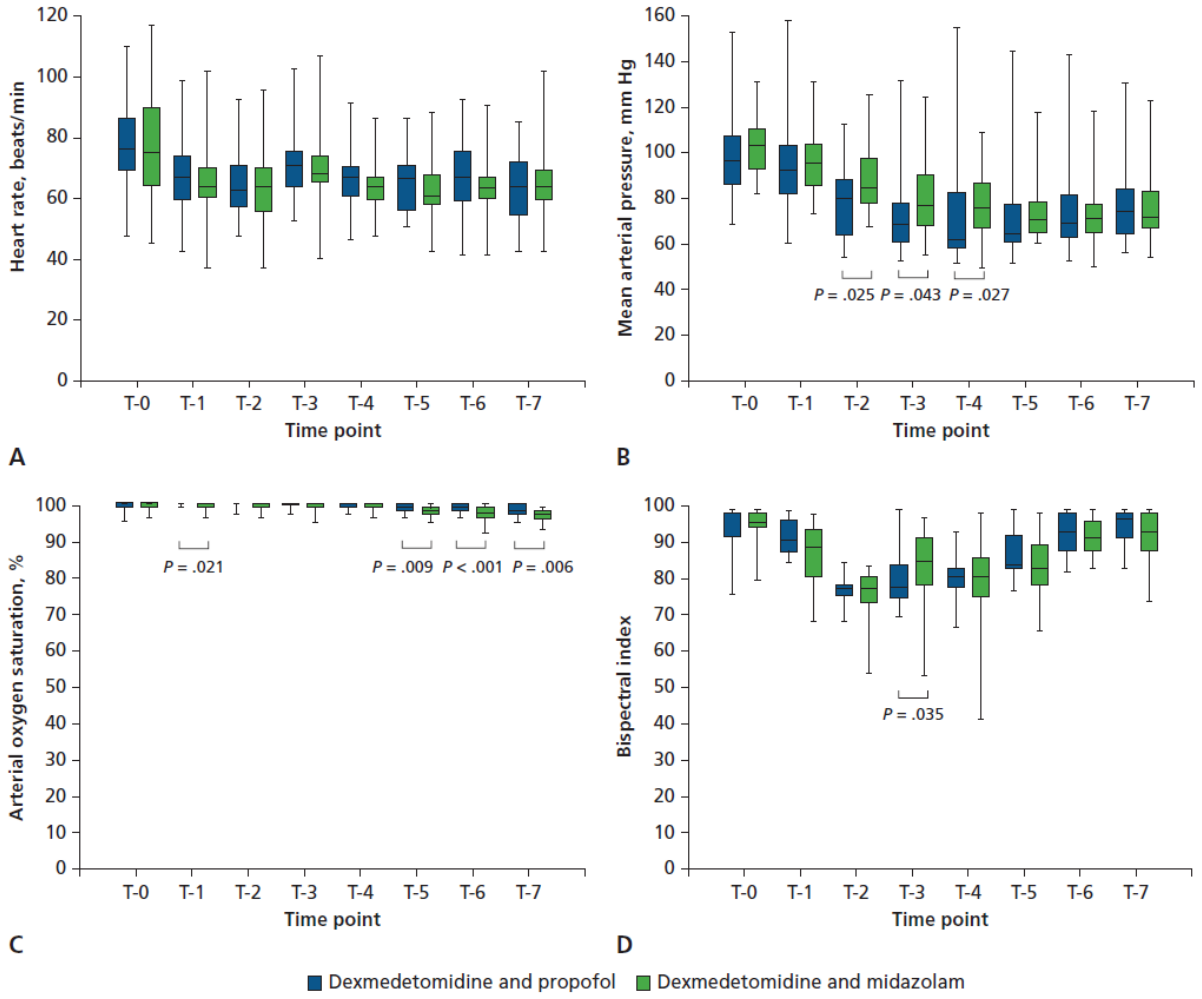
Nakagawa H, et al. J Am Dent Assoc. 2023 Nov;154(11):1008-1018.e2.

Dex IV load followed by CI propofol

Table 2. Recovery time, patient movement, cough, and snoring.

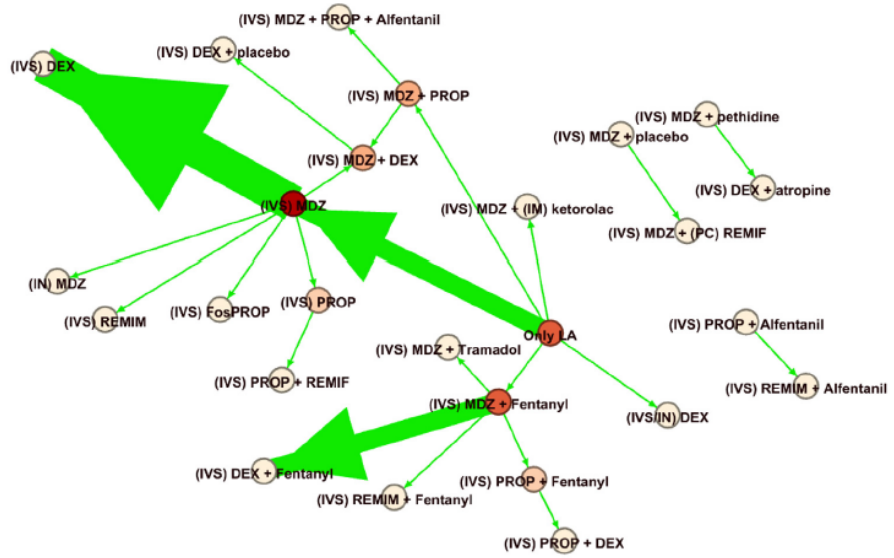
VARIABLE	DEXMEDETOMIDINE AND PROPOFOL GROUP (n = 27)	DEXMEDETOMIDINE AND MIDAZOLAM GROUP (n = 27)	*P* VALUE*
Recovery Time, Min,† Median (Interquartile Range)			
Aldrete time‡	3 (3-4.5)	5 (3.5-9)	< .001
Sitting time§	8 (7-10)	12 (8.5-20.5)	.002
Romberg time¶	14 (12-15)	22 (17.5-30.5)	< .001
Patient Movement,# No. (%)			
Acceptable	24 (89)	23 (85)	1
Unacceptable	3 (11)	4 (15)	
Patient Movement Score,# No. (%)			
0	16 (59)	18 (67)	.840
1	8 (30)	5 (19)	
2	2 (7)	3 (11)	
3	1 (4)	1 (4)	
Incidence of Cough Reflex,# No. (%)	8 (30)	8(30)	1
Cough Reflex, No.,† Median (Interquartile Range)	0 (0-1)	0 (0-1)	1
Snoring Score,# No. (%)			
0	21 (78)	17 (63)	.668
1	5 (19)	9 (33)	
2	1 (4)	1 (4)	
3	0 (0)	0 (0)	

* $P < .05$ was considered statistically significant. $P = 1$ is an artifact of the software system. † Mann-Whitney *U* test. ‡ Time from the end of sedation to attaining an Aldrete score of ≥ 9. § Time from the end of sedation until the participant could sit up. ¶ Time from the end of sedation to a negative Romberg sign. # Fisher exact text.



Nakagawa H, et al. J Am Dent Assoc. 2023 Nov;154(11):1008-1018.e2.

IV PSAA in oral surgery the literature – high amount of heterogeneity



ELSEVIER British Journal of Oral and Maxillofacial Surgery 62 (2024) 523–538 Surgery www.bjoms.com

Review

Efficacy and cost analysis of intravenous conscious sedation for long oral surgery procedures

Haidar Hassan [a,b,1,*], Rawand Shado [b,2], Ines Novo Pereira [c,3], Manisha Mistry [d], David Craig [d]

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Received 6 February 2024; revised 3 April 2024; accepted in revised form 11 April 2024
Available online 18 April 2024

Abstract

The aim of this study was to determine what is considered a long oral surgery and conduct a cost-effective analysis of sedative agents used for intravenous sedation (IVS) and sedation protocols for such procedures. Pubmed and Google Scholar databases were used to identify human studies employing IVS for extractions and implant-related surgeries, between 2003 and July/2023. Sedation protocols and procedure lengths were documented. Sedative satisfaction, operator satisfaction, and sedation assessment were also recorded. Cost estimation was based on The British National Formulary (BNF). To assess bias, the Cochrane Risk of Bias tools were employed. This review identified 29 randomised control trials (RCT), six cohorts, 14 case-series, and one case-control study. The study defined long procedures with an average duration of 31.33 minutes for extractions and 79.37 minutes for implant-related surgeries. Sedative agents identified were midazolam, dexmedetomidine, propofol, and remimazolam. Cost analysis revealed midazolam as the most cost-effective option (<10 pence per procedure per patient) and propofol the most expensive option (approximately £46.39). Bias analysis indicated varying degrees of bias in the included studies. Due to diverse outcome reporting, a comparative network approach was employed and revealed benefits of using dexmedetomidine, propofol, and remimazolam over midazolam. Midazolam, dexmedetomidine, propofol, and remimazolam demonstrated safety and efficacy as sedative agents for conscious IVS in extended procedures like extractions or implant-related surgeries. While midazolam is the most cost-effective option, dexmedetomidine, propofol, and remimazolam offer subjective and clinical benefits. The relatively higher cost of propofol may impede its widespread use. Dexmedetomidine and remimazolam stand out as closely priced options, necessitating further clinical investigations for comparative efficacy assessment.

Keywords: Intravenous conscious sedation; Long oral surgery procedures; Efficacy; Cost analysis; Dental extraction; Oral extraction; Dental implant; Oral implant; Midazolam; Propofol; Dexmedetomidine; Remimazolam

Hassan H, et al. Br J Oral Maxillofac Surg. 2024 Jul;62(6):523-538.

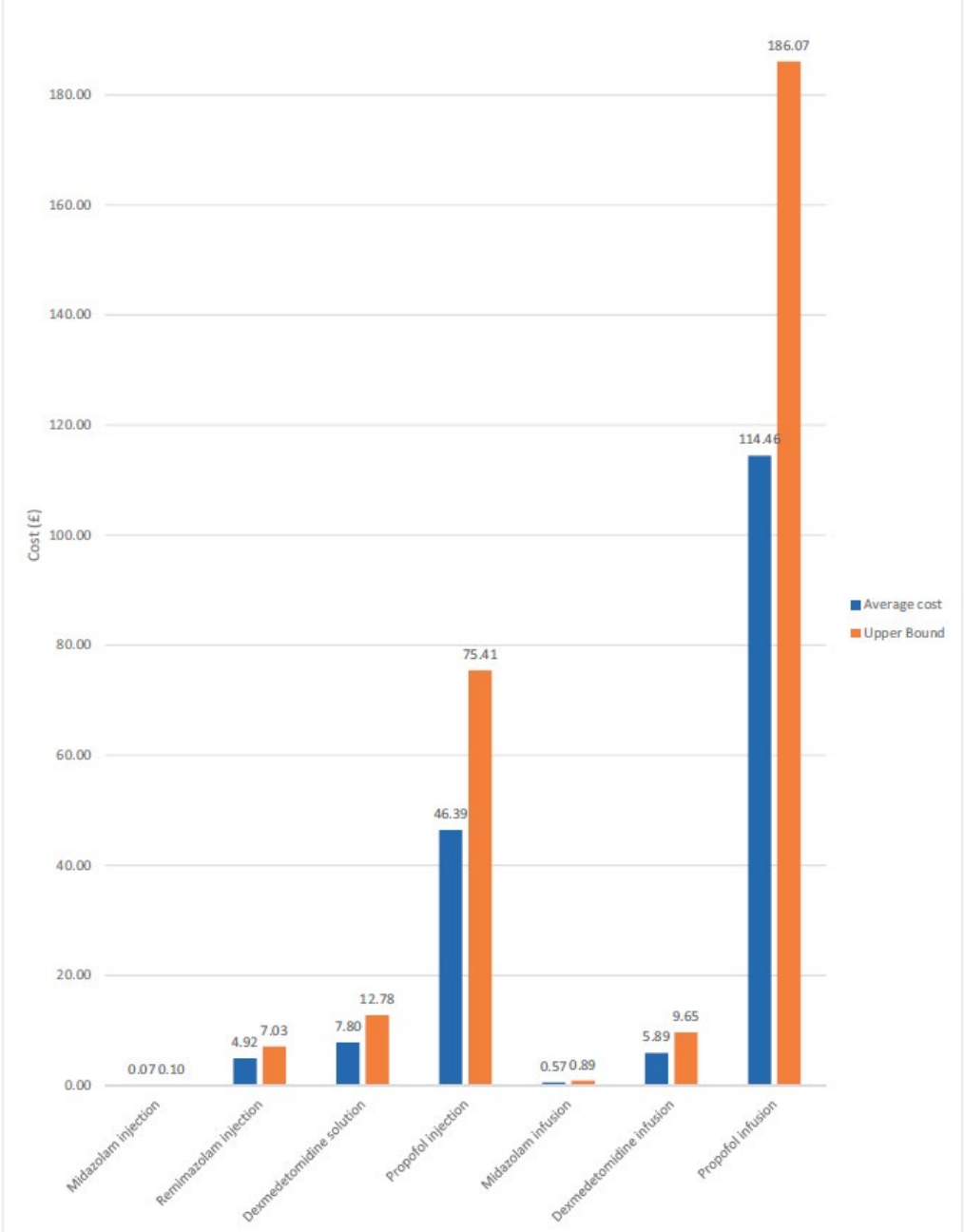
Table 2
Properties of intravenous sedative agents used in oral surgery.

	Ideal IVS agent	Midazolam	Propofol	Dexmedetomidine	Remimazolam
Mechanism of action	-	Acts on GABA receptor	Acts on GABA receptor	Acts on α2-adrenoceptor	Acts on GABA receptor
Anxiolysis	Yes*	Yes*	Yes*	Yes*	Yes*
Analgesia	Yes*	No	No	Yes*	No
Induction and recovery rate	Very Rapid*	Rapid	Rapid	Very rapid*	Very rapid*
Speed of change in sedation level	Very Rapid*	Rapid	Very rapid*	Very rapid*	Very rapid*
Ease of titration	Easy*	Easy*	Easy*	Easy*	Easy*
Cardiorespiratory stability	Stable*	Stable*	Stable*	Stable*	Stable*
Systemic toxicity	Low*	Low*	Moderate	Low*	Low*
Reversibility	Yes*	Reversible with flumazenil*	None	None	Reversible with flumazenil*
Injection/induction characteristics	Painless*	Painless*	Painful in small veins	Painless*	Painless*
Storage/shelf-life	Long*	3 years	3 years	2–5 years	4 years*
Distribution half-life	Short*	6-15mins	2-8 minutes	6 minutes	0.5–2 minutes*
Elimination half-life	Short*	1.5-2hrs*	2-24 hours		2.4–3.8 hours
Usual dose	-	2-7.5mg	1.5-2.5 mg/kg	0.2–1.5 μg/kg/hr	0.075–0.25 mg/kg
Late active metabolites	None*	lpha-1 hydroxy midazolam	None*	None*	None*

IVS = ; GABA = ; (-) = Not applicable, (*) = matching the property to the ideal agent.

Hassan H, et al. Br J Oral Maxillofac Surg. 2024 Jul;62(6):523-538.

Cost per patient

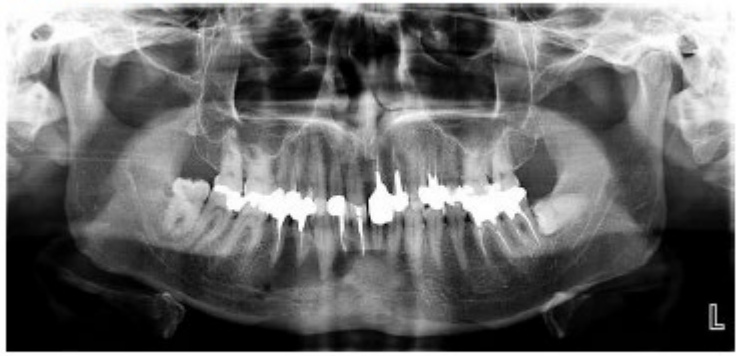


Hassan H, et al. Br J Oral Maxillofac Surg. 2024 Jul;62(6):523-538.

VT following dental procedural sedation

Case report

Figure 1. Preoperative Panoramic Radiograph



Unilocular radiolucency approximately 1.3 by 3.8 cm noted in right mandible.

CASE REPORT

Ventricular Tachycardia Following Ephedrine During Dexmedetomidine Dental Procedural Sedation

Shota Abe, DDS; Kanami Suzuki, DDS; Maki Hamamura, DDS; Takashi Tamanoi, DDS; Koji Takahashi, DDS; Keiichiro Wakamatsu, DDS; Kenji Yoshida, DDS, PhD; Hiroyoshi Kawaai, DDS, PhD; and Shinya Yamazaki, DDS, PhD

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We present the case of a 46-year-old man who received ephedrine for hypotension after surgery for a mandibular lesion under intravenous (IV) moderate sedation with dexmedetomidine (DEX) and experienced transient ventricular tachycardia (VT). The patient was scheduled to have cystectomy and multiple apicoectomies for the mandibular periapical infection and the simple bone cyst. Other than obesity, snoring, and a nonalcoholic fatty liver, he denied any other significant medical history, medications, or allergies. The surgery was successful; however, his blood pressure dropped after stopping the DEX infusion. Ephedrine was administered IV several times, which resulted in the onset of VT on the electrocardiogram (ECG). His blood pressure could not be measured at the time, but he was able to respond and breathe independently. A defibrillator was immediately made available. The ECG revealed a spontaneous transition from VT to atrial fibrillation with ST depression. Because he was unable to revert to a normal sinus rhythm, the patient was transferred to a general hospital, where he underwent additional testing. No abnormalities were observed in his heart or brain. After DEX administration, its long-lasting alpha-2 adrenoceptor agonist effects can cause vasodilation and inhibition of sympathetic activity, leading to hypotension in some patients. Should that occur, ephedrine can be used to increase blood pressure, but it may also provoke transient coronary artery spasms and lead to VT. Consequently, extreme caution should be exercised in patients who develop hypotension following DEX administration. We also recognize the significance of regular training sessions, such as advanced cardiac life support programs.

Key Words: Dexmedetomidine; Hypotension; Ephedrine; Ventricular tachycardia; Oral surgery.

Abe S, et al. Anesth Prog. 2023 Dec 1;70(4):184-190.

IN dex for ambulatory dental surgery: Patient satisfaction of general anesthesia vs MAC with dex

Single-center, Belgium

- GA
  - propofol induction (1–2 mg/kg)
  - remifentanil infusion (0.15 µg/kg/min)
  - sevoflurane/nitrous oxide maintenance (minimal alveolar concentration 0.8)
- MAC
  - IN dex (1 mcg/kg) 30 min before surgery
  - Bolus of propofol (10–50 mg)
  - fentanyl (50–75 mcg)

Garip et al. BMC Research Notes (2022) 15:376
https://doi.org/10.1186/s13104-022-06246-2

BMC Research Notes

RESEARCH NOTE Open Access

A comparative study of patient satisfaction about anesthesia with dexmedetomidine for ambulatory dental surgery

Levin Garip[1†], Jasmin Verbist[1†], Hendrik Stragier[1,2,5], Joeri Meyns[3], Dieter Mesotten[1,4,5] and Joris Vundelinckx[1,5*]

Abstract

Objective: Intranasal administration of dexmedetomidine for monitored anesthesia care (MAC) appears to be an effective, safe, and appropriate alternative to general anesthesia (GA) for ambulatory dental surgery. Based on the available evidence we evaluated a new MAC protocol with intranasal dexmedetomidine as the primary choice.

To assess a difference in patient satisfaction and anesthesia-related discomfort between GA and MAC in ambulatory dental surgery, a study was conducted among patients undergoing various dental procedures. Patient satisfaction and anesthesia-related discomfort were assessed on the first postoperative day using the Bauer patient satisfaction questionnaire.

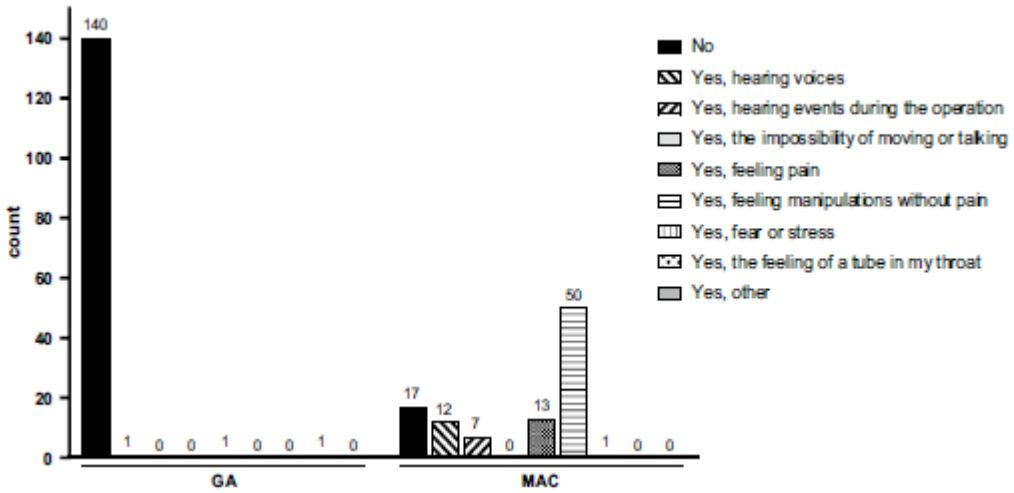
Results: Although the differences were small, patients in the MAC group were overall more satisfied with the general care compared to the GA group ($p < 0.02$). Patients in the MAC group reported more postoperative drowsiness compared to the GA group ($p < 0.05$), but less postoperative hoarseness and sore throat ($p = 0.005$ and $p < 0.001$, respectively). Moreover, postoperative thirst was more common in the GA group ($p = 0.002$).

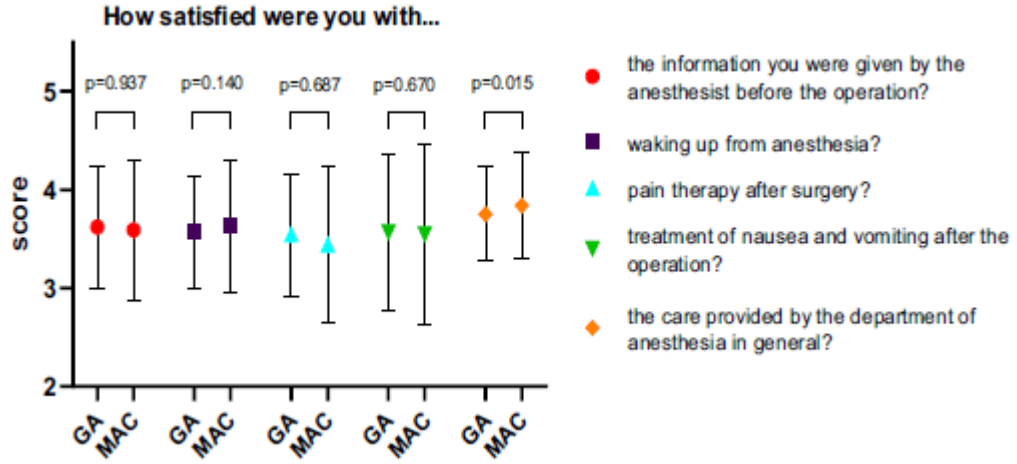
In conclusion, the differences in patient satisfaction and anesthesia-related discomfort between GA and MAC in this implementation study were small but appeared to favor MAC with intranasal dexmedetomidine over GA as anesthesia method during dental ambulatory surgery.

Keywords: Dexmedetomidine, Dental surgery, Ambulatory surgery, Patient satisfaction, Study, Monitored anesthesia care, General anesthesia

Garip L, et al. BMC Res Notes. 2022 Dec 22;15(1):376.

IN dex for ambulatory dental surgery: Patient satisfaction of general anesthesia vs MAC with dex





Garip L, et al. BMC Res Notes. 2022 Dec 22;15(1):376.

Systematic review and meta-analysis: IN (mostly) Dex vs many routes of midaz as premed and sedation in peds

Oral and Maxillofacial Surgery (2023) 27:547–557
https://doi.org/10.1007/s10006-022-01087-6

REVIEW ARTICLE

Systematic review and meta-analysis comparing the efficacy of dexmedetomidine to midazolam as premedication and a sedative agent in pediatric patients undergoing dental procedures

Saumya Taneja[1] · Anuj Jain[2]

Received: 11 May 2021 / Accepted: 2 June 2022 / Published online: 27 June 2022

Abstract

Introduction Pediatric dental surgeries are associated with the emotions of fear, anxiety, and other behavioral disturbances of children that need to be managed. Sedation using drugs like dexmedetomidine (DEX) and midazolam (MID) is a common pharmacological behavior managing technique. We conducted this meta-analysis to evaluate the efficacy of both these drugs in current literature.

Methodology A thorough literature search was conducted on PubMed, MEDLINE, Google Scholar, and Cochrane's database for randomized studies that compared sedative efficacy of dexmedetomidine with midazolam in children of 0–15 years of age undergoing dental surgeries. Sedation in children during dental procedure, when used as a premedication, at the time of separation from parents and at the time of mask induction, onset time, duration of anesthesia, and surgery were evaluated. The mean differences (MDs), odds ratio (OR), and their 95% confidence intervals (CIs) were calculated both for continuous and dichotomous outcome data using random-effects model.

Results Seven studies met out inclusion criteria and were analyzed. Results of premedication with DEX was associated with more anxiolysis (OR=0.29, 95% CI: 0.17–0.52, p=0.0001; I^2=0%) and at the time of separation from parents (OR=0.36, 95% CI: 0.19–0.69, p=0.002; I^2=52%) in comparison to MID. No significant differences in results were seen at mask induction (OR=0.63, 95% CI: 0.34–1.18, p=0.15; I^2=47%) and for sedation in children during dental procedures (OR=0.52, 95% CI: 0.07–3.70, p=0.51; I^2=72%). Also, there were no significant differences in onset time, duration of anesthesia, and surgery between the two agents.

Conclusion DEX proved to be a better premedicant than MID for pediatric patients. No significant difference in efficacy of both sedative agents was observed in children undergoing dental treatment. More clinical trials need to be conducted to see its efficacy in dental surgeries in children of standardized ages and with standard doses.

Keywords Midazolam · Dexmedetomidine · Pediatric dental procedures

Taneja S, et al. Oral Maxillofac Surg. 2023 Dec;27(4):547-557.

Dex vs Midaz as premed and sedation in peds

Table 2 Characteristics of studies included in meta-analysis*

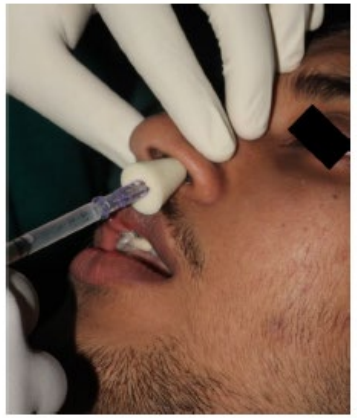
S. no.	Author and location	Mean age group	Route Of administration	Outcomes assessed				No. of cases		Better efficacy
				As premedication/ sedation during procedure	Separation from parents	At mask induction	Onset time and duration of anesthesia and surgery	DEX	MID	
1..	Keles and Kocaturk [15] (2018) Turkey	3–7 years	Oral	Yes (premedication)	Yes	Yes	Yes	26	26	DEX (p=0.29)
2.	Mahdavi et al. [16] (2018) Iran	2–6 years	Intranasal	Yes	No	No	No	20	20	MID (p=0.14)
3.	Oriby [17] (2019) Qatar	2–6 years	Intranasal	Yes (premedication)	No	No	Yes	38	38	DEX (p<0.05)
4.	Sathyamoorthy et al. [18] (2019) Mississippi	>5 years	Oral (MID) Intranasal (DEX)	Yes (premedication)	Yes	Yes	Yes (only duration)	36	37	DEX (p=0.03)
5.	Sheta et al. [19] (2013) Saudi Arabia	3–6 years	Intranasal	Yes (premedication)	Yes	Yes	Yes	21	21	DEX (p=0.01)
6.	Surendar et al. [20] (2014) India	4–14 years	Intranasal	Yes	No	No	No	21	21	DEX (p=0.24)
7.	Wang et al. [21] (2020) China	3–6 years	Oral (MID) Intranasal (DEX)	No	Yes	Yes	Yes (only duration)	21	21	DEX (p=0.95)

*Abbreviations used: *DEX* dexmedetomidine, *MID* midazolam

Taneja S, et al. Oral Maxillofac Surg. 2023 Dec;27(4):547-557.

IN dex vs IN saline transalveolar extraction for anxiety

- Single center in India
- 50 patients (25 in each group)
- All patients received local anesthesia
- Group A = IN dex 1.5 mcg/kg
- Group B = IN Saline 30 min before procedure
- Outcomes:
  - Oxygenation (pulse oximetry)
  - Heart rate
  - Anxiety (as measured by Ramsey Score)
  - Pain



5 Intranasal spray with nasal atomization device

Ramsay sedation scale	
1	Patient is anxious and agitated or restless, or both
2	Patient is co-operative, oriented, and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

J. Maxillofac. Oral Surg. (July–Sept 2023) 22(3):627–633
https://doi.org/10.1007/s12663-023-01933-4

COMPARATIVE STUDY

Comparative Evaluation of Intranasal Dexmedetomidine Spray Versus Intranasal Normal Saline Spray in Patients Undergoing Transalveolar Extractions for Anxiety Reduction: A Randomized Control Study

Mrudula Mulay[1] · Amit Mahajan[1] · Navin Shah[1] · Rakesh Shah[1] · Saurabh Chandalia[1] · Dharang Soni[1]

Received: 10 October 2022 / Accepted: 29 April 2023 / Published online: 4 June 2023

Abstract

Background Dexmedetomidine has dose-dependent selectivity for alpha 2 adrenoceptors. It is a good sedative with analgesic characteristics and good haemodynamic stability. Intranasal sedation is a non-invasive medication delivery method that is both safe and well accepted by both children and adults. One of the most common procedures in maxillofacial surgery is transalveolar extraction. In minor oral surgery, a painless transalveolar extraction with little postoperative pain would be ideal.

Aim To examine the effectiveness of intranasal dexmedetomidine spray against intranasal normal saline spray in patients undergoing transalveolar extractions for anxiety relief.

Method We compared sedation effect by Ramsay sedation scale, analgesia by visual analogue scale, monitored BP and pulse rate for anxiety, and spo2 levels for any complication in this prospective double-blinded randomized control study for two groups, A group with intranasal dexmedetomidine spray and the B group of intranasal NS spray for placebo effect at 0 min, 15 min, 30 min, and 45 min until transalveolar extraction.

Result As a result of the intranasal spray of dexmedetomidine, there were no related problems such as respiratory depression. There was a substantial difference in sedation and analgesia between group A and the placebo group, as well as a significant decrease in pulse rate and hypotension in the dexmedetomidine group to reduce anxiety.

Conclusion Intranasal injection of atomized dexmedetomidine (1.5 mcg/kg) for patient sedation having transalveolar extractions or other minor surgical operations in oral and maxillofacial surgery is clinically effective, convenient, lowers anxiety, and safe.

Clinical Trial Registration: No. CTRI/2021/07/035181.

Keywords Dexmedetomidine · Intranasal spray · Sedation · Transalveolar extraction

Mulay M, et al. J Maxillofac Oral Surg. 2023 Jun 4;22(3):1-7.

IN dex vs IN transalveolar extraction for anxiety (Group A is dexmedetomidine; Group B is saline)

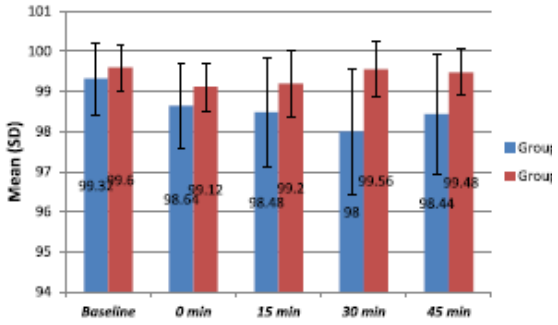


Fig. 1 Comparison of oxygen saturation

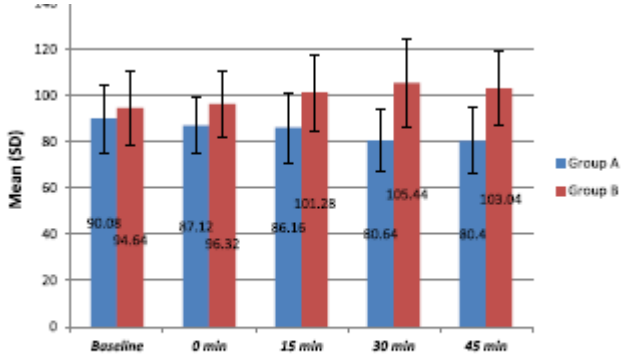
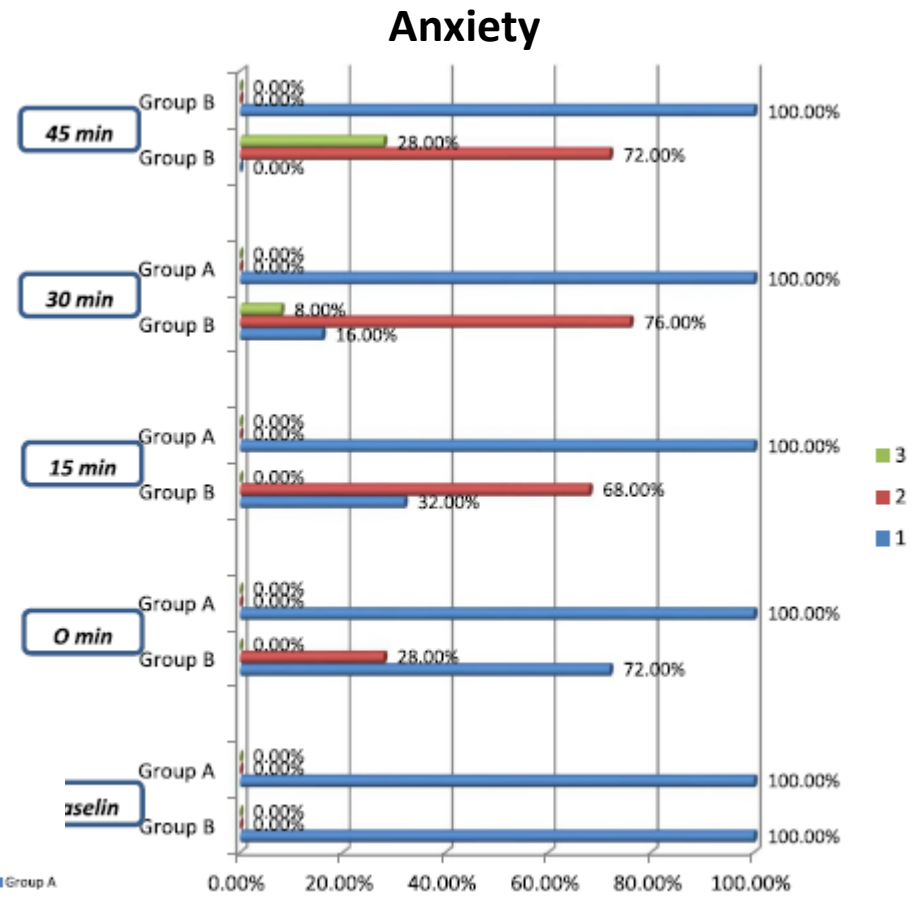
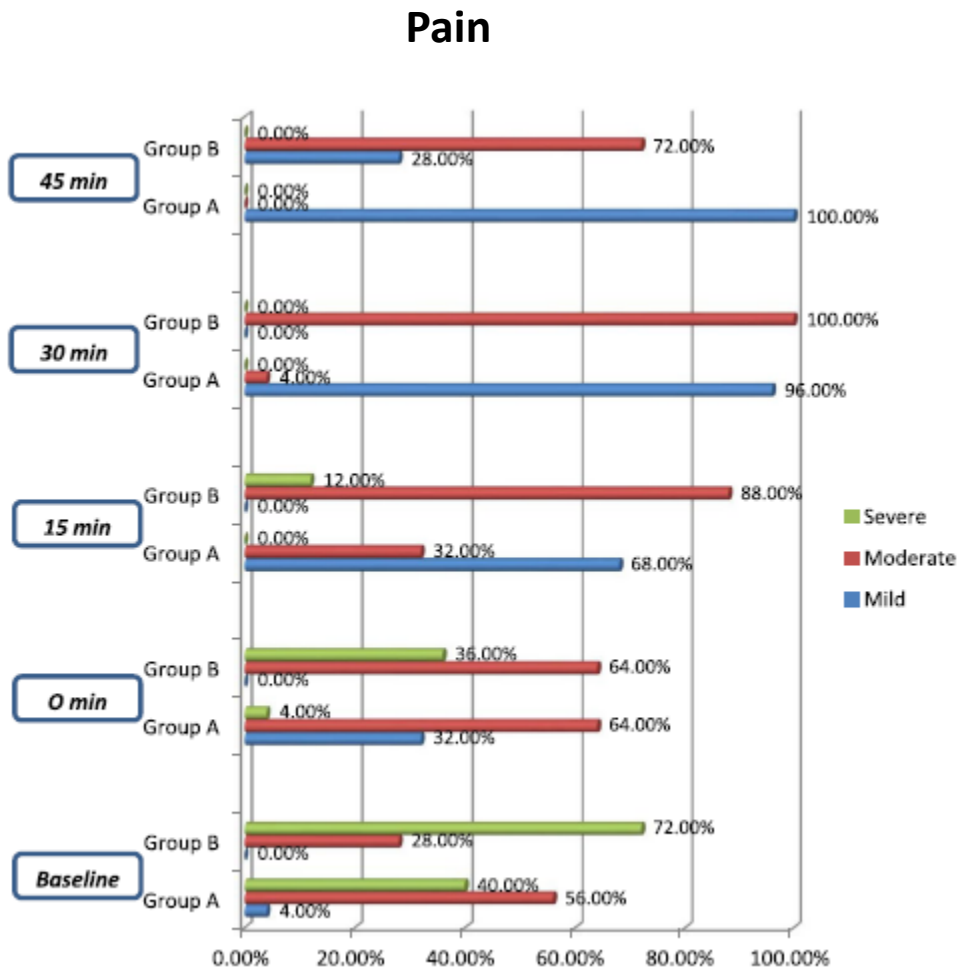


Fig. 4 Comparison of pulse rate

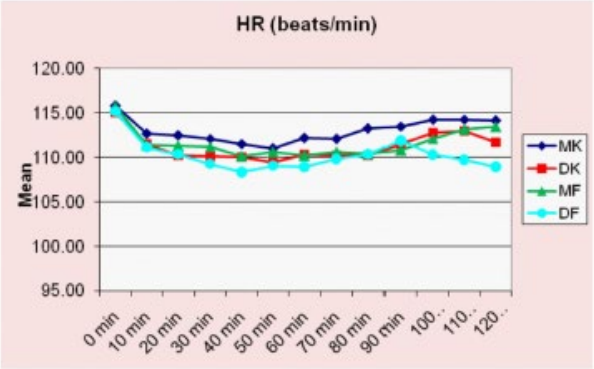


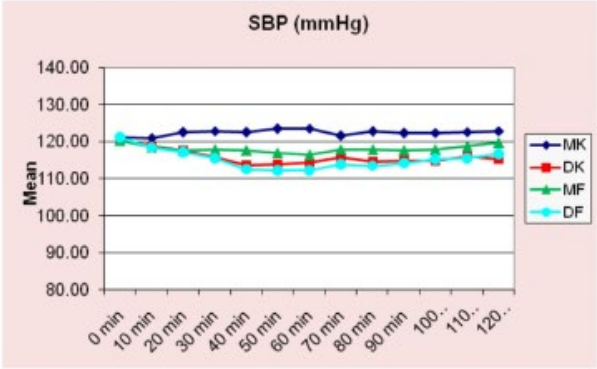


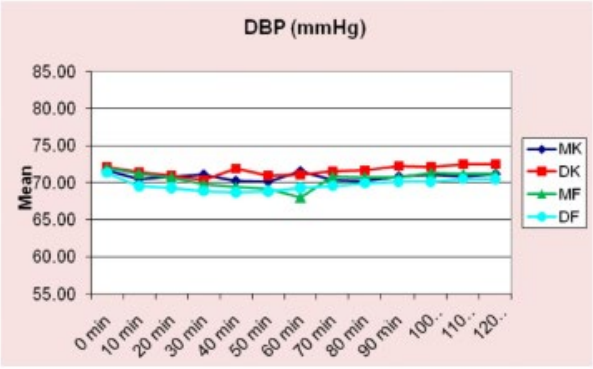
Mulay M, et al. J Maxillofac Oral Surg. 2023 Jun 4;22(3):1-7.

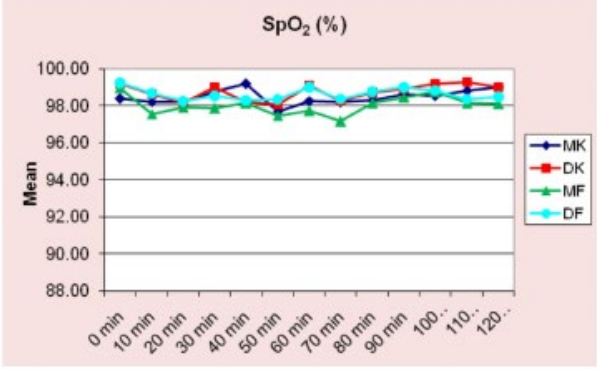
Intranasal – pediatric dental patients

- Single center in India
- 128 peds patients in 4 groups
- All meds intranasal
  - I (n=32) midaz 0.2 mg/kg & ketamine 4 mg/kg (MK)
  - II (n=32) dexmed 1 mcg/kg & ketamine 1 mg/kg (DK)
  - III (n=32) midaz 0.2 mg/kg & fentanyl 2 mcg/kg (MF)
  - IV (n=32) dexmed 1 mcg/kg & fent 1.5 mcg/kg (DF)









Original Article
pISSN 2383-9309 | eISSN 2383-9317
J Dent Anesth Pain Med 2023;23(2):69-81 | https://doi.org/10.17245/jdapm.2023.23.2.69

Comparative evaluation of intranasal midazolam-ketamine, dexmedetomidine-ketamine, midazolam-fentanyl, and dexmedetomidine-fentanyl combinations for procedural sedation and analgesia in pediatric dental patients: a randomized controlled trial

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Background: In order to assess the effectiveness of various analgesio-sedative combinations for pain relief and sedation in pediatric dental patients, a thorough evaluation of clinical studies and patient outcomes is necessary.
Methods: A total of 128 healthy, uncooperative pediatric dental patients were randomly allocated to receive one of the four combinations of drugs via the intranasal (IN) route: Group I received midazolam-ketamine (MK), Group II received dexmedetomidine-ketamine (DK), Group III received midazolam-fentanyl (MF), and Group IV received dexmedetomidine-fentanyl (DF) in a parallel-arm study design. The efficacy and safety of the combinations were evaluated using different parameters.
Results: The onset of sedation was significantly faster in the DF group than in the DK, MF, and MK groups ($P < 0.001$). The depth of sedation was significantly higher in the DK and DF groups than in the MK and MF groups ($P < 0.01$). DK and DF produced significant intra- and postoperative analgesia when compared with combinations of MK and MF. No significant adverse events were observed for any of the combinations.
Conclusions: The DK and DF groups showed potential as analgesio-sedatives in view of their anxiolytic and analgesic effects.

Keywords: Analgesio-sedation; Dental anxiety; Dexmedetomidine; Fentanyl; Ketamine; Midazolam.

Agarwal A, et al. J Dent Anesth Pain Med. 2023 Apr;23(2):69-8

Intranasal – pediatric dental patients

- Time to satisfactory sedation – shorter with MK and MF
  - non-dexmedetomidine groups
- DK & DF combinations has prolonged post-anesthetic recovery
  - Dexmedetomidine groups

Table 1. Demographic and clinical data of the participants according to the intervention groups

VARIABLES	MK (n = 32)	DK (n = 32)	MF (n = 32)	DF (n = 32)	P Value
Sex: n (%)					
Female	16 (50.0)	17 (53.1)	17 (53.1)	18 (56.3)	0.969
Male	16 (50.0)	15 (46.9)	15 (46.9)	14 (43.8)	
Weight (kg) Mean ± SD	21.09 ± 2.81	20.72 ± 2.82	20.63 ± 2.71	19.81 ± 2.89	0.320
Age (yrs) Mean ± SD	5.99 ± 1.02	6.22 ± 1.08	6.45 ± 1.27	6.28 ± 1.11	0.444
ASA grade: n (%)					
I	31 (96.9)	31 (96.9)	30 (93.8)	31 (96.9)	0.891
II	1 (3.1)	1 (3.1)	2 (6.3)	1 (3.1)	
Sedation Onset Time (mins) Mean ± SD	9.60 ± 1.65	17.10 ± 2.18	10.79 ± 1.53	18.24 ± 2.07	< 0.001***
Duration of session under sedation (mins) Mean ± SD	48.44 ± 14.10	44.00 ± 12.28	46.78 ± 14.05	40.69 ± 12.71	0.106
Recovery Time (mins) Mean ± SD	45.71 ± 5.54	80.36 ± 5.71	40.19 ± 4.93	70.43 ± 6.19	< 0.001***
Adverse Effects:					
n (%)	2 (6.3)	1 (3.1)	1 (3.1)	0 (0.0)	0.559
Emesis (vomiting)					

*Statistically significant at P value < 0.05

ASA, American Society of Anesthesiologists; DF, dexmedetomidine-fentanyl; DK, dexmedetomidine-ketamine; MF, midazolam-fentanyl; MK, midazolam-ketamine; n, number; SD, standard deviation.

Agarwal A, et al. J Dent Anesth Pain Med. 2023 Apr;23(2):69-81.

IN dex for impacted 3rd molar

Single center in India

- 25 “anxious” adult patients
- IN dex 1.5 mcg/kg 30 min prior
- Effect take effect 30-45 minutes
- Nearly back to baseline at 105 minutes

Cureus

Open Access Original Article

DOI: 10.7759/cureus.36721

Received 02/12/2023
Review began 02/21/2023
Review ended 03/22/2023
Published 03/26/2023

Efficacy of Intranasal Atomized Dexmedetomidine for Sedation in Surgical Removal of Impacted Mandibular Third Molars: A Prospective Study

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Abstract

Aims and objectives: To assess the efficacy of dexmedetomidine atomized intranasally for sedation during surgical removal of impacted mandibular third molars.

Materials and methods: A prospective randomized trial was conducted on 25 anxious patients between the ages of 18 and 40 who had impacted the lower third molars. An intranasal atomization device was used to give the medication 30 minutes prior to the surgical procedure. The Ramsay sedation score and Observer's assessment of alertness/sedation score were used to assess intranasal sedation.

Results: The results of our study state that the sedative effect began to take effect between 30 and 45 minutes later and was nearly back to baseline by 105 minutes after the administration of intranasal dexmedetomidine.

Conclusion: Intranasal delivery of 1.5mg/kg atomized dexmedetomidine for patients undergoing surgical removal of impacted mandibular third teeth is safe, feasible, and clinically efficient in daycare settings based on the sedation scores, and secondary variables which were assessed.

Bhargavi M, et al. Cureus. 2023 Mar 26;15(3):e36721.

IN dex for impacted 3rd molar

Ramsay sedation score	Time in minutes							Total	Chi-square	P value
	15	30	45	60	75	90	105			
1. Anxious and agitated or restless, or both N (% respondents)	3 (12.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.7%)		
2. Cooperative, oriented and tranquil N (% respondents)	22 (88.0%)	15 (60.0%)	4 (6.0%)	1 (4.0%)	1 (4.0%)	12 (48.0%)	24 (96.0%)	79 (45.1%)		
3. Responsive to commands only N (% respondents)	0 (0.0%)	10 (40.0%)	17 (68.0%)	20 (80.0%)	19 (76.0%)	12 (48.0%)	1 (4.0%)	79 (45.1%)	123.96	0.001
4. Exhibiting brisk response to light glabellar tap or loud auditory stimulus N (% respondents)	0 (0.0%)	0 (0.0%)	4 (16.0%)	4 (16.0%)	4 (16.0%)	0 (0.0%)	0 (0.0%)	12 (6.9%)		
5. Exhibiting a sluggish response to light glabellar tap or loud auditory stimulus N (% respondents)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	2 (1.1%)		
Total N (% respondents)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	175 (100%)		

TABLE 1: Ramsay sedation score

% - percentage

N - number of respondents

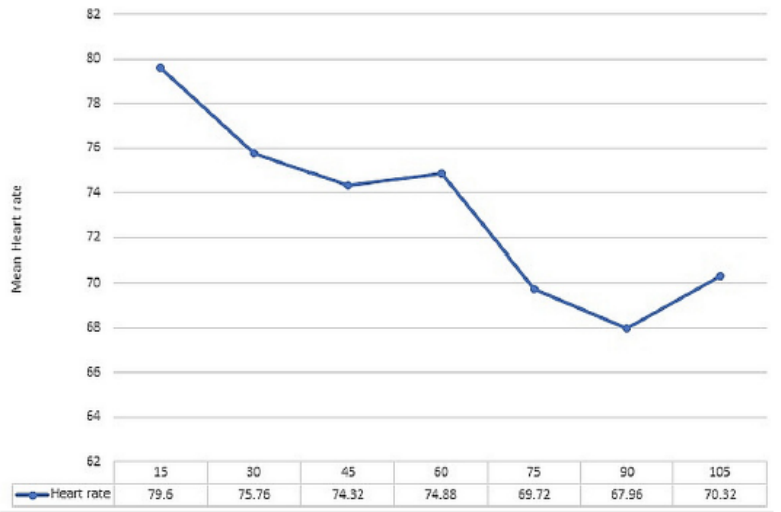

FIGURE 4: Heart rate plotted against time

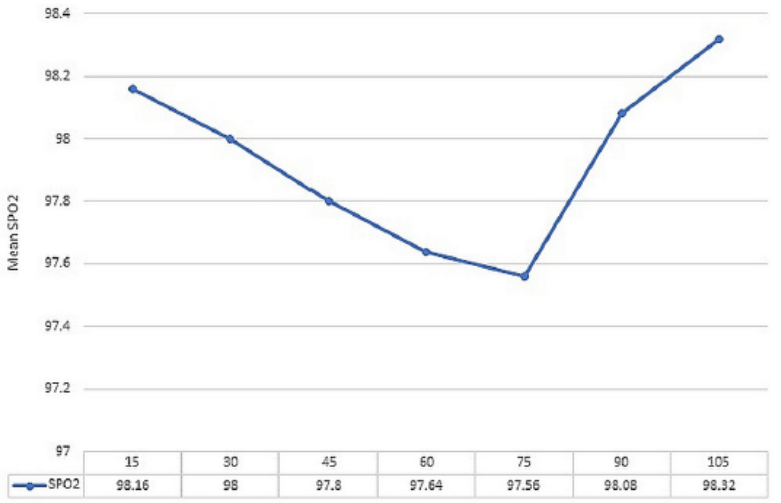

FIGURE 5: SPO2 plotted against time

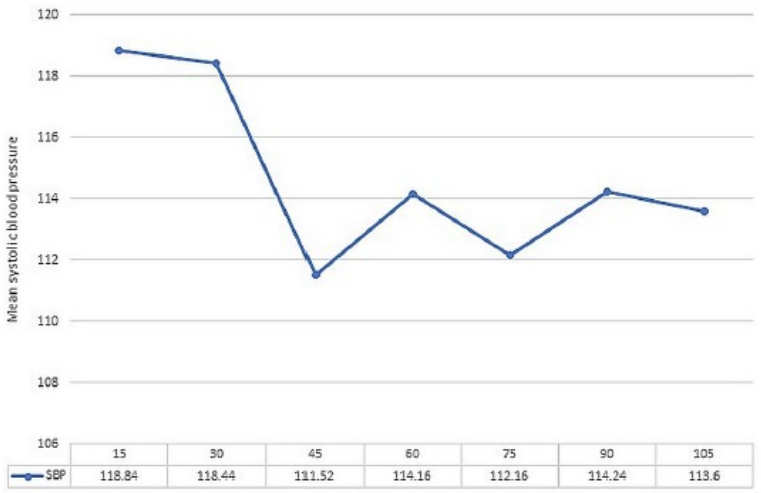

FIGURE 6: Systolic blood pressure plotted against time

Bhargavi M, et al. Cureus. 2023 Mar 26;15(3):e36721.

IN dex vs IN midaz and iNitrous peds

Single center, India

- 14 patients
- IN 1 mcg/kg dex did not provide the same level of sedation compared to IN midaz

- IN dex had a significantly longer onset compared to IN midaz

Janiani P, et al. J Indian Soc Pedod Prev Dent. 2024 Apr 1;42(2):141-148.

Comparative evaluation of intranasal dexmedetomidine, intranasal midazolam, and nitrous oxide for conscious sedation of anxious children undergoing dental treatment: A randomized cross-over trial

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ABSTRACT

Background: Pharmacological methods, specifically sedatives, have gained popularity in managing the behavior of children during dental appointments. **Aim:** The aim of this study was to compare 1 μ/kg intranasal dexmedetomidine, 0.3 mg/kg intranasal midazolam, and nitrous oxide in evaluating the level of sedation, behavior of the child, onset of sedation, physiologic signs, and adverse effects. **Materials and Methods:** In this cross-over trial, 15 children aged 6–8 years were randomized to receive intranasal atomized dexmedetomidine, intranasal atomized midazolam, and inhalation nitrous oxide at three separate visits. After administering the sedative agent, a single pulpectomy was performed during each appointment, and the outcomes were recorded. The washout period between each visit was 1 week. **Results:** All three sedative agents were equally effective in controlling overall behavior. Dexmedetomidine showed lower sedation level scores (agitated; score 9) than the other groups. There was a statistically significant difference in the onset of sedation, with dexmedetomidine having the longest onset of 36.2 ± 9.47 min. Coughing and sneezing were predominantly observed after administration of intranasal midazolam. Oxygen saturation levels were statistically lower in the intranasal midazolam group during local anesthesia administration and post-treatment. **Conclusion:** 0.3 mg/kg intranasal midazolam is as effective as nitrous oxide sedation for controlling behavior and providing adequate sedation in pediatric dental patients. However, 1 μ/kg dexmedetomidine did not provide the same level of sedation and had a significantly longer onset. 0.3 mg/kg intranasal midazolam is an effective alternative to

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Access this article online	
Quick response code	Website: https://journals.lww.com/jped
	DOI: 10.4103/jisppd.jisppd_104_24

Introduction

Pharmacological approaches, such as sedation and general anesthesia, are employed to manage the behavior of children during dental procedures when nonpharmacological methods prove to be ineffective.[1] The efficacy of conscious sedation, often preferred over general anesthesia due to its lower cost

How to cite this article: Janiani P, Gurunathan D, Manohar R. Comparative evaluation of intranasal dexmedetomidine, intranasal

IN dex vs IN midaz and iNitrous peds

Table 2: Inter-group comparison of the level of sedation

Score	Nitrous oxide, *n* (%)	In midazolam, *n* (%)	In dexmedetomidine, *n* (%)
Anxious/agitated (score 1)	2 (14.3)	0	9 (64.3)
Co-operative (score 2)	12 (85.7)	10 (71.4)	5 (35.7)
Responds to command (score 3)	0	3 (21.4)	0
Brisk response (score 4)	0	1 (7.1)	0
Sluggish response (score 5)	0	0	0
No response (score 6)	0	0	0
Chi square test value (*P*)	23.071 (0.001*)		

*P=0.001 is statistically significant

Janiani P, et al. J Indian Soc Pedod Prev Dent. 2024 Apr 1;42(2):141-148.

Safety and sedation effect of IN dex in mandibular third molar surgery- SR MA

5 RCTs met criteria

- IN dex 30 min prior to surgery vs placebo

Drug Design, Development and Therapy

Dovepress
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ORIGINAL RESEARCH

Safety and sedative effect of intranasal dexmedetomidine in mandibular third molar surgery: a systematic review and meta-analysis

This article was published in the following Dove Medical Press journal:
Drug Design, Development and Therapy

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Objective: The focus of this meta-analysis was to assess the sedative effect and safety of intranasal dexmedetomidine (Dex) in mandibular third molar surgery.

Methods: The PubMed/Medline, Web of Science, Cochrane Library, and China National Knowledge Infrastructure databases were searched for studies published until May 1, 2018. Eligible studies were restricted to randomized controlled trials (RCTs) and controlled clinical trials. The evaluation indicators mainly included the bispectral index, observer assessment of alertness/sedation scale, systolic blood pressure, and heart rate. Data for each period in the Dex and control groups were pooled to evaluate its sedative effect and safety.

Results: Five RCTs met the inclusion criteria. This study included 363 patients: 158 patients received intranasal inhalation of Dex before surgery, and 158 patients were negative controls. The pooled results showed a good sedative effect during tooth extraction when intranasal inhalation of Dex was performed 30 minutes before third molar extraction (assessment of alertness/sedation, Dex vs control SMD −1.20, 95% CI −1.73 to −0.67, I^2=0, P=0.95; bispectral index, Dex vs control SMD −11.68, 95% CI −19.49 to −3.87, I^2=89%; P=0.0001), and parameters returned to normal within 90 minutes after inhalation. During the operation, blood pressure and heart rate decreased to some extent, but the decreases did not exceed 20% of the baseline, and all patients returned to normal conditions within 90 minutes after inhalation.

Conclusion: Intranasal inhalation of Dex 30 minutes before third molar extraction can provide a good sedative effect, and large-sample multicenter RCTs are needed to evaluate the analgesic effect of Dex.

Keywords: intranasal dexmedetomidine, sedation, mandibular third molar, meta-analysis

Liu S, et al. Drug Des Devel Ther. 2019 Apr 23;13:1301-1310.

Safety and sedation effect of IN dex in mandibular third molar surgery- SR MA

Table 1 Main characteristics of included studies

Reference	Year	Location	Study design	n	Jaw	Age, years (mean ± SD or range)	Total surgery time, minutes (mean ± SD)	Dexmedetomidine dosage	Control (type)	Evaluation indicator
Cheung et al[26]	2011	Hong Kong	RCT (parallel)	60	Mand	27.1±6.2[D] 26.9±5.7[P]	25.6±13.6[D] 24.7±12.5[P]	1.0 μg/kg	0.9% saline	OAA/S, BIS, pain, HR, SBP
Gu et al[27]	2014	Nanjing, China	RCT (parallel)	30	Mand	25–35	27±6[D] 28±7[P]	1.5 μg/kg	0.9% saline	OAA/S, HR, SBP
Nooh et al[25]	2013	Riyadh, Saudi Arabia	RCT (split mouth)	18	Mand	25±3.9	28±9[D] 30±7[P]	1.5 μg/kg	Water	OAA/S, BIS, pain, HR, SBP
Ryu et al[24]	2016	Seoul, South Korea	RCT (parallel)	240	Mand	26.0±8.1[D] 25.6±1.6[P]	20.1±10.3[D] 20.3±11.5[P]	1.5 μg/kg	No treatment	Pain, adverse events, patient satisfaction, and BIS
Shetty and Aggarwal[23]	2016	Mysore, India	RCT (split mouth)	15	Mand	18–35	NR	1.5 μg/kg	0.9% saline	OAA/S, pain

Notes: [D]Dexmedetomidine; [P]placebo. Dexmedetomidine administered intranasally.
Abbreviations: RCT, randomized controlled trial; Mand, mandibular third molar surgery; OAA/S, observer assessment of alertness/sedation; BIS, bispectral index; HR, heart rate; SBP, systolic blood pressure; NR, not reported.

Liu S, et al. Drug Des Devel Ther. 2019 Apr 23;13:1301-1310.

Local with dexmed

Single center in Taiwan

- 40 patients
- Intervention
  - Dexmed 15 mcg added to lidocaine
- Control
  - Lidocaine

Table 2: The mean pain scores and number of painkillers used in the two groups at different times.

Variable	Time	Intervention	Control	*P* value	Spearman (r)	Spearman *P* value
Pain scores (mean ± SD)	0	0.25 ± 0.44	0.8 ± 1.00	0.031	−0.33	0.03
	6	4.40 ± 2.50	7.55 ± 2.03	<0.001	−0.37	0.01
	12	2.80 ± 2.52	5.50 ± 2.39	0.003	−0.46	<0.01
	24	1.60 ± 2.37	4.00 ± 2.49	0.003	−0.17	0.26
Painkillers used (number ± SD)	6	1.4 ± 0.75	1.6 ± 0.75	0.313	—	—
	12	0.75 ± 0.55	1.1 ± 0.71	0.109	—	—
	24	0.45 ± 0.60	0.70 ± 0.80	0.348	—	—

Time, time after the surgery (hours); intervention, intervention group (dexmedetomidine + lidocaine); control, control group (lidocaine); Spearman (r): Spearman correlation (r).

Research Article

Injection of Lidocaine Alone versus Lidocaine plus Dexmedetomidine in Impacted Third Molar Extraction Surgery, a Double-Blind Randomized Control Trial for Postoperative Pain Evaluation

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Received 9 December 2020; Revised 24 December 2020; Accepted 15 January 2021; Published 27 January 2021

Academic Editor: Mohammad Alam

Objectives. Administration of medications such as dexmedetomidine as a topical anesthetic has been suggested in the pain control in dentistry. This double-blind randomized control trial study evaluated postoperative pain and associated factors following impacted third molar extraction surgery. Lidocaine alone was taken as the control and lidocaine plus dexmedetomidine as the intervention. *Materials and Methods.* Forty patients undergoing mandibular third molar extraction entered the study and were randomly allocated to the control and interventional groups. 0.15 ml of dexmedetomidine was added to each lidocaine cartridge and the drug concentration was adjusted to 15 μg for the intervention group while only lidocaine was used in the control group. A visual analog scale was used to measure and record pain levels at the end of the surgery and 6, 12, and 24 hours after the surgery and number of painkillers taken by the patients after the surgery was also recorded. *Results.* Pain scores of the intervention group decreased significantly during the surgery and also 6, 12, and 24 hours after the surgery compared to the control group. The pain score was correlated significantly with our intervention during the surgery and also 6 and 12 hours after that (all P value < 0.05). There was a nonsignificant reduction in the number of painkillers taken by the patients at 6, 12, and 24 hours after surgery (all P value > 0.05). *Conclusion.* In patients undergoing molar surgery, administration of a combination of dexmedetomidine and lidocaine is beneficial for the pain control. *Clinical Relevance.* Compared to the injection of lidocaine alone, combination of dexmedetomidine and lidocaine can be used for a better pain control in molar surgeries.

Alizargar J et al. Pain Res Manag. 2021 Jan 25;2021:6623792.

Average wholesale cost of select medication used for PSAA

- Opioids
  - Fent 100 mcg ~ $1.54
  - Morphine 2 mg ~ $2.87
  - Hydromorphone 1 mg ~ $4.32
  - Sufentanil – 50 mcg/1mL ~ $8.58
  - Remifentanil – 1 mg ~ $61.29

- Sedatives
  - Midaz 2mg ~ $0.65
  - Midaz 5mg ~ $1.16
  - Propofol 20 mg ~ $4.32
  - Dexmedetomidine 200 mcg vial ~ $5.25
  - Ketamine 10 mg/mL (20 mL) ~ $19.78

- Dexmedetomidine – alternative dosage forms
  - IV 80 mcg/20 mL (4 mcg/mL) vial ~ $32
  - IV 200 mcg/50 mL (4 mcg/mL) bag~ $18
  - Buccal film 120 mcg or 180 mcg~ $125

Delirium – postoperative OMFS

- Postoperative delirium has many synonyms
  - Acute cognitive impairment
  - Delirium
  - Emergence agitation
- Movement toward standardization of language
- Is likely common; up to 20% incidence, however
  - No standard assessment or diagnostic method (pre or postop)
- Associated with:
  - Prolonged recovery time
  - Elevated inflammatory markers
  - Extended hospital stay
  - Insomnia
  - Transplant revision
  - Nutritional risk
  - Cognitive distress
  - Dementia
  - PTSD

Alhammadi et al. Head & Face Medicine (2024) 20:39
https://doi.org/10.1186/s13005-024-00439-9

Head & Face Medicine

REVIEW Open Access

Postoperative delirium in oral and maxillofacial surgery: a scoping review

Eman Alhammadi[1,4*], Julian Max Kuhlmann[2], Majeed Rana[1], Helmut Frohnhofen[3] and Henriette Louise Moellmann[1*]

Abstract

Background Postoperative delirium (POD) in the oral and maxillofacial settings has gained more attention in recent decades. Due to advances in medical technology, treatment possibilities have expanded treatment for elderly and frail patients. This scoping review explores the correlation between POD and oral and maxillofacial surgery, summarizing screening and management protocols and identifying risk factors in this surgical field.

Methods This review follows the Scoping Review extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-ScR). A comprehensive literature search was performed using multiple databases, focusing on articles published from 2002 to 2023 that discuss delirium in oral and maxillofacial surgery settings. The review was registered beforehand in the Open Science Framework (https://osf.io/r2ebc).

Results From the initial 644 articles, 68 met the inclusion criteria. These studies highlighted the significant heterogeneity in POD diagnosis methods. The review identifies multiple risk factors across the preoperative, intraoperative, and postoperative phases that influence the occurrence of POD. Significant and independent risk factors in multiple regression analysis were highlighted, creating a clinical prediction list for the occurrence of POD.

Conclusion It is crucial to preoperatively identify patients at risk for POD and actively modify these risks throughout the patient's hospital stay. Implementing nonpharmacological preventive measures for at-risk patients is recommended to decrease the incidence of POD. Future research should focus on creating standardized specialty-specific protocols incorporating validated assessment tools and addressing the full spectrum of risk factors associated with POD.

Keywords Postoperative delirium, Maxillofacial surgery, Risk management, Scoping review, Oral and maxillofacial surgery, Head and neck surgery

- Risk factors
  - Modifiable
    - Medications?
  - Non-modifiable
    - Older age
    - Patient frailty
    - Higher ASA scores III & IV
    - Dementia
    - Surgery duration
    - Many others
- Ongoing research

Alhammadi E, et al. Head Face Med. 2024 Jul 23;20(1):39.

Delirium assessment

- Delirium assessment
  1. Acute onset or fluctuating course
  2. Inattention
     - Example - Recognize a letter in a sequence of 10 letters
       - Squeeze my hand when I say the letter “A”
       - S-A-V-E-H-E-A-R-T
  3. Disorganized thinking
  4. Altered level of consciousness

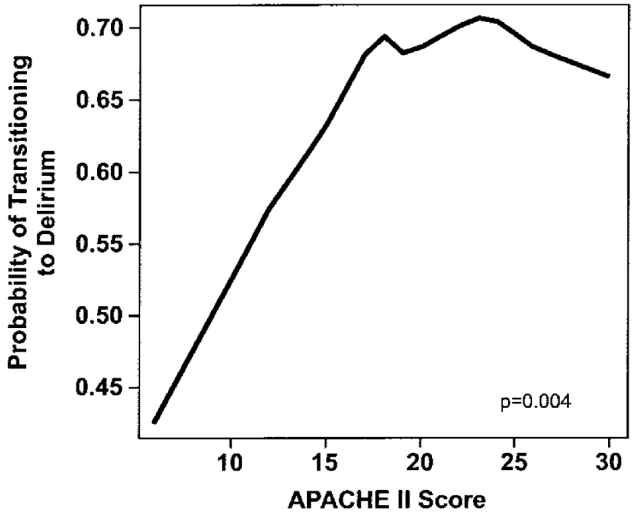
Assessment of ICU Delirium
CAM ICU Worksheet

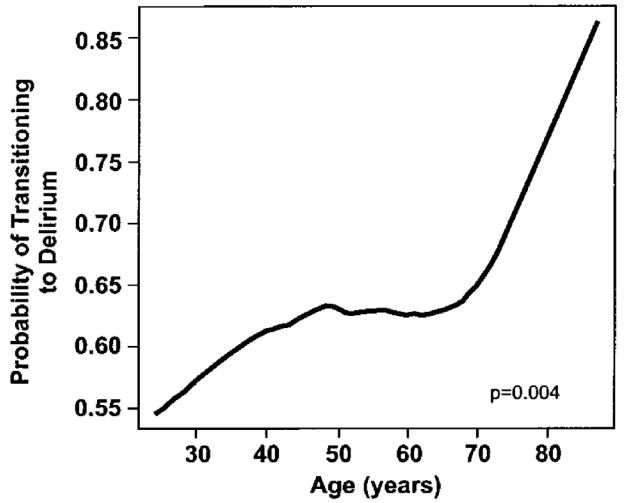
CAM ICU Features and Descriptions		
1. Acute Onset or Fluctuating Course	**Absent**	**Present**
A. Is there evidence of an acute change in mental status from baseline? OR B. Did the abnormal behavior fluctuate during the past 24 hours (e.g., tend to come and go, or increase and decrease in severity as evidenced by fluctuation of the VAMASS, GCS or previous delirium assessment)?		
2. Inattention	**Absent**	**Present**
Did the patient have difficulty focusing attention as evidenced by scores less than 8 on either the auditory or visual component of the Attention Screening Examination (ASE)? • Use the 5+5 pictures, or recognize a letter intermixed in a sequence of 10 letters		
3. Disorganized Thinking	**Absent**	**Present**
Does the patient have disorganized or incoherent thinking as evidenced by incorrect answers to 2 or more of the following 4 questions and/or demonstrate an inability to follow commands? Questions (Alternate Set A and Set B): **Set A** 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? **Set B** 1. Will a leaf float on water? 2. Are there elephants in the sea? 3. Do 2 pounds weight more than one pound? 4. Can you use a hammer to cut wood? **Other**: 1. Are you having any unclear thinking? 2. Hold up this many fingers (examiner holds own fingers up in front of patient). 3. Now do the same with the other hand (examiner demonstrates by displaying a different number of fingers).		
4. Altered Level of Consciousness	**Absent**	**Present**
Is the patient’s level of consciousness anything other than alert (e.g. vigilant, lethargic or stuporous), or is VAMASS < or > 3 (and not decreased due to sedation)? **Alert**: Looks around spontaneously, fully aware of environment, interacts appropriately. **Vigilant**: Hyperalert. **Lethargic**: Drowsy but easily aroused. Unaware of some elements in the environment, or no appropriate spontaneous interaction with interviewer. Becomes fully aware and appropriate with minimal noxious stimulation. **Stupor**: Becomes incompletely aware with strong noxious stimulation. Can be aroused only by vigorous and repeated stimuli. As soon as stimulus removed, subject lapses back into unresponsive state.		
Overall CAM ICU Score: **If 1 + 2, and either 3 or 4 is present, patient has delirium.**	**Yes**	**No**

Reproduced from Ely et al (2002): Vanderbilt University.

Delirium – critical care

- Up to 80% of critically ill ICU patients on a ventilator will experience delirium
- Develops over a short period of time (hours to days) fluctuates over time
- Patients in the ICU develop the spectrum of 3 delirious states (hyper, hypo, and mixed)
- Delirium remains unrecognized in as many as 66-84% of patients
- Delirium is associated with
  - Prolonged need for mechanical ventilation
  - Prolonged hospitalization
  - Increased risk of nosocomial pneumonia
  - Death in intubated ICU patients





Pandharipande P, et al. Anesthesiology. 2006 Jan;104(1):21-6.

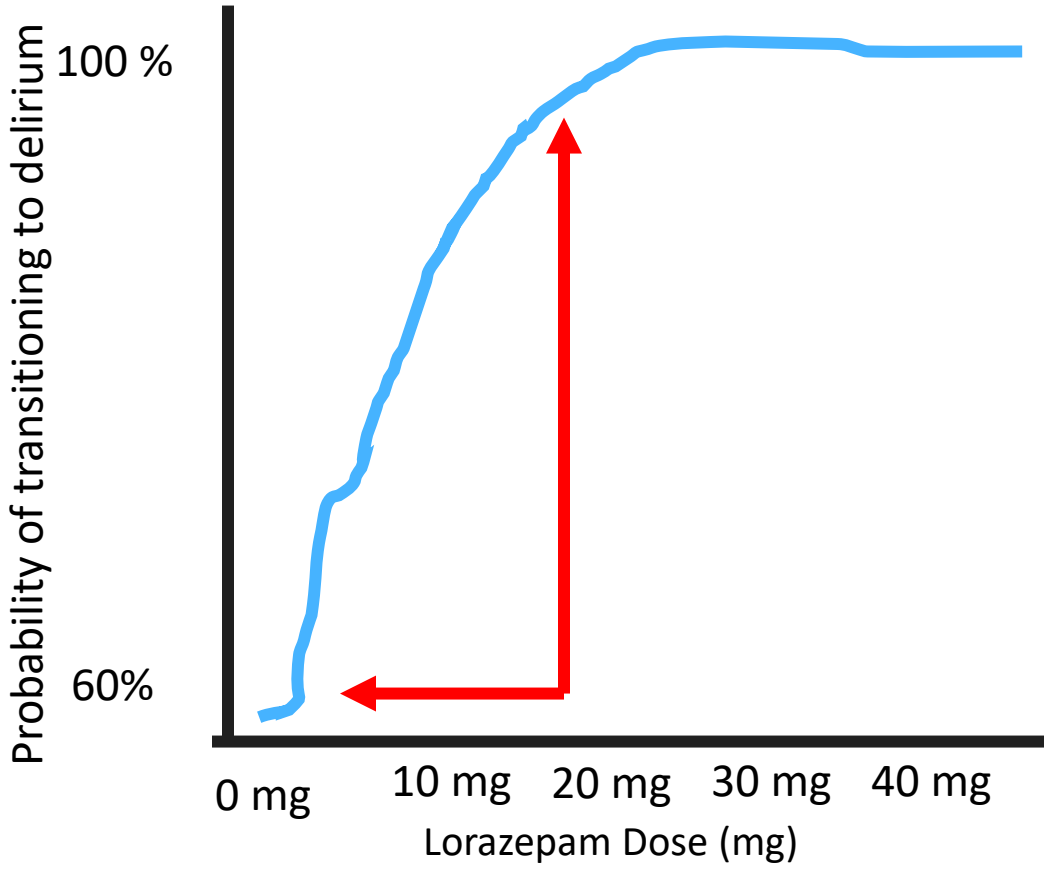
Pathophysiology of Delirium in Critically ill Patients

Subtype	Mechanism	Etiologies
Toxic Metabolic	Hypercarbia Hypoxia Encephalopathies Elevated Ammonia Elevated BUN Hyperthermia Electrolyte abnormalities Toxin mediated Infection/Inflammation	Respiratory Failure Cardiopulmonary bypass Organ failure: Liver, renal, heart Overdose Toxin Ingestion Intoxification of Alcohols (ethanol, ethylene glycol, methanol) Sepsis
Alteration of neurotransmitters	GABA and Glutamate Dopamine Norepinephrine Serotonin NMDA Acetylcholine	Ethanol abuse Excessive or inappropriate tapering of benzodiazepines/ barbiturates/ opioids Sleep deprivation and circadian rhythm alteration Pain

Most cases are Multifactorial!! = Treatment is Multi-Modal!!

Bongard FS, Sue DY (Eds): *Current Critical Care Diagnosis & Treatment*. 2nd edition. 2002

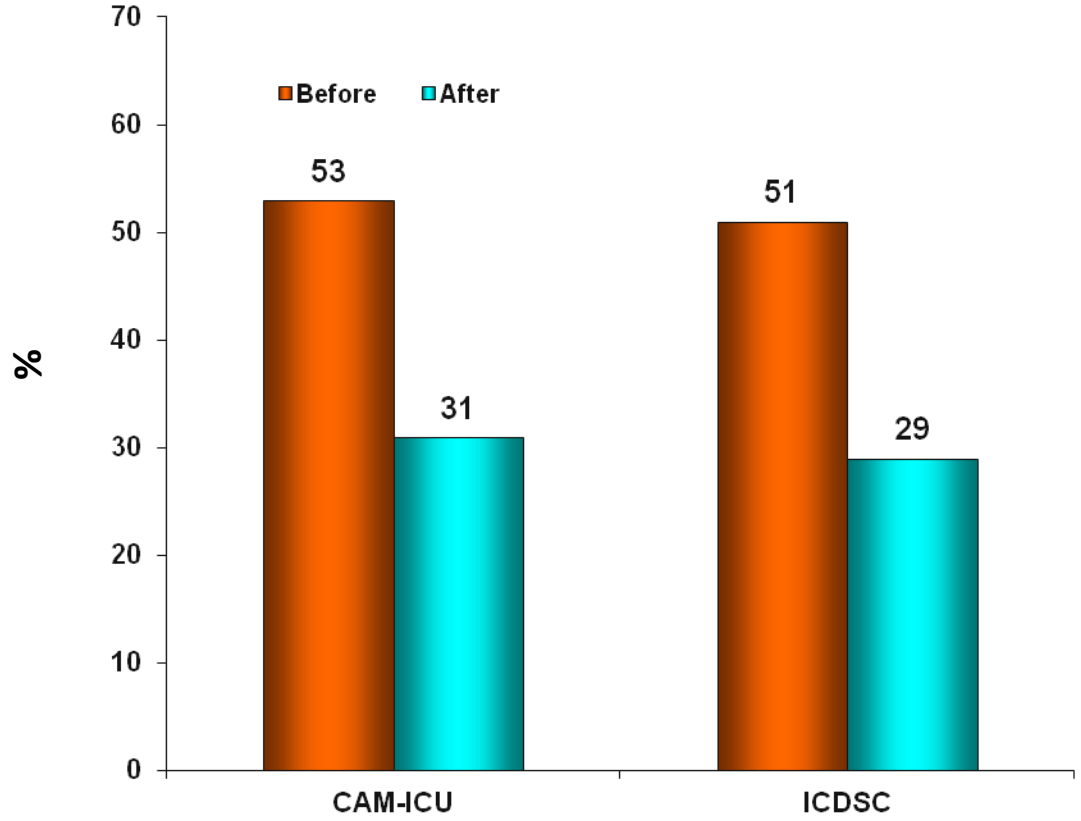
Probability of Transitioning to Delirium in Mechanically Ventilated Patients



Pandharipande P et al. *Anesthesiology*. 2006; 104(1):21-6.

Effect of Sedation Level on the Prevalence of Delirium

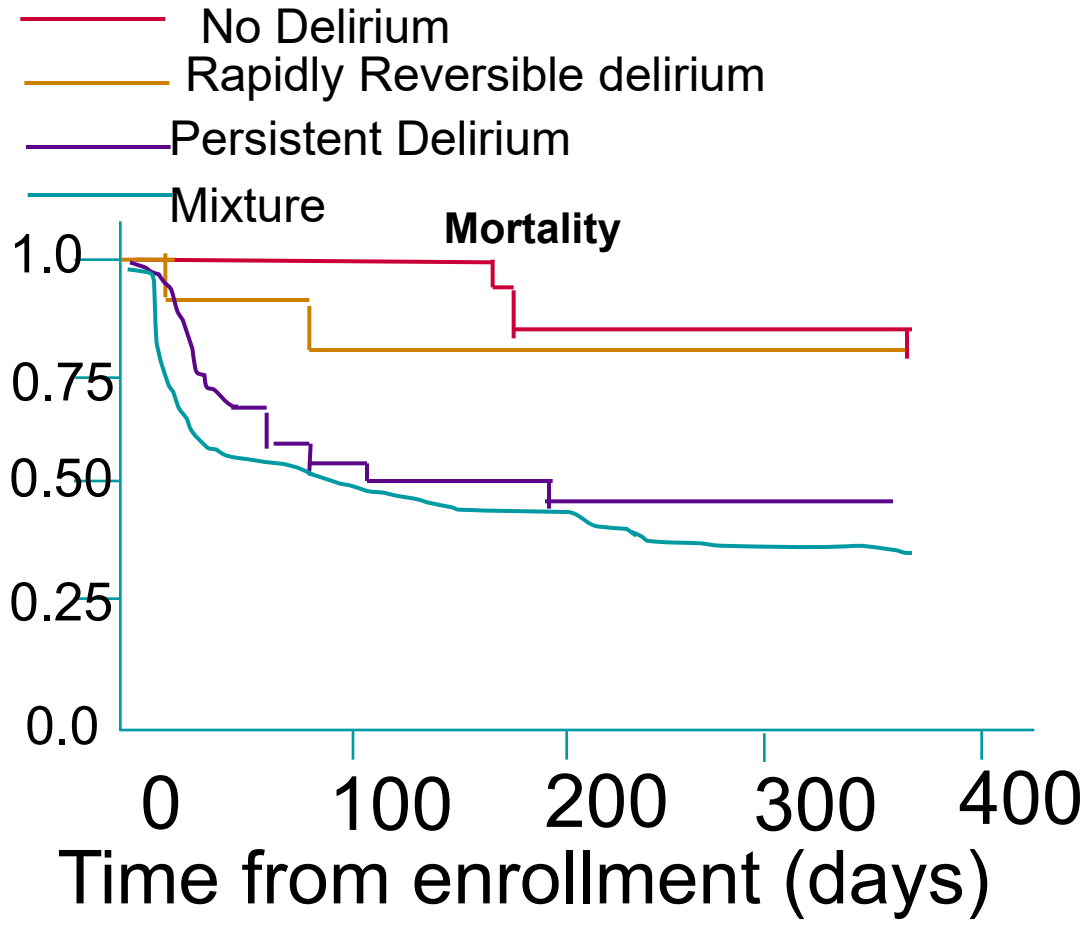
Delirium assessment: prior to (pt RASS -2/-3) and 2 hours after SAT

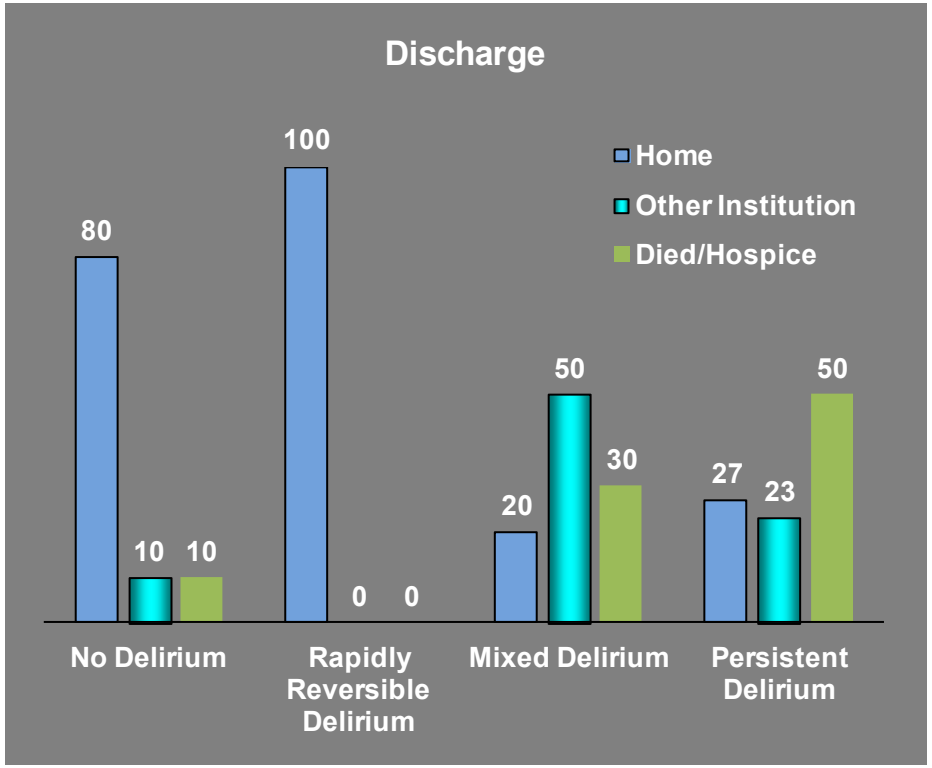


Single center in Switzerland, prospective, double-blind trial of 104 mixed medical/surgical ICU. 80 patients enrolled (467 patient days) and delirium assed via the ICDSC and CAM-ICU during SAT.

Haenggi M et al. *Intensive Care Med*. 2013 Dec; 39(12):2171-9.

Associated Mortality and discharge status with Rapidly Reversible, Sedation-Related Delirium





Single center, prospective, cohort of 102 intubated adult medical ICU patients at the University of Chicago. CAM-ICU assessed before and after SAT daily. Rapidly reversible delirium defined by CAM-ICU assessment abated within 2 hours of an SAT.

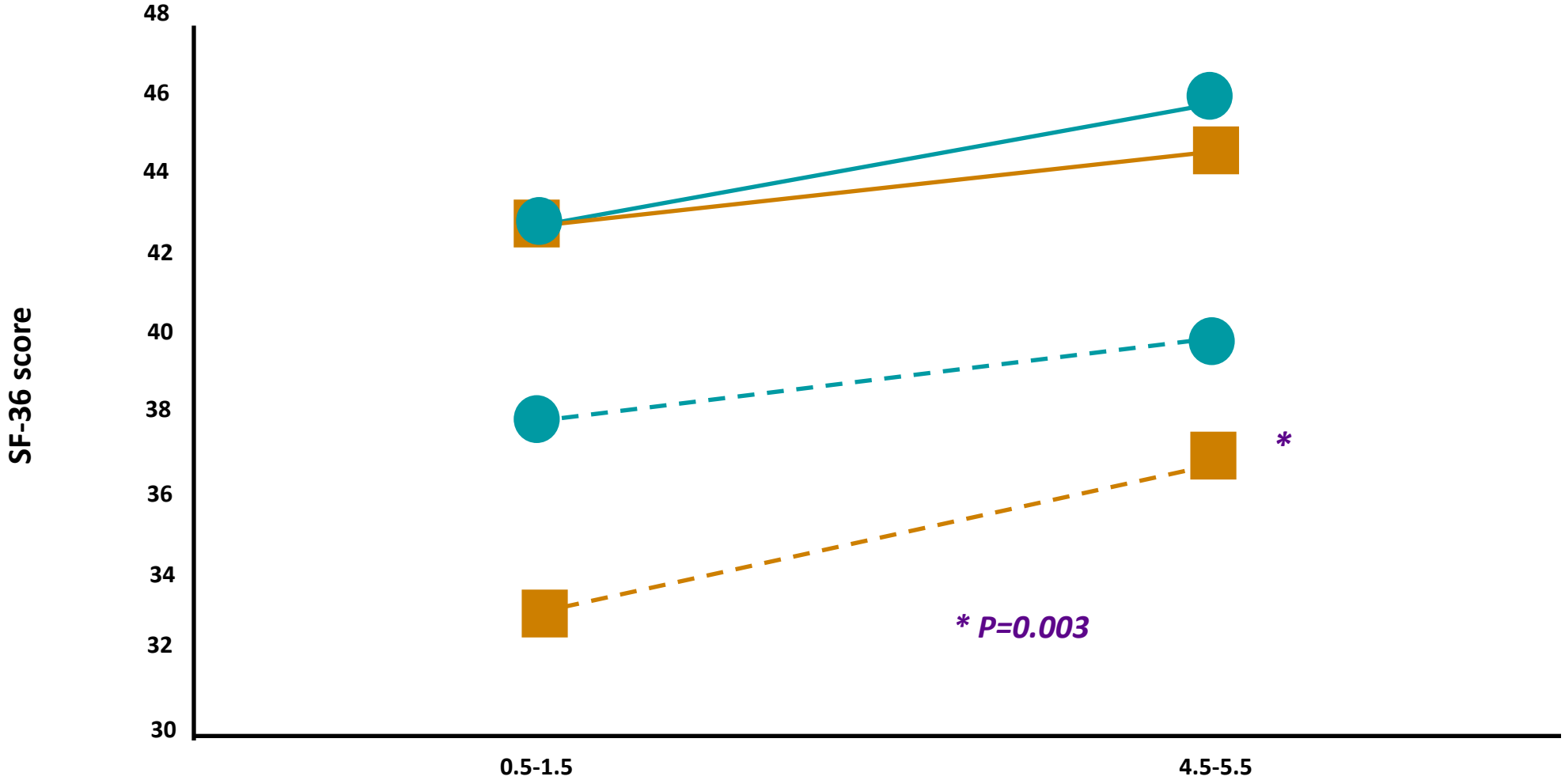
Patel SB, et al. Am J Respir Crit Care Med. 2014;189(6):658-665.

Delirium phenotypes and long-term cognitive impairment

Delirium phenotype	Prevalence (n=1040)	Frequency among delirium days (n=4187)	Duration of delirium, days	RBANS global cognition at 3 months	RBANS global cognition at 12 months
Any delirium	740 (71%)	4187 (100%)	4 (2-7)		
Hypoxic	579 (56%)	2247 (54%)	3 (1-5)	-3.85 (-7.07 to -0.64)	-3.76 (-7.16 to -0.37)
Septic	534 (51%)	2405 (57%)	3 (2-6)	-2.65 (-6.05 to 0.75)	-3.67 (-7.13 to -0.22)
Sedative-associated	663 (64%)	2634 (63%)	3 (1-5)	-6.52 (-9.66 to -3.37)	-4.03 (-7.80 to -0.26)
Metabolic	260 (25%)	1149 (27%)	3 (1-6)	0.15 (-1.52 to 1.81)	1.44 (-0.12 to 3.01)
Unclassified	224 (22%)	591 (14%)	2 (1-3)	-4.72 (-6.93 to -2.51)	-4.70 (-7.16 to -2.25)

Girard TD, et al. *Lancet Repir Med* 2018;6:213-222

Factual vs. Delusional Memories



Ringdal M, et al. *Crit Care Med* 2010;38(1):38-44.

Prevention is the key:

- Prevention is primary non-pharmacological (non-medication specific)
  - Major question is, will the choice of medication for PSAA have an impact on postoperative delirium in oral surgery?
- Management is largely non-pharmacological

2 seconds of bottle of glass of wine vs. bottle of tequila

A bottle of tequila or a glass of wine?

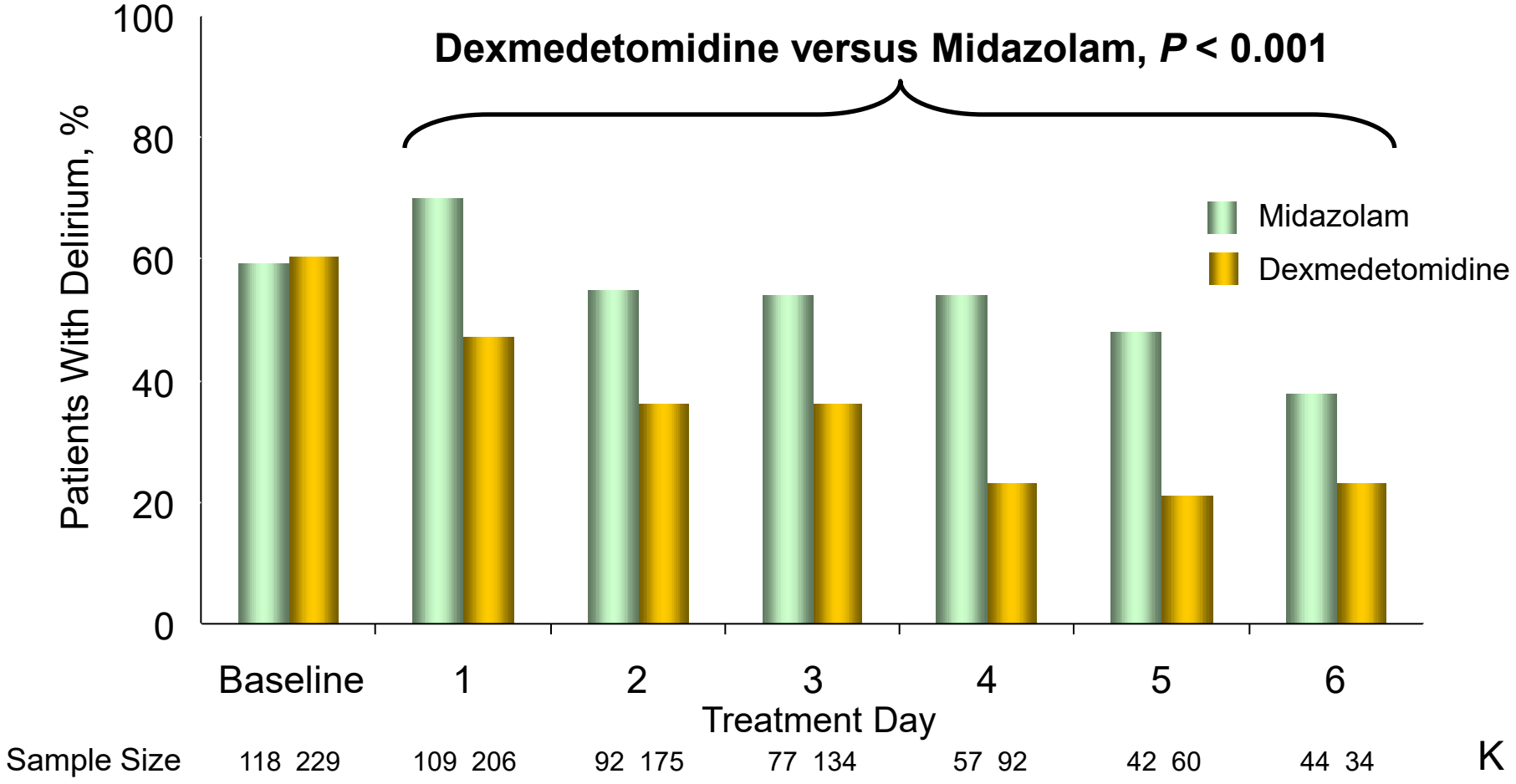
BWH BRIGHAM AND WOMEN'S HOSPITAL

Question

lorazepam 3 mg/hr is dose equivalence to PO lorazepam?

A. Total daily dose = 10 mg PO lorazepam
B. Total daily dose = 0.5 mg PO lorazepam
C. Total daily dose = 2 mg PO lorazepam
D. Total daily dose ~ 35 to 70 mg PO lorazepam (depending on your conversion factors)

Dexmedetomidine vs Midazolam: *SEDCOM TRIAL*



Riker RR, et al. *JAMA*. 2009 Feb 4;301(5):489-99.

Dexmedetomidine vs Midazolam: *SEDCOM TRIAL; Key Critiques*

	Dexmedetomidine (n = 244)	Midazolam (n = 122)	*p* Value
Time in target sedation range*	77.3	75.1	$p = 0.18$
Mean Dose	0.83 mg/kg/hr	0.056 mg/kg/hr	
Extubation time, d**	3.7 (3.1-4.0)	5.6 (4.6-5.9)	$p = 0.01$
ICU LOS**	5.9 (5.7-7.0)	7.6 (6.7-8.6)	$p = 0.24$

*Value expressed as mean %

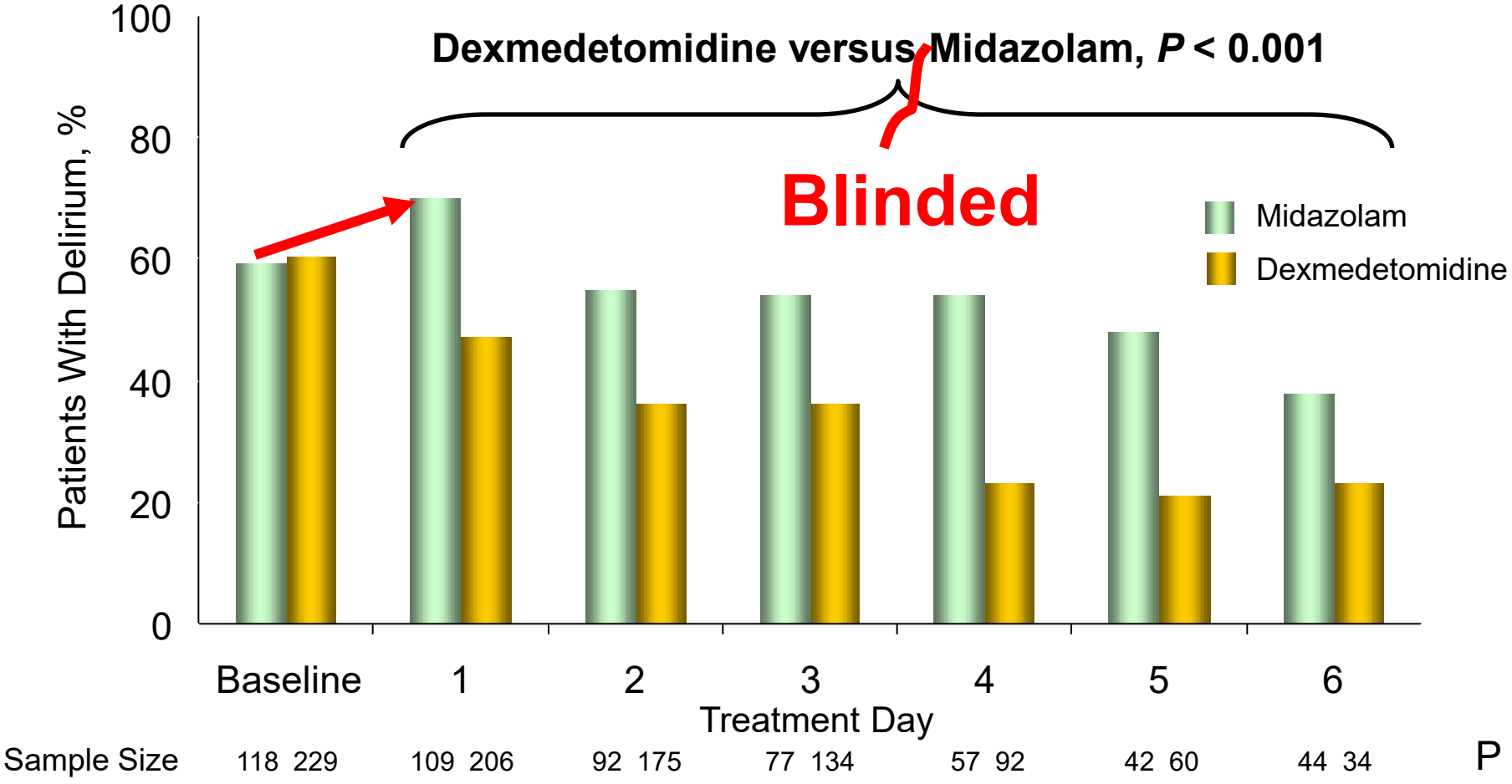
** Value expressed as median (IQR)

A bottle of tequila or a glass of wine?

4.9 mg/hr based on average wt of midaz group

Riker RR, et al. *JAMA*. 2009 Feb 4;301(5):489-99.

Dexmedetomidine vs Midazolam: *SEDCOM TRIAL; Key Critiques*



Riker RR, et al. *JAMA*. 2009 Feb 4;301(5):489-99.

Why blinded midaz drips are harmful – Kinetics!

Supratherapeutic

Therapeutic Range

Steady state

Subtherapeutic

Serum Concentration

Bolus + Infusion

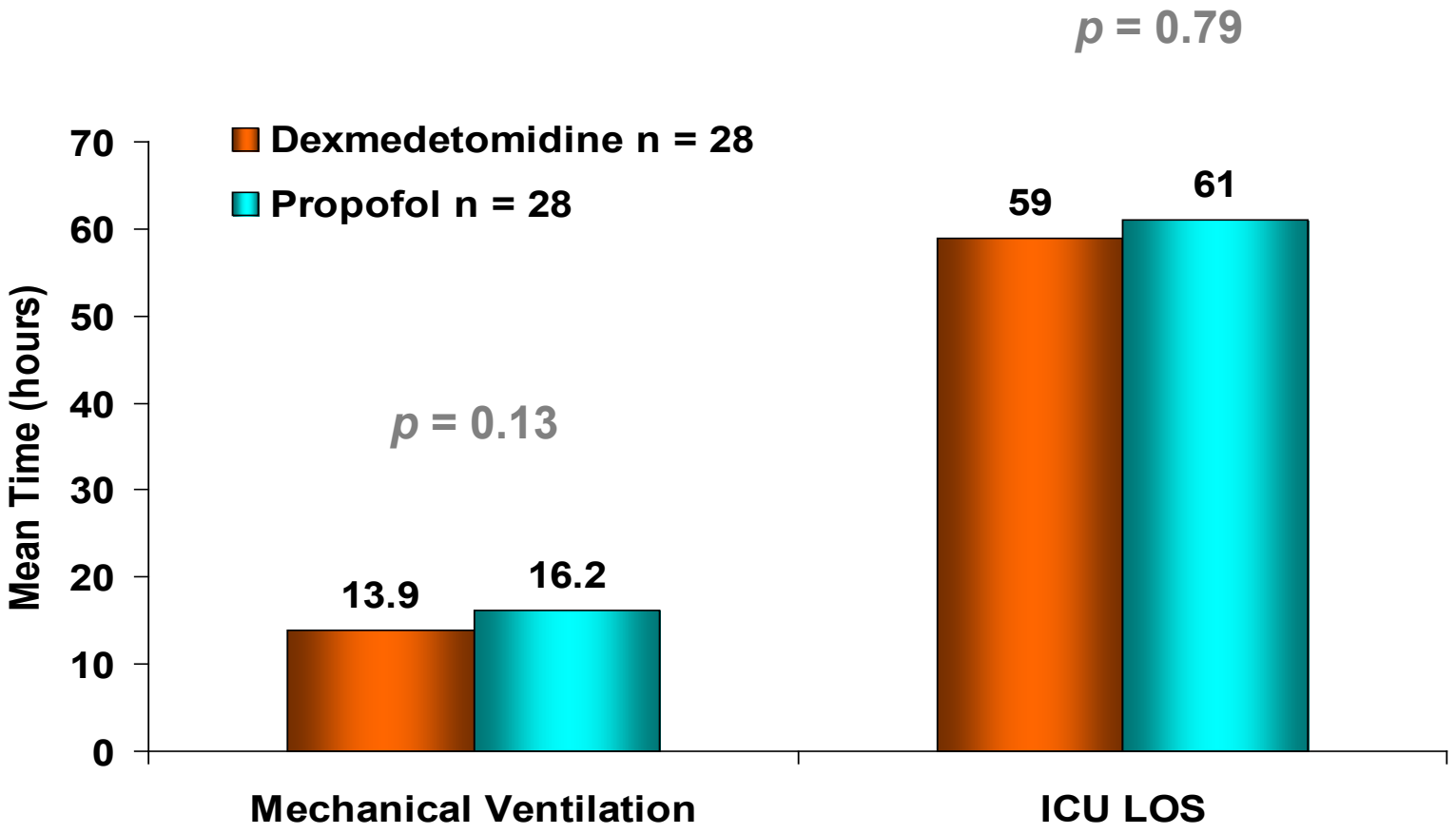
Infusion

Infusion (blind titration)

1 2 3 4 5 6 7

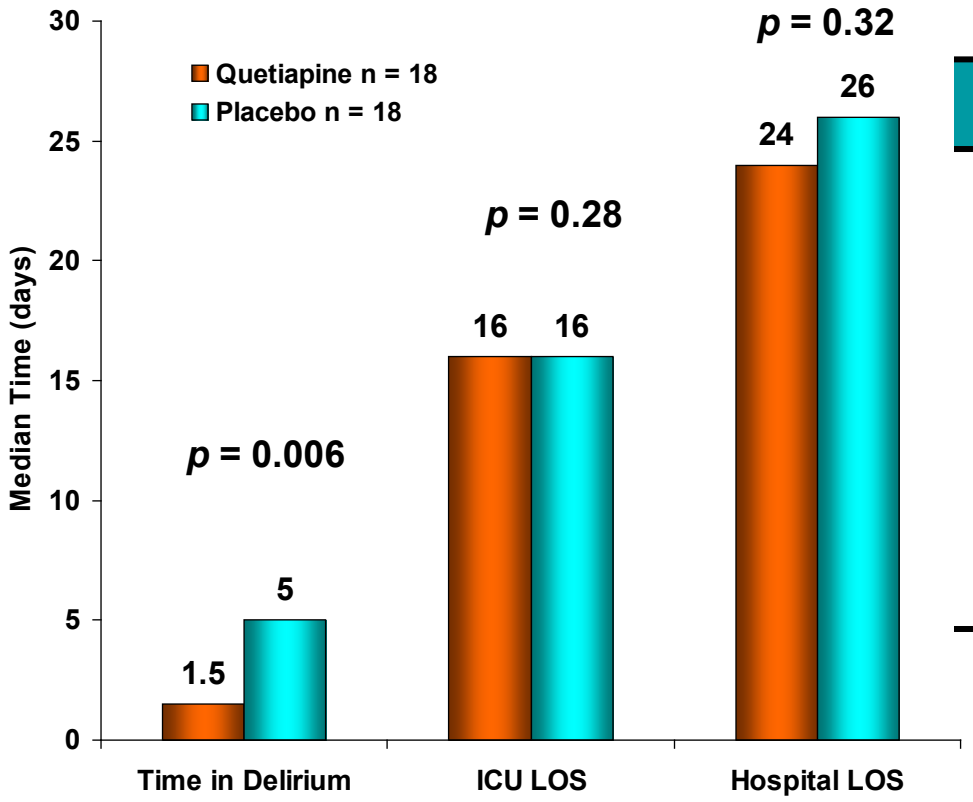
Half Lives

Dex vs Prop in Cardiac Surgery



Anger KE, Szumita PM et al. Crit Pathw Cardiol. 2010 Dec;9(4):221-6.

Quetiapine for the Treatment of Delirium in Mixed ICU Patients



	Quetiapine	Placebo	P value
SAS ≥5, hrs*	6	36	0.02
SAS ≤2, hrs*	0	0	0.54
Haloperidol mg/day*	1.9	4.3	0.26
Midazolam equivalents mg/day*	5.3	26	0.32

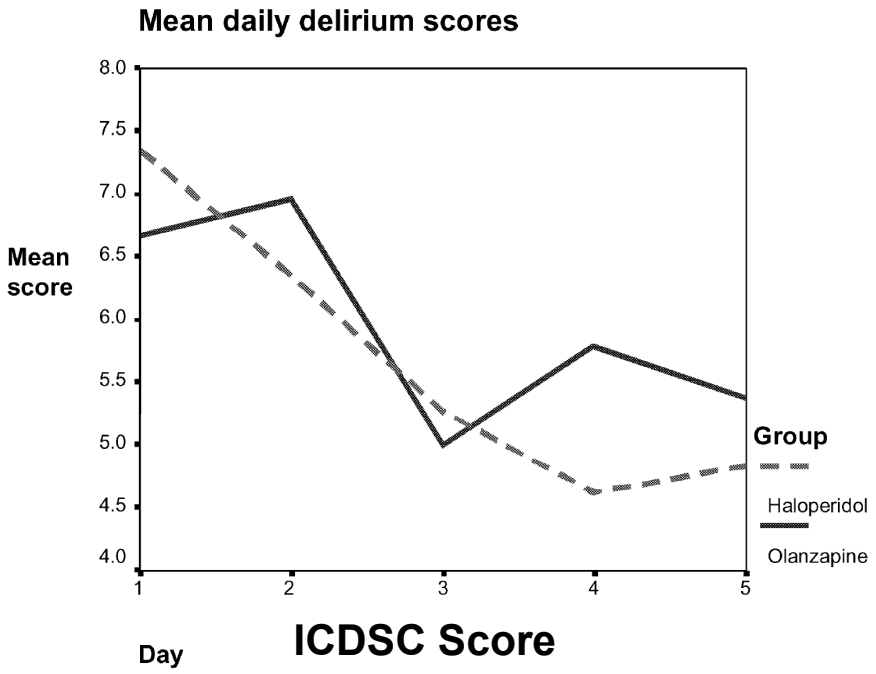
*Data presented in median

†Data presented as n (%)

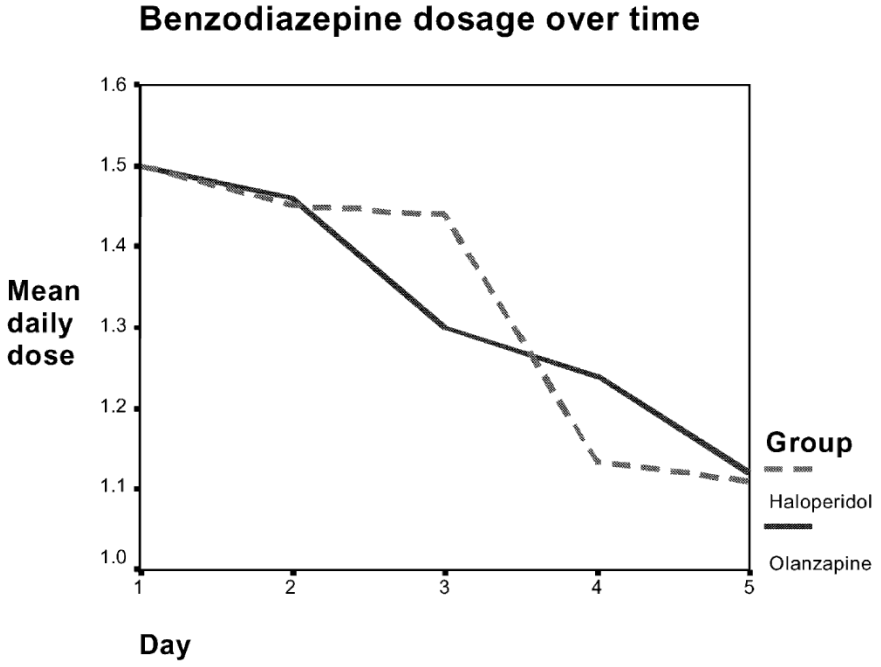
Three Center, prospective, double-blind trial of 36 mixed medical/surgical ICU patients with delirium via ICDSC scale and tolerating tube feeds, randomized to quetiapine 50mg BID (titrated up to 200mg BID) or placebo with open label IV haloperidol in both groups. 258 screened, 36 enrolled.

Devlin JW, et al. *Crit Care Med*. 2010 Feb;38(2):1-9.

Olanzapine vs. Haloperidol for the Treatment of Delirium in SICU Patients



Mean olanzapine dose: 4.5mg/day



Mean haloperidol dose: 6.5mg/day

Single center, prospective, open label trial of 73 mixed medical/surgical ICU patients with delirium via ICDSC scale tolerating tube feeds, randomized to olanzapine 5mg QD or haloperidol 2.5–5 mg every Q8hrs “titrated per response,” with rescue haloperidol. Patients > 60 yrs received a lower initial dosage (haloperidol 0.5–1 mg, or olanzapine 2.5 mg).

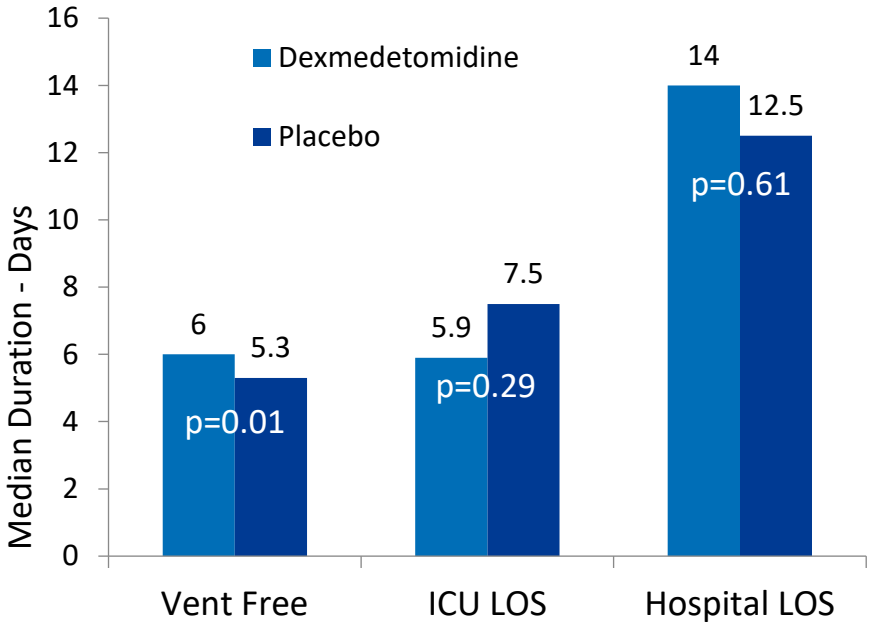
Skrobik YK, et al. *Intensive Care Med*. 2004;30:444–9.

Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients: A Nonrandomized Controlled Trial

- Nonrandomized , controlled, single center in Barcelona, Spain
- Agitated delirium
- Dexmedetomidine added for non-responders to haloperidol (n = 47) vs. responders haloperidol (n= 86)
  - Dexmedetomidine patients had a higher percentage of time at satisfactory sedation level 92.7% vs. 59.3% p= 0.0001
- Dexmedetomidine may be useful as a rescue drug for treating agitation due to delirium in patients who fail to respond to haloperidol

Carrasco G, et al. *Crit Care Med*. 2016 Jul;44(7):1295-306.

Effect of Dexmedetomidine Added to Standard Care for Agitated Delirium



Other Metrics			
	Dex (n=39)	Placebo (n=32)	P value
Any day antipsychotic %	36.8	65.6	0.02
Study day with any antipsychotic %	26.3	40	0.08
Underwent tracheostomy %	17.9	6.3	0.14
Time to tracheostomy Median hours	41.9	71.1	< 0.01
Any day propofol Median (mg)	980	5390	<0.001

Multicenter RCT in New Zealand and Australia in mixed medical/surgical ICUs. Dex (39) or placebo (32) added to standard of care in agitated delirious patients.

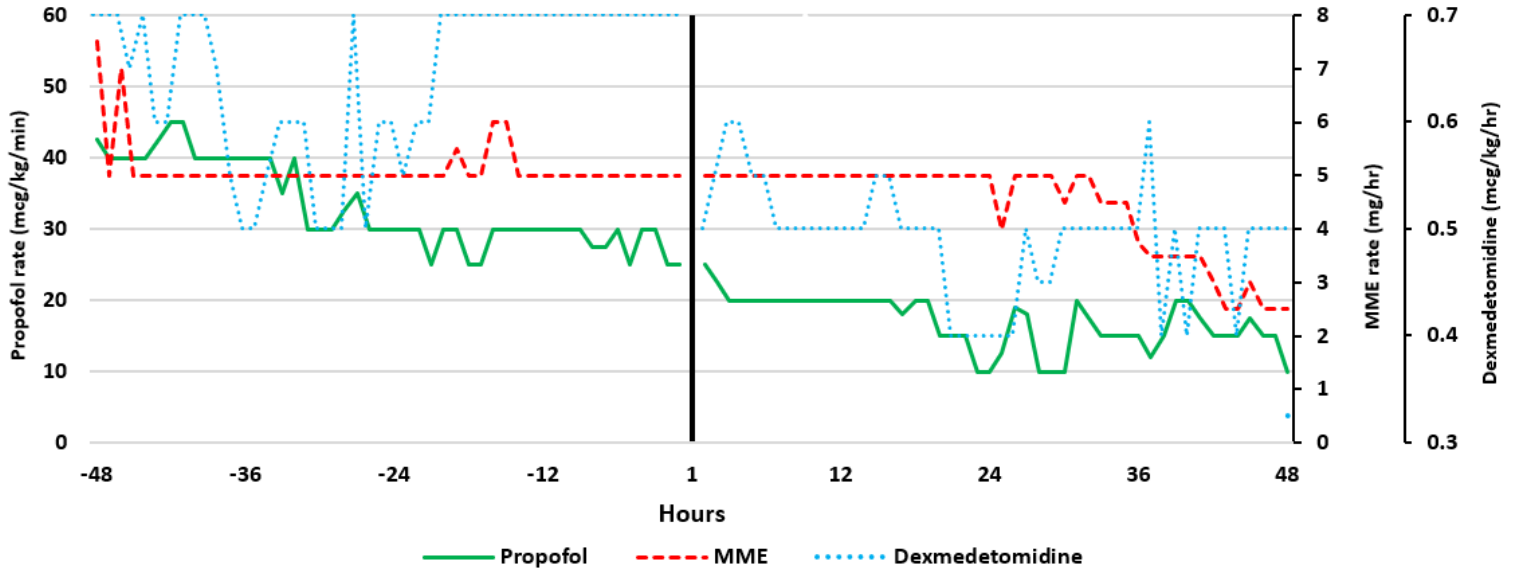
Reade MC, et al. *JAMA*. 2016 Apr 12;315(14):1460-8.

Pharmacologic Management

Recommend against the use of pharmacologic agents for prevention of delirium

Antipsychotics

- Some data to suggest decreased delirium over time with treatment of hyperactive delirium
- No role in hypoactive delirium



BWH data ahead of print

Assadoon MS, Kovacevic MP, Dube KM, Szumita PM, Lupi KE, DeGrado JR. Evaluation of Atypical Antipsychotics for the Facilitation of Weaning Sedation in Mechanically Ventilated Critically Ill Patients. J Intensive Care Med. 2023 Jul 10:8850666231188029.

Delirium Prevention

Non-Pharmacologic and pharmacologic

- Avoid medications which may be deliriogenic
- Use of sedation scales and appropriate goals
- Use of scheduled pain management protocols and pain scales
- Reorientation of patients
- Timely removal of catheters and restraints
- Early correction of dehydration
- Minimizing unnecessary stimuli

Prophylactic IN dex to prevent emergence delirium in peds patients from general anesthesia

- Single center, China
- 90 peds patients receiving sevoflurane and remifentanil for general anesthesia
- IN dex 1 mcg/kg, 2 mcg/kg, or placebo 30 min prior to surgery

Study Group	Group Control	Group D1	Group D2	P value
PAED score max	13.0 [8.0–16.0]	8.0 [5.8–11.3]	5.0 [3.0–7.0]	<0.001
Watcha score	3.0 [2.0–3.0]	2.0 [2.0–3.0]	1.0 [1.0–2.0]	<0.001
FLACC score	5.0 [4.8–7.0]	4.0 [2.8–5.0]	2.0 [1.0–3.0]	<0.001
Incidence of ED	21 (70%)	11 (36.7%)	3 (10%)[ab]	<0.001
Incidence of severe ED	11 (36.7%)	1 (3.3%)	0 (0%)[a]	<0.001

He H, et al. Drug Des Devel Ther. 2023 Nov 30;17:3563-3570.

Drug Design, Development and Therapy

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Open Access Full Text Article

ORIGINAL RESEARCH

The Effect of Intranasal Dexmedetomidine on Emergence Delirium Prevention in Pediatric Ambulatory Dental Rehabilitation Under General Anesthesia: A Randomized Clinical Trial

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Purpose: Sevoflurane is the preferred anesthetic agent for induction and maintenance of ambulatory surgery due to its property of fast onset and recovery. However, it has been recognized as one of the major contributors of emergence delirium. The aim of this study was to evaluate the preventive effect of intranasal dexmedetomidine on the occurrence of emergence delirium in pediatric patients under general anesthesia with sevoflurane.

Patients and Methods: Ninety pediatric patients undergoing dental rehabilitation under sevoflurane anesthesia were enrolled in this study. The patients were divided into three groups (n=30 each in the 2 μg/kg dexmedetomidine, 1 μg/kg dexmedetomidine, and control with saline groups). The same volume (0.02mL/kg) of the mixed solution was dropped into the nasal cavity of the children 30 minutes before surgery. We used the Pediatric Anesthesia Emergence Delirium Scale (PAED) to assess the level and incidence of delirium in the post-anesthesia care unit.

Results: Compared with the control group, prophylactic use of different dosages of intranasal dexmedetomidine significantly reduces the incidence of ED and severe ED in PACU (P<0.001). Intranasal administration of 2 μg/kg dexmedetomidine was associated with a better acceptance of mask induction and a better tolerance of separation with parents.

Conclusion: Both 2 μg/kg and 1 μg/kg intranasal dexmedetomidine can achieve ED preventive effects in PACU in dental rehabilitation under general anesthesia. A dosage of 2 μg/kg is more effective in preventing severe ED and providing better mask acceptance.

Keywords: intranasal dexmedetomidine, emergence delirium, sevoflurane anesthesia, pediatric patients, dental rehabilitation

Goals of PSAA in dental surgery: General principals we can all agree on in no particular order

- Facilitate the procedure
- Minimize pain
- Minimize anxiety/agitation
- Minimize unpleasant memories of the procedure
- Minimize over-sedation/prolonged sedation
- Minimize adverse effects of medications
- Minimize LOS/time in recovery/office chair time/hospital time
- Minimize delirium
- Minimize long-term consequences of operative/procedural pain
- Minimize mortality

Questions:

1. **What therapy is best to optimized these outcome?**
    - **Likely depends on many factors/variables**

Ito T, et al. J Pers Med. 2023 Mar 1;13(3):461. doi: 10.3390/jpm13030461.

Delirium prevention = Dose/Drug Minimization Strategies

1. Set a clear goal, and have all involved in the care aware of the goal
2. Assessment, Assessment, Assessment; and discussion of assessment
3. Non-pharm strategies
4. Manage pain with local
5. Awake and alert (RASS 0)
6. Symptom triggered/preemptive bolus only
7. Sedation Holiday
8. Analgosedation or no sedation
9. Patient specific pharmacotherapy
10. Rotation of medication (avoid accumulation)

Patient Case

A 10-year-old female presents for a painful but short procedure. The patient does not currently have an IV.

- Very anxious
- HR: 130 bpm
- RR: 20 breaths/min

You consider using IN dexmedetomidine for the procedure. What are the potential advantages and disadvantages of IN dexmedetomidine in this patient.

Potential advantages and disadvantages of IN dexmedetomidine in this patient?

- Advantages
  - May be a reasonable to manage the anxiety of the procedure
  - Avoid IV access
  - Minimal risk of respiratory depression
  - Minimal risk of deep sedation
  - May decrease emergence delirium

- Disadvantages
  - Dexmedetomidine possess only mild analgesic properties, and the procedure is anticipated to be moderately painful requiring additional analgesia
  - Monitor for adverse CV effects
  - Delayed onset
  - May prolong recovery
  - Have nasal administration delivery device?
  - Cost? Dexmedetomidine can be relatively expensive, but the nasal atomizer can be costly

Periop pain

Patient Case CC

- 55 YO male who presents for invasive oral surgery requiring inpatient stay
- Past medical history
  - Type 2 Diabetes
  - Atrial fibrillation
  - Hyperlipidemia
- Past surgical history: prior coronary artery disease with PCI (2021)

Patient Case CC

- Postoperative day (POD) 0
- Neuro
  - Pain scores ranging from 5-8
  - Hydromorphone: 0.5 mg x 11 doses
  - Oxycodone: 10 mg x4 doses
  - No additional analgesia ordered

Home Meds	Restarted POD0?
Apixaban 5 mg BID	No
Atorvastatin 80 mg QD	Yes
Gabapentin 800 mg TID	No
Metformin 500 mg BID	No
Metoprolol XR 50 mg QD	No

Labs	Pre-op	POD1
Na (mmol/L)	143	140
K (mmol/L)	4.4	4.3
Cl (mmol/L)	101	98
SCr (mg/dL)	0.78	1.51
Glu (mg/dL)	101	115

How can we best optimize CC's pain regimen?

a) Restart home gabapentin 800 mg 3 times daily

b) Start ketamine infusion at 10 mcg/kg/min

c) Start acetaminophen 1000 mg every 8 hours

d) Consult post-operative pain service for a hydromorphone patient-controlled analgesia (PCA)

Incidence of Postoperative Pain

- Management of postoperative pain remains a challenge for healthcare providers and patients
- Two national surveys:

	Apfelbaum 2003 n = 250	Gan 2014 n = 300
Experienced pain after surgery	80%	86%
Moderate to extreme pain	86% of 80%	75% of 86%
Experienced adverse effects from pain medications administered	25%	80%
Healthcare provider discussed their pain with them	66%	Not reported

Apfelbaum JL, et al. Anesth Analg. 2003 Aug;97(2):534-540
Gan TJ et al. Curr Med Res Opin. 2014 Jan;30(1):149-60

Pathophysiology of Pain

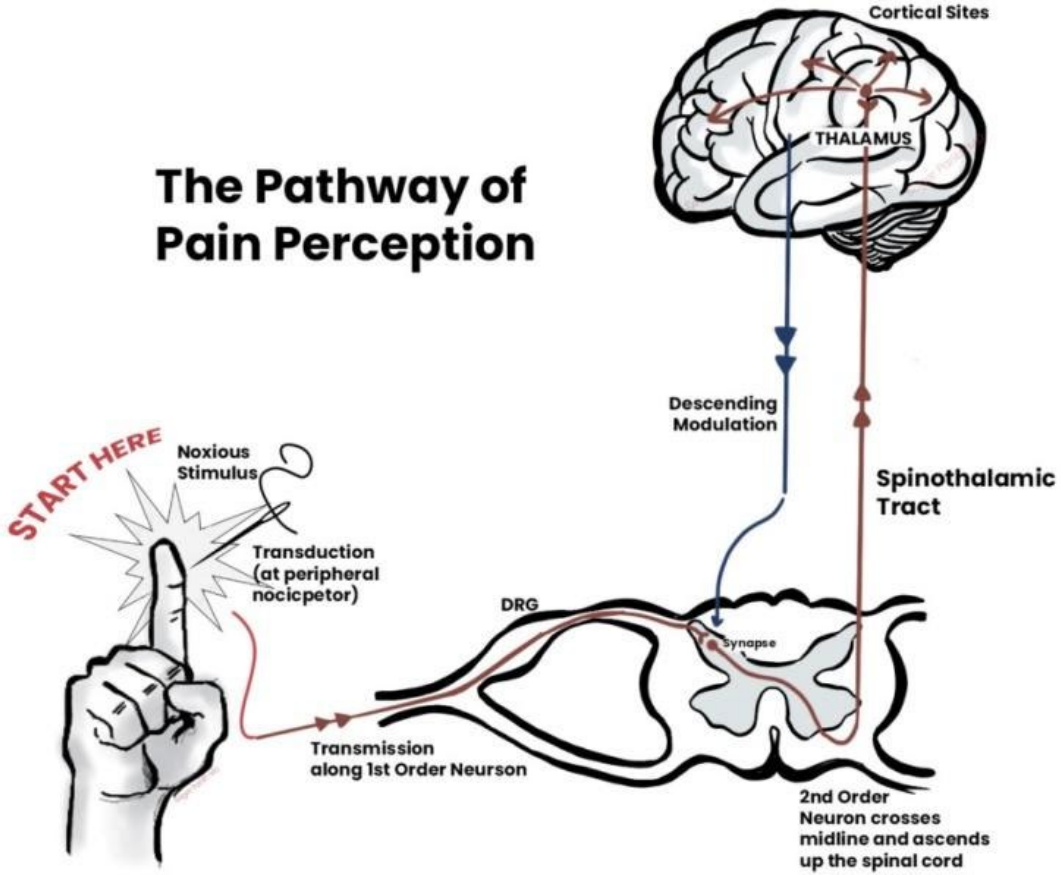
- Nociception: physiological response to painful stimulus
  - Somatic pain (periphery): joints, bones, skin and muscles
  - Visceral pain (internal): chest, abdomen, pelvis, intestines

- Pain can be controlled through targeting of receptors involved in these steps of pathophysiology

Osterweis M, et al. Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives. 1987.

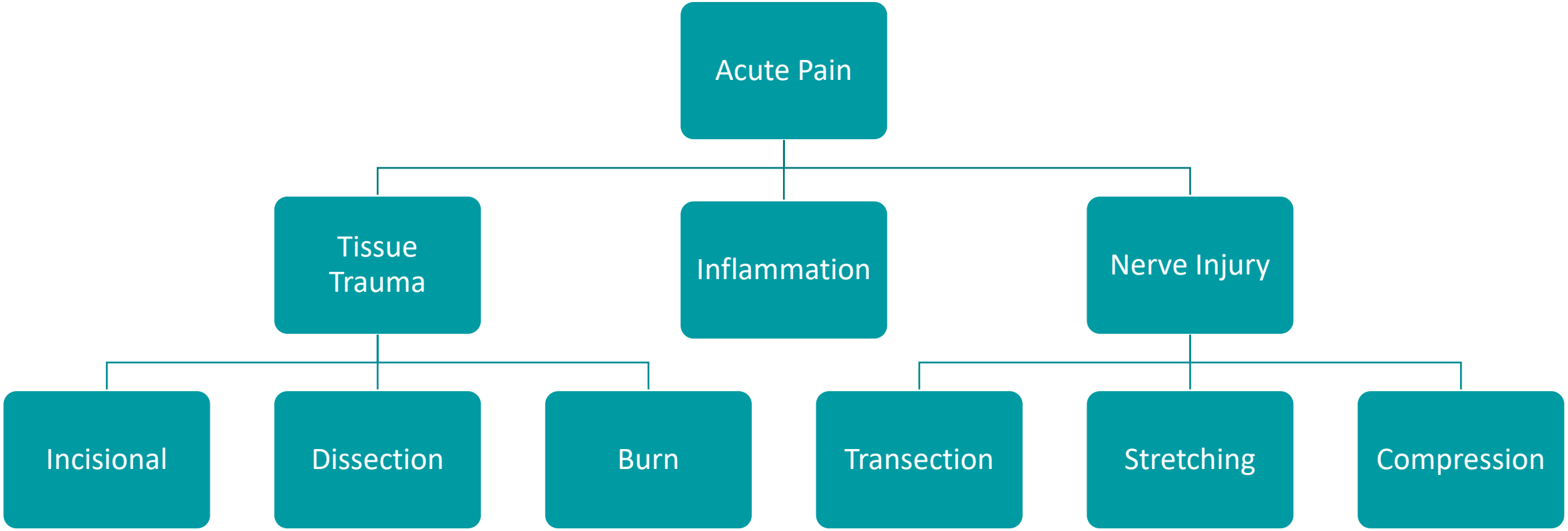
Pathophysiology of Pain

- Pain originates in the peripheral nerves or visceral tissue from a noxious stimulation (*transduction*)
- This signal is *transmitted* to the central nervous system in the spinal cord
- Once this signal reaches the spinal cord inhibitory and excitatory neurons are activated (*modulation*)
- *Perception* of pain is the brain's response and interpretation of pain signals



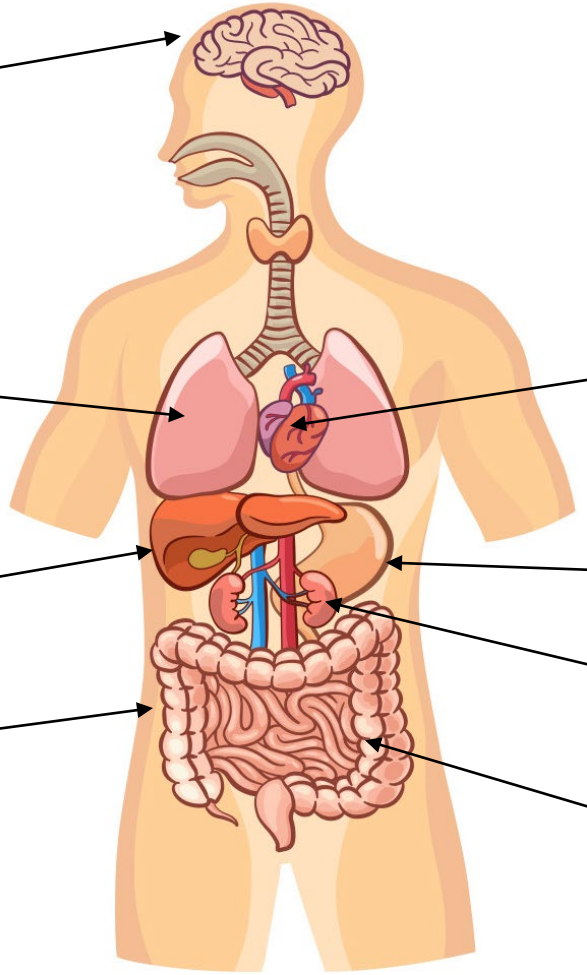
Osterweis M, et al. Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives. 1987.

Pathophysiology of Post-operative Pain



Osterweis M, et al. Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives. 1987.

The Physical Cost of Postoperative Pain



Anxiety
Impaired Sleep

Hypoventilation
Pneumonia

May impact coagulation

Ileus

Coronary ischemia
Myocardial infarction

Nausea
Vomiting

Urinary retention
Oliguria

Reduced motility

*May decrease wound healing and immune response (infection risk)

*Decreased physical activity

Gan TJ. J Pain Res. 2017; 10: 2287–2298

The Physical Cost of Postoperative Pain

- Chronic pain
  - Pain at 4 months post surgery:
    - Thoracotomy: 37%
    - Hysterectomy: 11%
- Patients with high levels of pain 4 days post-procedure shown to have increased functional limitations (OR 1.87), poor global recovery (OR 2.61) and impaired quality of life
- Higher pain scores on day of surgery associated with increased opioid use at 6 months
- Risk factors for persistent pain after surgery: younger age, female, obesity, smoking, duration of surgery

Montes A, et al. Anesthesiology. 2015;122(5):1123–1141
Peters ML, et al. Ann Surg. 2007;245(3):487–494
Goesling J, et al. Pain. 2016;157(6):1259–1265

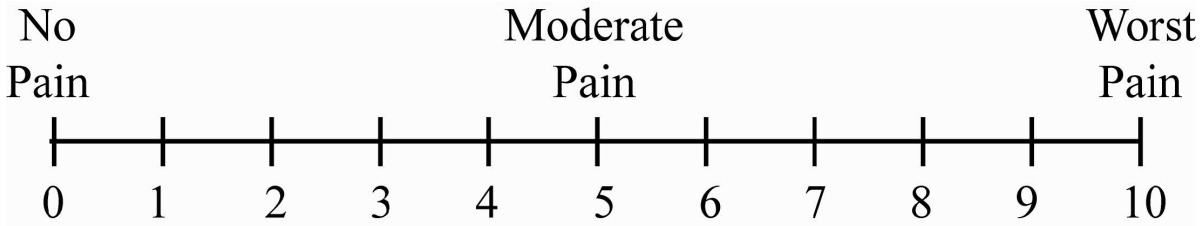
The Economic Cost of Postoperative Pain

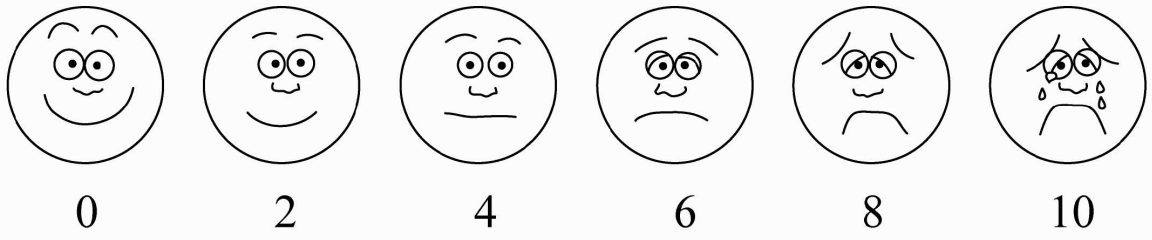
- Inadequate pain relief has shown to increase:
  - Hospital length of stay
  - Readmission rates
  - Time before ambulation
- For elective surgeries, analysis found pain was the #1 reason for readmission post-procedure (38%)
- Cost for follow up in inadequate pain control $1869 ± $4553 per visit (1999)
- In 2008, the estimated annual cost to society of chronic pain: $560-635 billion
  - Greater than heart disease, cancer and diabetes
- Cost of treating chronic pain that stemmed from acute pain: $1 million/patient (1996)

Joshi GP, et al. Anesthesiol Clin North America. 2005;23(1):21–36
Coley KC, et al. J Clin Anesth. 2002;14(5):349–353
Cousins MJ, et al. Reg Anesth Pain Med. 2000;25(1):6–21.

Assessment of Pain

- Numeric Rating Scale (NRS)/Visual Analog Scale (VAS)
  - Rating of pain 0-10
  - Validated in numerous populations (medical/surgical ICU, postoperative)
- Critical-Care Pain Observation Tool (CPOT)
  - Recommended for patients who are unable to self-report pain
  - CPOT >2 means likely to be in pain





Indicator	0	1	2
Facial description	No muscular tension observed: Relaxed, neutral	Presence of frowning, brow lowering, orbit tightening, and levator contraction: Tense	All of the above facial movements plus eyelid tightly closed: Grimacing
Body movements	Does not move at all (does not necessarily mean absence of pain): Absence of movements	Slow cautious movements, touching or rubbing the pain site, seeking attention through movements: Protection	Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed: Restlessness
Muscle tension (evaluation by passive flexion and extension of upper extremities)	No resistance to passive movements: Relaxed	Resistance to passive movements: Tense, rigid	Strong resistance to passive movements, inability to complete them: Very tense or rigid
Compliance with the ventilator (intubated patients), *OR*	Alarms not activated, easy ventilation: Tolerating ventilator or movement	Alarms stop spontaneously: Coughing but tolerating	Asynchrony: blocking ventilation, alarms frequently activated: Fighting ventilator
Vocalization (extubated patients)	Talking in normal tone or no sound	Sighing, moaning	Crying out, sobbing

Gelinas C, et al. Am J Crit Care. 2006 Jul;15(4):420-7

Best Practices in Analgesic Therapy

- Assess Assess Assess
  - Is pain well controlled?
    - If not, what receptors have we not yet targeted
      - NSAIDs, gabapentinoids, lidocaine, ketamine
    - If so, what can we peel back to remove the risk of adverse effects
      - Still need 1g Q6 of acetaminophen?
- Factoring in patient history
  - Home medications? Chronic pain? Opioid use disorder?
- Multimodal analgesia
  - Using multiple mechanisms of action to your advantage
  - Overall can limit adverse effects of a singular agent by targeting multiple receptors
- Non-pharmacologic therapies

Opioids

- Mechanism
  - Presynaptic: Block calcium channels on nerves to inhibit release of substance P and glutamate
  - Postsynaptic: Open potassium channels which increase threshold to receive pain transmission
  - Modulated by mu-, kappa-, and delta-opioid receptors
- Numerous formulations, differences in pharmacokinetics, and some additional receptor involvement
  - Methadone binds to NMDA antagonizing glutamate -> methadone's efficacy in neuropathic pain
  - Serotonin: tramadol, oxycodone, fentanyl, methadone, codeine

Advantages	Disadvantages
Effective, potent	Adverse effects • Confusion, respiratory depression • Nausea, vomiting, constipation
Variety of formulations allow patient specific selection	Addictive
Analgosedation	Tolerance

Trescot AM, et al. Pain Physician. 2008 Mar;11(2 Suppl):S133-53

Comparison of Opioids

Medication	Time to Onset, min	Half-life	Prolonged Clinical Effect Due to Context-Sensitive Half-life	Primary Metabolic Pathway	Prolonged Clinical Effect Due to Organ Failure	Practical Considerations
Fentanyl	1	2-4 h	Yes: significant	N-dealkylation CYP450 3A4/5	Hepatic	• Requires phase 1 metabolism; therefore, a prolonged clinical effect with inhibitors of CYP450 3A4/5 • Accumulation risk in obese patients • Rare, potentially life-threatening increased risk of serotonin syndrome and chest wall rigidity
Hydromorphone	5-10	2-3 h	Not applicable	Glucuronidation	Hepatic	• Therapeutic substitute for fentanyl or morphine in patients with hepatic or renal dysfunction
Morphine	5-10	3-4 h	Not applicable	Glucuronidation	Renal and hepatic	• Histamine release—leading to hypotension • Metabolite accumulation in renal dysfunction leading to central nervous system toxicity • Cholecystitis
Remifentanil	1-3	3-10 min	Yes: minor	Hydrolysis by plasma and tissue esterases	Renal: minimal	• High risk of opioid-induced tachyphylaxis • High risk of opioid-induced hyperalgesia • May increase ammonia levels • Accumulation in obese patients, suggest ideal body weight dosing

Posa P, Singh J, Stollings J. ICU Liberation. 2020. Second Edition. Mount Prospect, IL. Society of Critical Care Medicine.
Baker SN, et al. J Pharm Pract. 2011;24(2):189-195.
Kern J, et al. Emerg Med Pract. 2022;24(6):1-24.
Kisilewicz M, et al. Emerg Med J. 2017;34:294-301.

Comparing the Opioids

Opioid	Metabolism	Onset (min)	Half-life (hrs)	IV to PO	Considerations
Hydromorphone	Glucuronidation	PO: 15-30 IV: 5	3-4	5:1	• Useful opioid in hepatic/renal failure
Fentanyl	CYP3A4	1-2	0.5-1	IV only	• Accumulation in hepatic failure/obesity • Increased risk of serotonin syndrome
Morphine	Glucuronidation	PO: 30 IV: 5-10	3-5	3:1	• Accumulation in renal/hepatic failure • Histamine release: hypotension
Oxycodone	CYP3A4	10-15	3 to 6	PO only	• Accumulation in renal dysfunction
Methadone	CYP3A4 and 2B6	PO: 30-60 IV: 10-20	4-8, 8-12 with repeat doses	2:1	• Accumulation in renal/hepatic failure • Increased risk of serotonin syndrome • QTc Prolongation
Remifentanil	Hydrolysis through tissue esterases	1-3	3-10 (min)	IV only	• Primarily used in procedural areas • Risk of tachyphylaxis

Society of Critical Care Medicine. ICU Liberation. 2020;2

Opioids: Guidelines

Society of Critical Care Medicine: Pain, Agitation, Delirium, Immobility, and Sleep Guidelines (2018)	American Pain Society: Guidelines on the Management of Postoperative Pain (2016)
Remain a mainstay for pain management	Remain mainstay of postoperative pain management
Important to keep in mind side effect profile: • Sedation • Delirium • Respiratory depression • Ileus • Immunosuppression • May increase ICU length of stay	Oral therapy preferred over intravenous when oral is possible
	Short-acting preferred over long-acting to ensure assessment and re-evaluation of need
	Recommends against patient controlled analgesia (PCA) use in opioid-naïve adults
Multi-modal analgesia key to reduce opioid use and optimize post-operative analgesia	Incorporate around-the-clock non-opioid analgesics to minimize need for systemic opioids

Devlin JW, et al. Crit Care Med. 2018 Sep;46(9):e825-e873.
Chou R, et al. J Pain 2016;17:131-57.

2016 American Pain Society (APS)/American Society of Regional Anesthesia and Pain Medicine (ASRA) /American Society of Anesthesiologists (ASA) Management of Postoperative Pain (not specific to critical care)

- Recommends oral over IV administration of opioids for postoperative analgesia in patients who can use the oral route
- Recommends IV patient-controlled analgesia be used for postoperative systemic analgesia when the parenteral route is needed (without basal infusion rate if opioid naïve)
- Recommends multimodal analgesia
- Recommends use of a variety of analgesic medications and techniques (local, neuraxial, regional, topical)
- Recommends nonpharmacological interventions

Chou R, et al. *J Pain* 2016;17:131-57. Erratum in: *J Pain* 2016;17:508-10.

2016 APS / ASA Guidelines – Guidance for postoperative pain management for patients on chronic opioids

- Conduct perioperative evaluation of preoperative opioid use
- Provide education regarding use of opioids before surgery
- **Recognize postoperative opioid requirement will typically be greater and pain might be difficult to control**
- Consider pain specialty consultation
- **Consider nonpharmacological interventions**
- **Consider nonopioid adjunctive medications**
- Consider peripheral regional and neuraxial local analgesic techniques
- **Consider PCA with basal infusion of opioids for difficult to maintain pain**
- **Provide education and instruction on tapering opioids to target dose after discharge**

Chou R, et al. *J Pain* 2016;17:131-57. Erratum in: *J Pain* 2016;17:508-10.

Opioid Analgesics for PSAA

- Opioids alone are rarely adequate to complete a PSAA
- The large number of available agents makes them a ubiquitous co-medication during PSA
  - Allows for the opportunity for individualized patient assessments
- Availability of naloxone for reversal of adverse events is considered a benefit in combining opioids with sedative-amnestic agents
- Caution – consider peak pharmacokinetic properties when combining with other sedatives

Miller MA, et al. *Emerg Med Clin North Am*. 2005;23(2):551-572.
Kern J, et al. *Emerg Med Pract*. 2022;24(6):1-24.

Kinetic Considerations for Fentanyl

- Highly lipophilic (~580-times greater than morphine)
- Rapid onset of <1 minute
- Short duration of action (~30 minutes)

Chen A, et al. *Pain Med* 2015;16 Suppl 1:S27-S31.

The Case for Fentanyl as the primary go-to

- Years of experience
- Fast on, fast off (most of the time)
- Most hemodynamically neutral opioid
- Does not accumulate in renal dysfunction

Peng PW, et al. *Anesthesiology* 1999; 90(2):576-99.
Richardson S, et al. *JAMA* 2020 Apr 22;323(20):2052-9.
Alhazzani W, et al. *Intensive Care Med* 2020 May;46(5):854-87.

Perioperative analgesic efficacy and adverse events of fentanyl in dentistry: A systematic review.

- Years of experience
- Fast on-fast off
- Most hemodynamically neutral opioid
- Does not accumulate in renal dysfunction

REVIEW ARTICLE

ORAL DISEASES WILEY

Perioperative analgesic efficacy and adverse events of fentanyl in dentistry: A systematic review

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Abstract

Objectives: To assess the efficacy and adverse events linked to the utilization of fentanyl for perioperative pain management in dentistry.

Methods: This systematic review of randomized clinical trials (RCTs) adhered to the PRISMA guidelines and incorporated various databases.

Results: Eleven RCTs studying 674 patients were analyzed. Perioperative pain was predominantly evaluated in patients undergoing surgery for impacted molars, although some studies also included patients with other conditions such as oral submucous fibrosis, maxillary cancer, bony temporomandibular joint ankylosis, irreversible pulpitis, among others. Combined with dexmedetomidine, fentanyl produced enhanced analgesic effects. It demonstrated comparable efficacy when compared to nefopam and nalbuphine. Both intranasal and intravenous administration routes proved equally effective. In four RCTs, the transdermal fentanyl patch outperformed the control group, except in the clinical trial where it was compared to ropivacaine. The main adverse events associated with the use of fentanyl included nausea, vomiting, drowsiness, delirium, and respiratory depression; however, they were like those reported in the comparison groups.

Conclusions: While fentanyl demonstrated satisfactory perioperative analgesic efficacy, there were other alternatives that displayed better or comparable outcomes. Due to the risks and potential for misuse of fentanyl, these alternatives must be considered although adverse events were also reported.

KEYWORDS
adverse drug reaction, analgesia, clinical efficacy, dental care, fentanyl, pain

Peng PW, et al. *Anesthesiology* 1999; 90(2):576-99.
Richardson S, et al. *JAMA* 2020 Apr 22;323(20):2052-9.
Alhazzani W, et al. *Intensive Care Med* 2020 May;46(5):854-87.
Ardila CM, et al. Oral Dis. 2024 Jul;30(5):2807-2819.

Fentanyl Advantageous Disadvantages?

- Ultimately a low risk for chest wall rigidity and serotonin syndrome… even with high-dose continuous infusion

Peng PW, et al. *Anesthesiology* 1999; 90(2):576-99.
Richardson S, et al. *JAMA* 2020 Apr 22;323(20):2052-9.

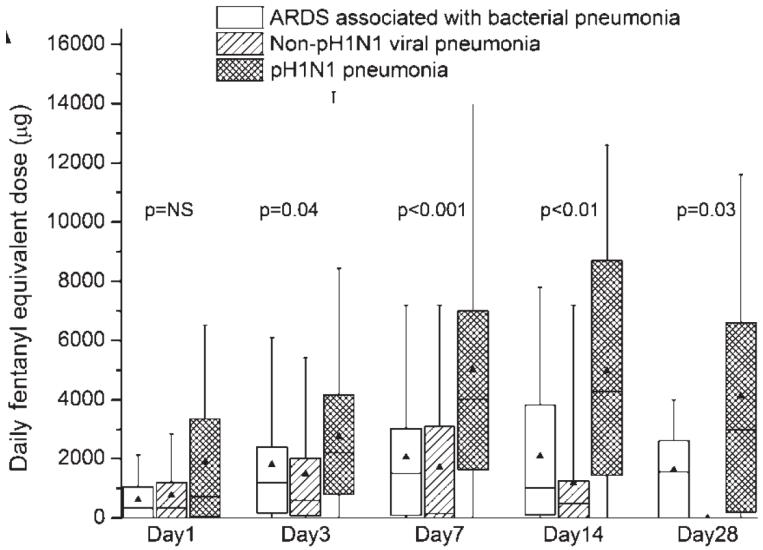
When to consider alternative opioids?

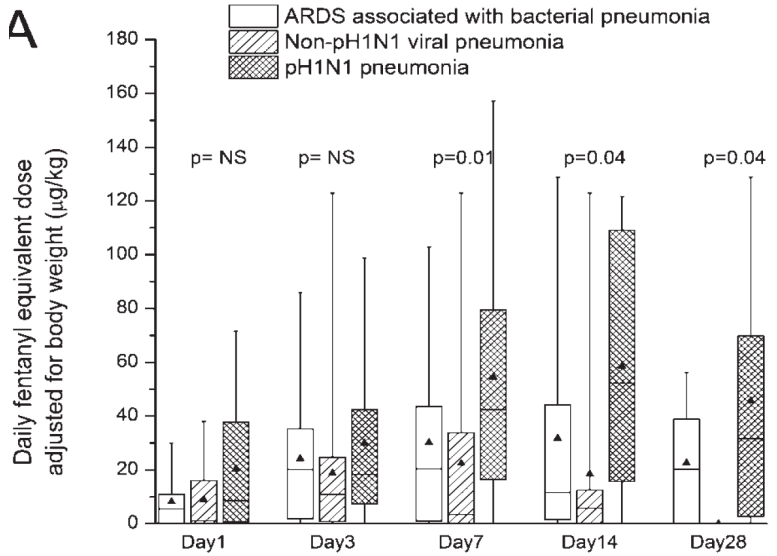
- When to consider:
  - Poor analgesic efficacy despite aggressive dose titration
    - Perhaps due to NMDA receptor agonism?
  - Given prolonged surgery/high dose
  - Clinical status that suggests benefit from an agent with different pharmacokinetic properties
  - Occurrence of intolerable adverse effects during dose titration
  - Potential drug-drug internation
  - Patients pharmacogenetic considerations
- Goal: establish an opioid regimen that is more effective than prior therapy
  - Improved analgesic efficacy; reduced adverse effects; improved outcomes

Bhatraju, et al. *N Engl J Med* 2020 May 21;382(21):2012-22.
Fine PG, et al. *J Pain Symptom Manage* 2009; 38(3): 418-25.

Guidance from the Past – wide variety of dosing in different populations

- Dosing variation based on patient population
- Anecdotal and published observations reveal similar observations as the 2009 H1N1 pandemic
- May need higher doses to maintain patient-ventilator synchrony





Olafson K, et al. *Ann Pharmacother.* 2012;46(1):9-20.
Kapp CM, et al. *Anesth Analg*. 2020 Jul 14;10.1213/ANE.0000000000005131.

Opioids and Metabolites

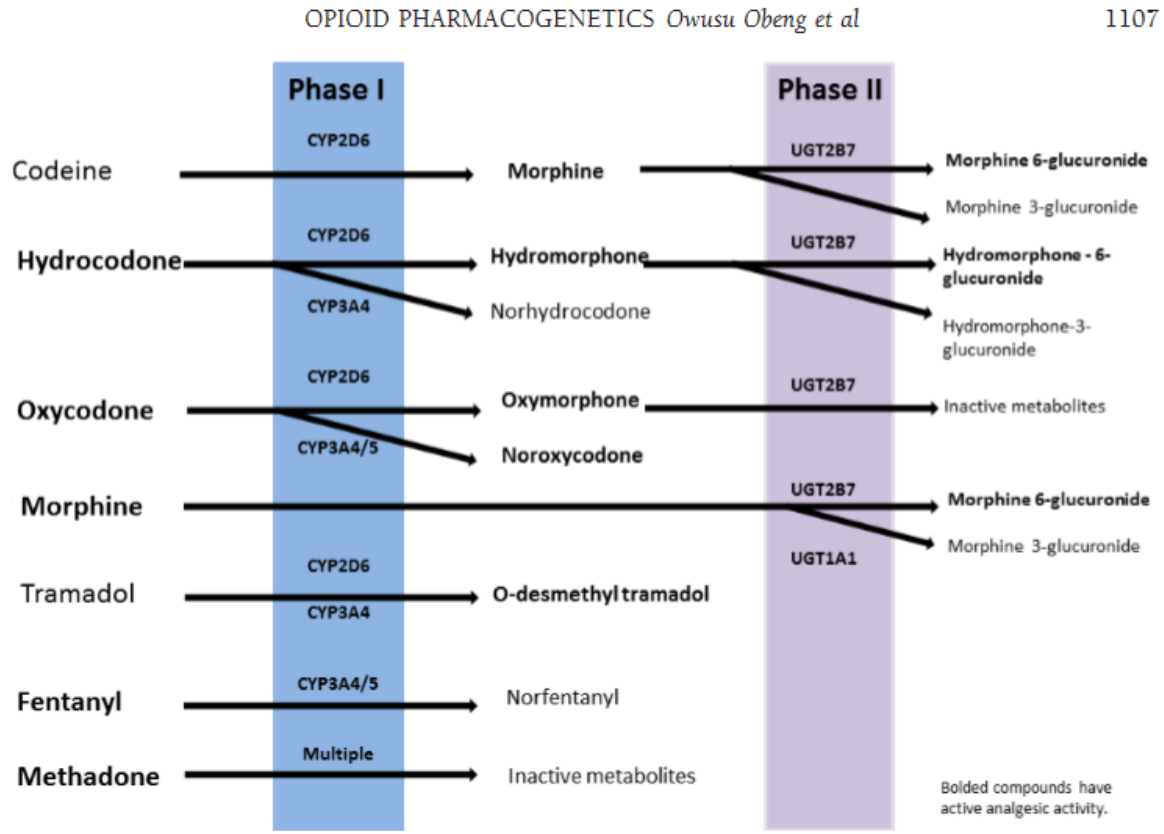


Figure 1. Metabolic pathways of opioid analgesics in the liver. CYP = cytochrome P450; UGT = uridine diphosphoglucuronysyltransferase.

Obeng O, et al. Pharmacotherapy. 2017 Sep;37(9):1105-1121

Analgosedation with Opioids = Many Potential "Unwanted" Effects

- Class effects
  - Respiratory depression
  - Sedation
  - Constipation
  - N/V
  - Pruritis
  - Withdrawal
  - Hypotension
  - Delirium
  - PTSD
  - Immunomodulation
  - hyperalgesia
  - Opioid use disorder (post-ICU)
- Specific agent effects
  - Fentanyl/sufentanil
    - Chest wall rigidity (perhaps masked as ARDS)
    - Serotonin Syndrome
    - Unpredictable pharmacokinetics
    - Growing context-sensitive half-life
  - Remifentanil
    - ↑ Ammonia levels, Tachyphylaxis
  - Morphine
    - Cholecystitis, Neurotoxicity, Histamine release
  - Meperidine
    - Tremors/seizures
  - Methadone
    - QTC prolongation

Riker RR, Fraser GL. *Pharmacotherapy.* 2005 May;25(5 Pt 2):8S-18S.
Devlin JW, et al. *Crit Care Med*. 2010 Jun;38(6 Suppl):S231-43.
Chen A, et al. *Pain Med* 2015;16 Suppl 1:S27-S31.
Hammond DA, et al. *Pharmacotherapy*. In press.
Peng PW, et al. *Anesthesiology* 1999; 90(2):576-99.
Richardson S, et al. *JAMA* 2020 Apr 22;323(20):2052-9.
Alhazzani W, et al. *Intensive Care Med* 2020 May;46(5):854-87.
Duprey MS, et al. *Am J Respir Crit Care Med*. 2021 Sep 1;204(5):566-572.

Opioid Rotation

Defined as a change in opioid drug or route of administration with the goal of improving outcomes

Goals of opioid rotation are to establish an opioid regimen that is more effective than the prior therapy

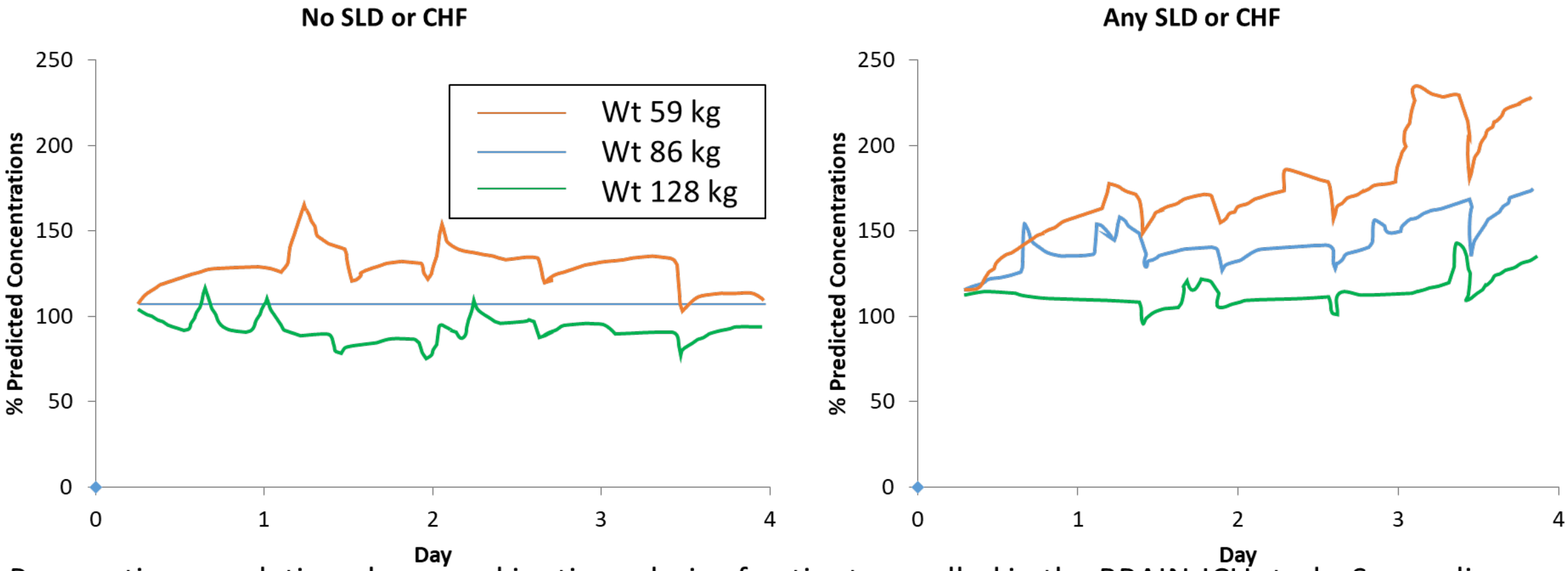
- Improved analgesic efficacy
- Reduced adverse effects
- Improved treatment-related outcomes

"Indications" for rotation **(or simply a better fit from the beginning?)**

- Occurrence of intolerable adverse effects during dose titration
- Poor analgesic efficacy despite aggressive dose titration
- Problematic drug-drug interactions
- Change in clinical status that suggests benefit from an opioid with different pharmacokinetic properties

Fine PG, et al. *J Pain Symptom Manage*. 2009; 38(3): 418-425.

Fentanyl Pharmacokinetics in Critically Ill Patients



Prospective population pharmacokinetic analysis of patients enrolled in the BRAIN-ICU study. Severe liver disease (SLD) and congestive heart failure (CHF) were found to significantly increase % of predicted fentanyl concentrations.

Choi L, et al. *Crit Care Med*. 2016; 44(1): 64-72. [117]

Fentanyl vs. Hydromorphone – a signal?

Patients requiring ECMO on either fentanyl or hydromorphone for at least 6 hours.

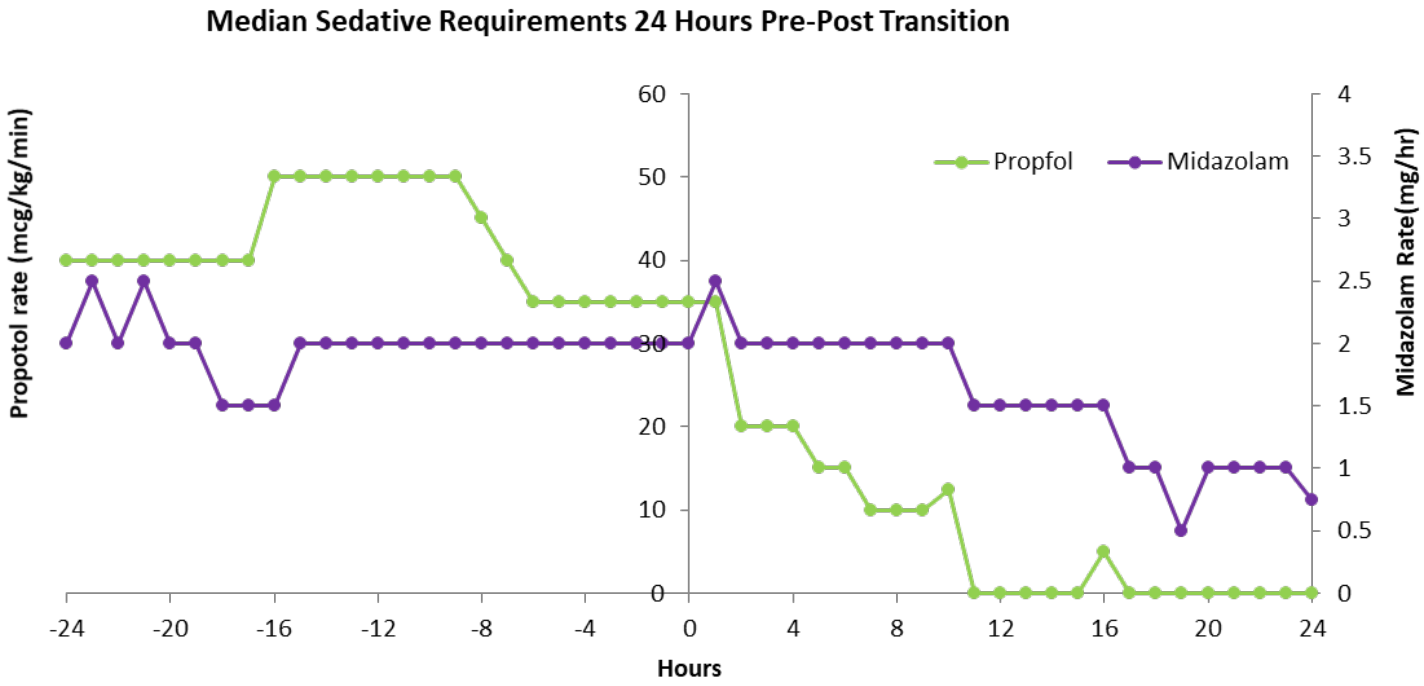
After matching in ECMO patients			
	Hydromorphone n =54	Fentanyl N = 54	
Delirium free coma free - 7 days; days n (%)	125 (53.2)	85 (42.1)	P= 0.006
ICU LOS, days; median [IQR]	17.4 [10.6-33]	20 [9.9-44.1]	SD= 0.002
CRRT, n (%)	24 (44.4)	22 (40.7)	SD= 0.02
Fentanyl equivalents, mcg; median [IQR]	554.8 [286.7-905.1]	2291.1 [1052.5-4022.7]	P< 0.005
Midazolam equivalents, mg; median [IQR]	1.1 [0.5-25]	1.4 [0.7-3.7]	P= 0.35
Propofol equivalents, mg; median [IQR]	281.9 [109.2-806.8]	405.7 [150.4-888.2]	P= 0.50

Landolf KM, et al. *Pharmacotherapy.* 2020 May;40(5):389-397.

Fentanyl vs. Hydromorphone – a signal?

Rationale for Rotation (N = 46)	N (%)
Improved ventilatory compliance	13 (28)
Tachyphylaxis/pain control	9 (20)
Opioid rotation	7 (15)
Reduction in sedatives	6 (13)
Liver impairment	5 (11)
ECMO	2 (4)

ECMO: Extracorporeal membrane oxygenation



Kovacevic MP, Szumita PM, et al. *J Pharm Pract.* 2020 Apr;33(2):129-135.

Methadone

- MOA: longer acting opioid agonist, NMDA antagonist
- Indicated for opioid use disorder and treatment of chronic pain
- Dosing
  - Chronic pain: 2.5 to 5 Q8-12, slow titration as tolerated
  - Off label ICU pain/sedation: 10-40 mg q6-12, opioid infusion sparing
  - Opioid use disorder: patient specific starting dose 2.5-20 mg QD, slow titration up to 60-120 mg QD
  - IV to PO- 2:1, but more rapid, higher peak, suggest dividing to Q6-8
- Adverse effects
  - QTc Prolongation
  - Standard opioid AE profile
- CYP substrate, use with caution with CYP inhibitors and inducers

IV Fentanyl to Enteral Methadone Rotation

Al-Qadheeb et al.:

- Decreased fentanyl dose requirements
- Decreased time to fentanyl infusion discontinuation
- Increased likelihood of fentanyl discontinuation

Wanzuita et al.:

- Trend toward increased ventilator-free days
- Higher probability of being mechanical ventilation-free at day 5
- Among patients able to be weaned from mechanical ventilation:
  - Decreased time to extubation

Wanzuita R, et al. *Crit Care.* 2012; 16: 49-57.
Al-Qadheeb NS, et al. *Ann Pharmacother.* 2012; 46: 1160-1166.

Pharmacogenetic Considerations for PSAA

- Cytochrome (CYP) P-450 gene is responsible for metabolism of many opioids and sedatives
- In one analysis, 93% of patients were categorized as “non-normal” metabolizers of 5 common enzymes (CYP2D6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5)
- CYP gene polymorphisms result in altered effects of midazolam, fentanyl, morphine and likely more
- More research needed
- Not ready for clinical practice

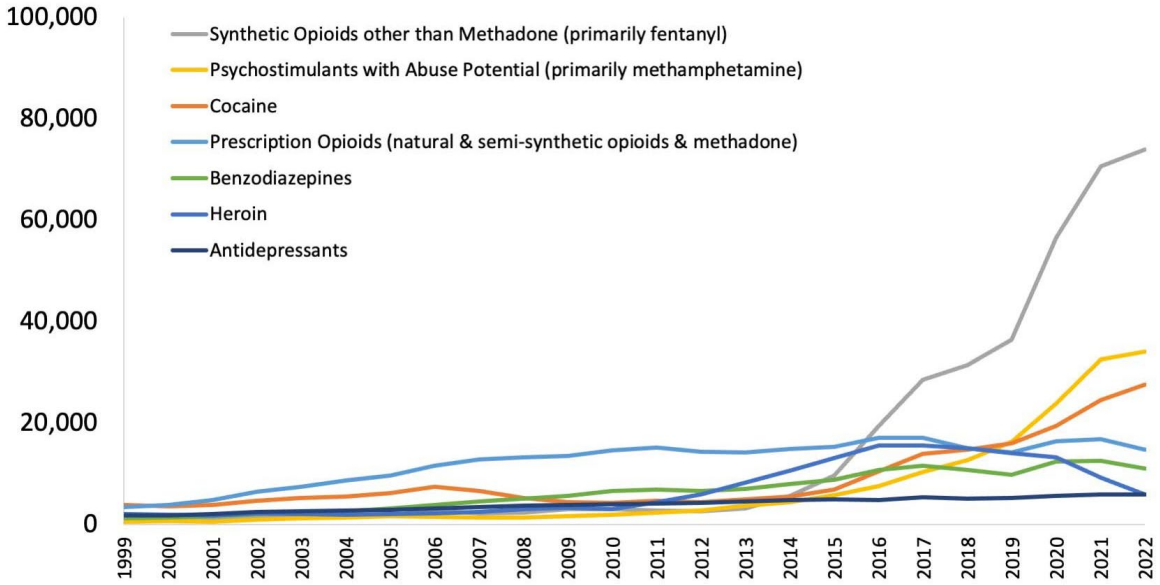
Hocum BT et al. *Am J Health-Syst Pharm.* 2016; 73(2):61-7.
MacKenzie M et al. *Can J Anaesth.* 2017; 64(1):45-64.

Pro-Con: Fentanyl as First-Line Analgesia PSAA

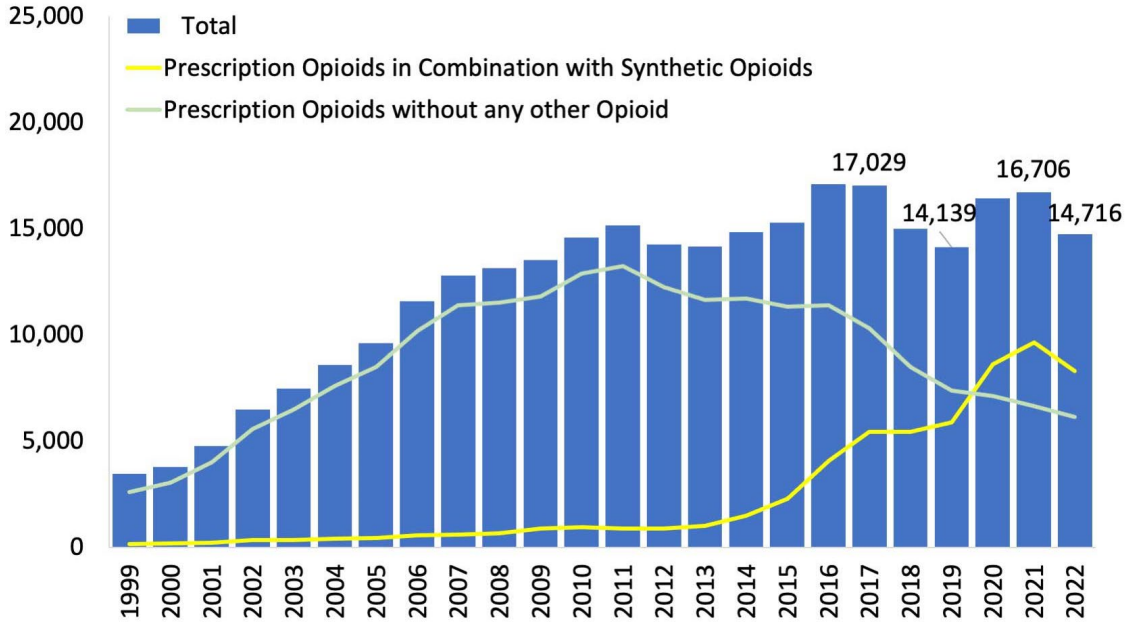
- Fentanyl is likely very reasonable as a first-line analgesic in patients for PSAA
- Certain patient characteristics may warrant alternative initial therapy or considerations early rotation to alternative therapies
  - Obese
  - Liver failure
  - On medications interacting with CYP450 metabolism
  - On SSRI or other meds which may increase the risk of Serotonin Syndrome
  - Context-sensitive half-life concern- high-dose, longer term infusions

Opioid Use Disorder/Epidemiology

National Drug Overdose Deaths
Among All Ages, 1999-2022



National Overdose Deaths Involving Prescription Opioids
Among All Ages, 1999-2022



Drug Overdose Death Rates. NIH. 2024

Chemical Mechanism of Pain

Many chemical mediators interact with nociceptive neurons

- Pro-inflammatory cytokines, chemokines, neurotrophins:
  - Vanilloid type 1 receptor, 5-hydroxytryptamine receptors, Histamine type 1 , Protaglandin E2, Prostanoid receptors EP subtype, bradykinin receptors, interleukin-1 beta, inteleukin-1 receptor, nerve growth factor, tyrosine kinase A receptor, adenosine triphosphate, purinergic receptor subtype, hydrogen ion, calcium, protein tetrodotoxin-resistant voltage-gated sodium channel, substance P, acid-sensing channel.

Result

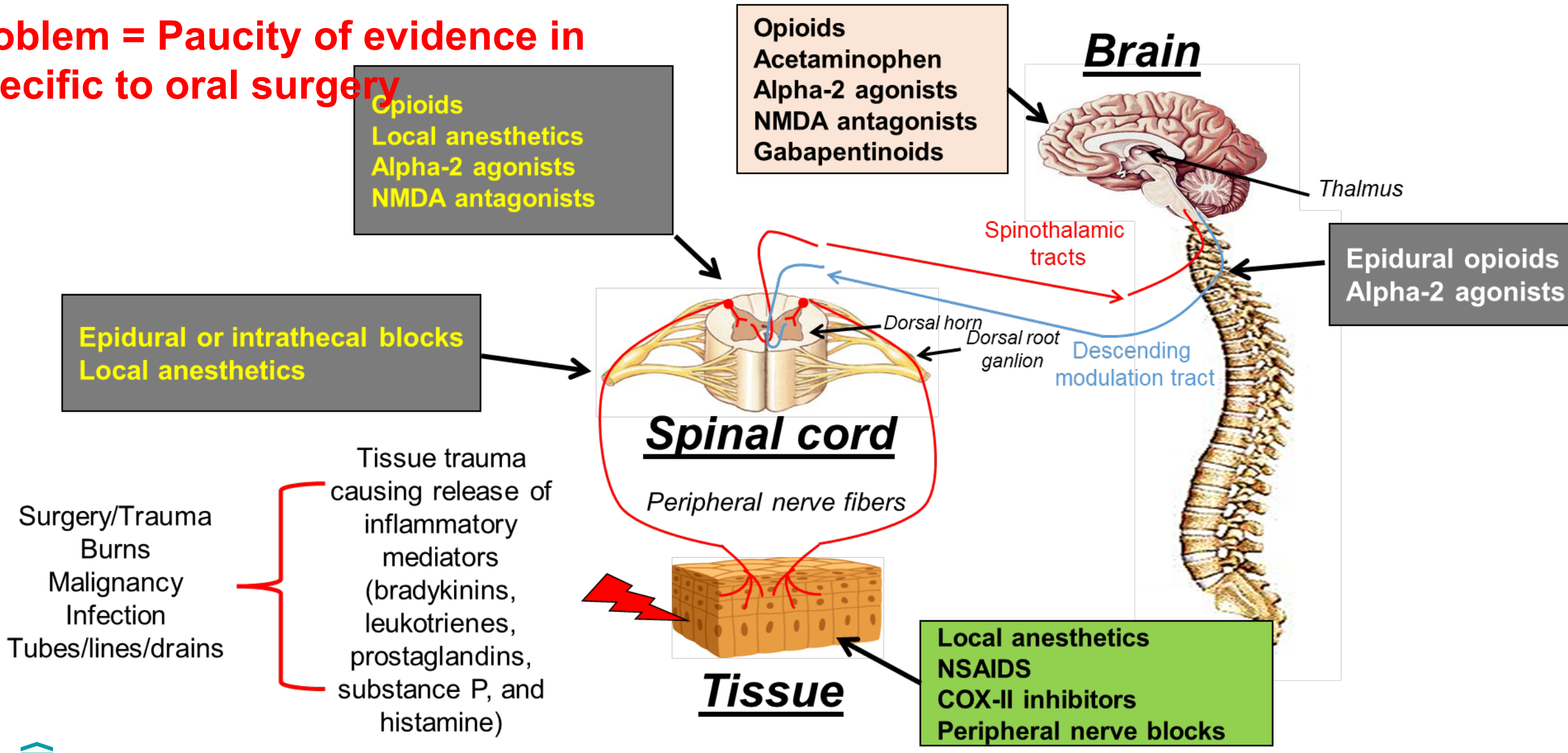
- Activating intracellular signaling cascade leading the activation of protein kinase A (PKA) or protein kinase C (PKC)

Cesare P, et al. Neuron 1999; 23: 617-24

Aley KO, et al. J Neurosci 1999; 19:2181-6

Effective Analgosedation: Not Just Opioids

Problem = Paucity of evidence in Specific to oral surgery



Multimodal Analgesia

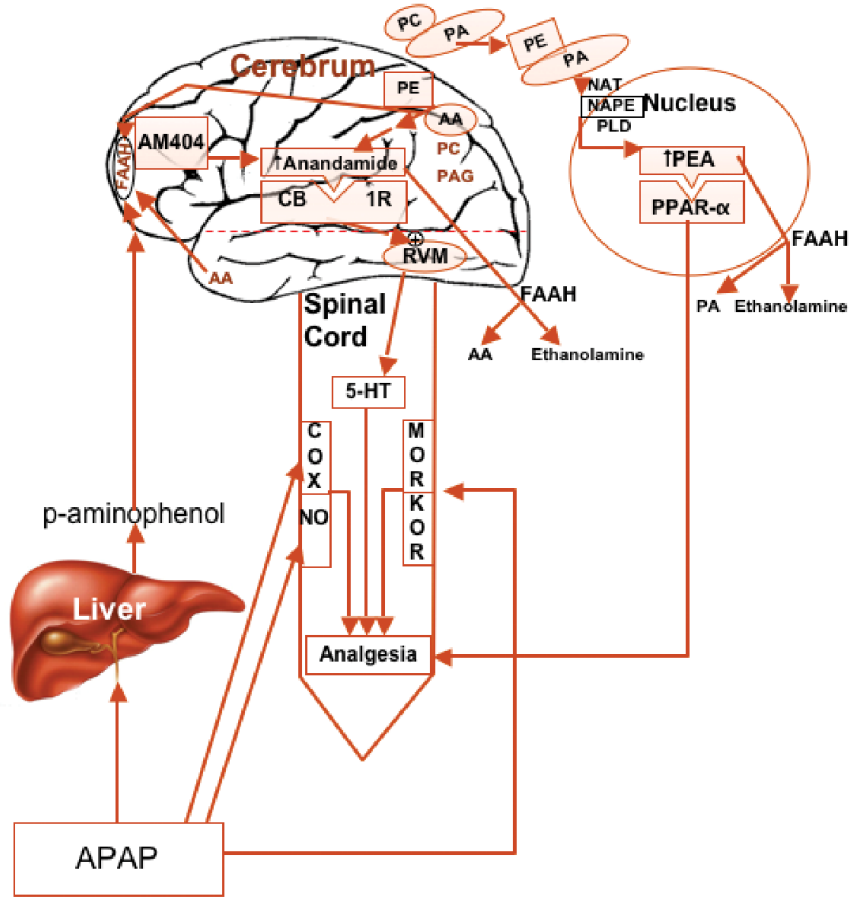
- Definition
  - Combining different analgesics that act by different mechanisms and at different sites in the nervous system, resulting in additive or synergistic analgesia with lowered adverse effects compared to sole administration of individual analgesics
- Also known as “balanced analgesia”
- Established 1993
- Recommended by perioperative practice guidelines
- A standard part of all Enhanced Recovery after Surgery (ERA) pathways
- Limited focused literature

American Society of Anesthesiologists. *Anesthesiology.* 2012 Feb;116(2):248-73.
Buvanendran A, et al. *Curr Opin Anaesthesiol*. 2009 Oct;22(5):588-93.
Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.
Kehlet H. *Anesth Analg*. 1993 Nov;77(5):1048-56.
Young A, et al. *Anesthesiol Clin*. 2012 Mar;30(1):91-100.

Non-Opioid Analgesia Options

Acetaminophen/Paracetamol

- Mechanism of action (MOA)
  - Not fully known, thought to involve activation of descending serotonergic pathways
    - Possible cyclooxygenase (COX) inhibition
    - Possible inhibition of prostaglandin synthesis
    - Endocannabinoid, opioidergic receptors
- Dosing
  - 650-1000 mg every 4-6 hours
  - Not to exceed 4 g/24 hours



Pain Physician 2009; 12:1:269-280

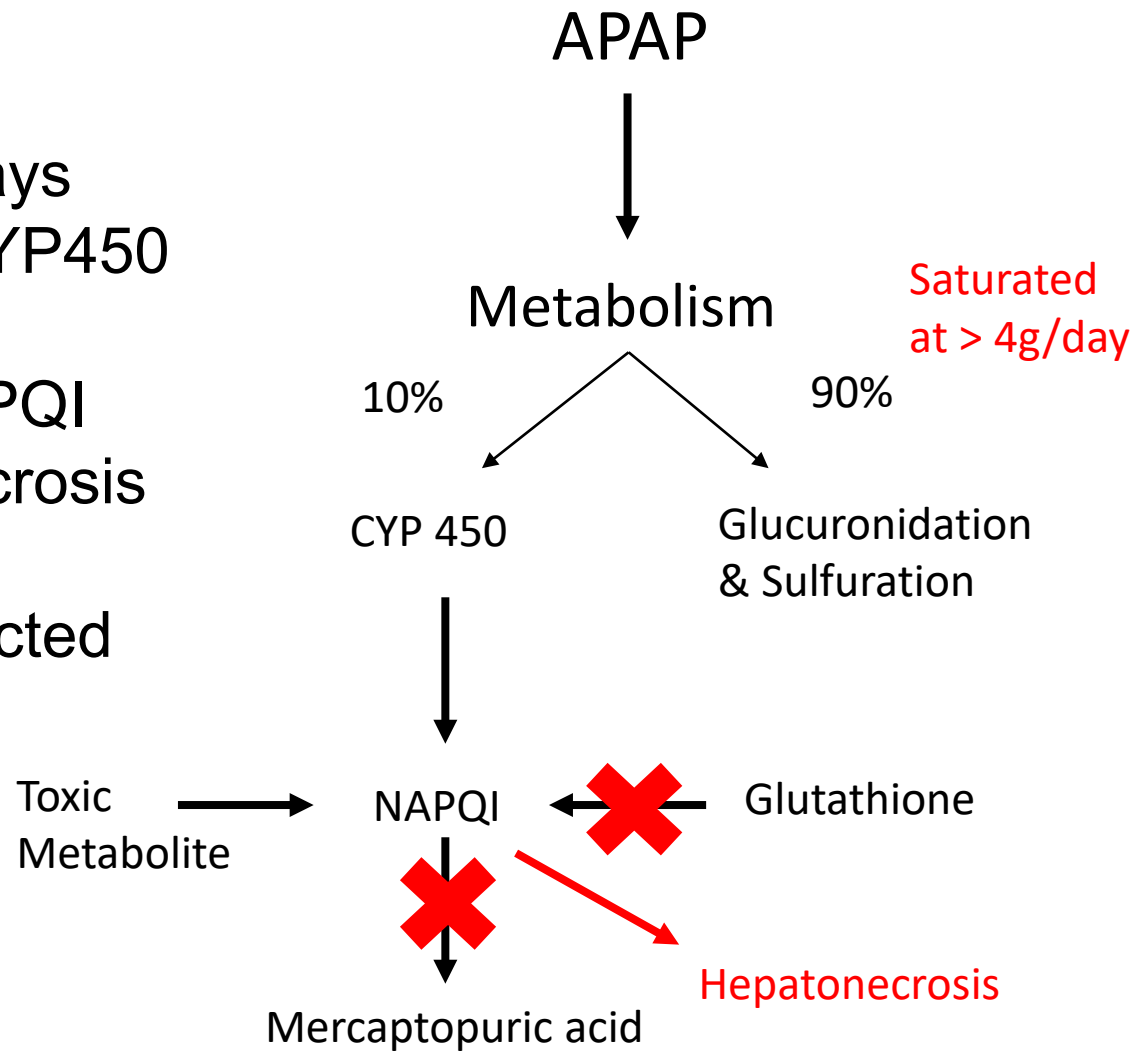
Acetaminophen/Paracetamol: Adverse Effects/Considerations

Box warning for hepatotoxicity

- Dose dependent
- Overdosing: primary metabolism pathways saturated -> metabolized primarily by CYP450 -> Byproduct: NAPQI, a toxic metabolite
- Glutathione depleted in overdosing, NAPQI binds to hepatic cells causing hepatonecrosis

Other considerations

- Antipyretic effect: can mask fever in infected patients



More SS, et al. Chem Res Toxicol. 2017 Mar 20;30(3):777-784

Paracetamol for Postoperative Pain: Cardiac Surgery (2007)

- Double-blind, randomized, controlled trial
- Population
  - Non-emergent cardiac surgeries with midline sternotomy and vein harvesting if indicated
- Intervention
  - Paracetamol 1g Q6H or placebo for 72 hours postoperatively
    - Standard analgesic regimen of tramadol and rescue morphine

	Paracetamol n = 56	Placebo n = 57	p value
Pain scores at 12 hours	1 [0-6]	2 [1-10]	0.0041
Pain scores at 18 hours	1 [0-5]	2 [0-8]	0.0039
Pain scores at 24 hours	1 [0-5]	2 [0-8]	0.0044
MME at 72 hours	48 mg	97 mg	NS
PONV (n,%)	3 (6)	1 (2.1)	NS

Cattabriga I, et al. Eur J Cardiothorac Surg. 2007 Sep: 32(3): 527-31

Paracetamol as Adjunctive Treatment for Postoperative Pain After Cardiac Surgery

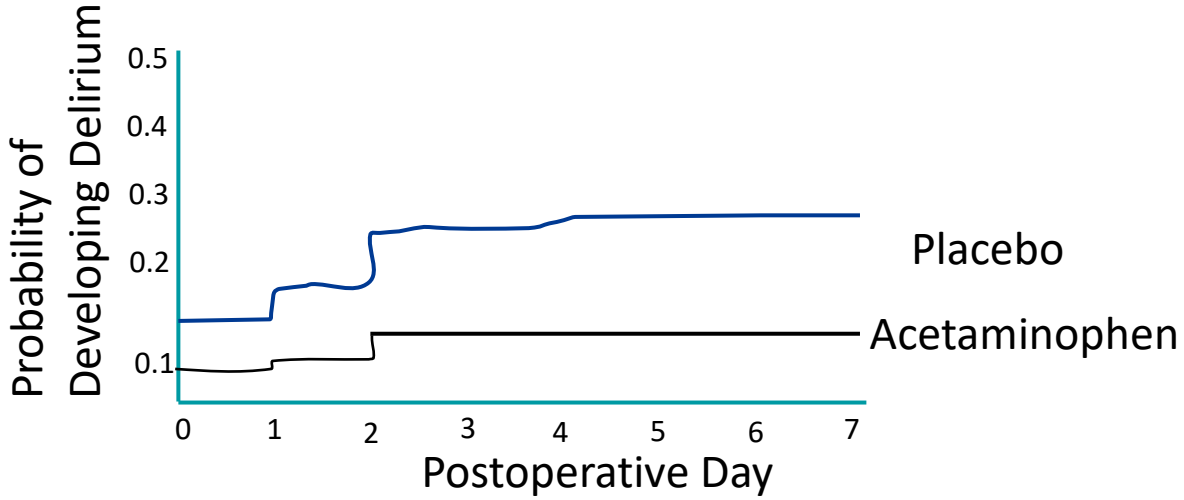
	Paracetamol (n = 56)	Placebo (n=57)	p value
Pain at 12 hr*	1 [0-6)	2 [1-10]	0.0041
Pain at 18 hr*	1 [0-5]	2 [0-8]	0.0039
Pain at 24 hr*	1 [0-5]	2 [0-8]	0.0044
Morphine total dose 1st 3 days$^{\beta}$	48 mg	97 mg	NS
Morphine total dose 1st 3 days^	5 mg [2-10]	5 mg [5-15]	NS
Rescue dose of morphine@	8 mg (14.2)	14 mg (24)	NS
*visual analog scale mean [range] β Mean		^ Median [range] @ n (%)	

- Paracetamol 1 g every 6 hr for 72 hr vs. placebo
- Standard analgesia was tramadol with morphine as needed

Cattabriga I, et al. *Eur J Cardiothorac Surg*. 2007 Sep: 32(3): 527-31.

Acetaminophen vs Placebo

Single-center RCT (BIDMC, Boston, MA): post-op cardiac surgery
4 groups: placebo-propofol (30 patients), placebo-dexmedetomidine (30 patients), IV acetaminophen-propofol (31 patients), IV acetaminophen-dexmedetomidine (29 patients)



Subramaniam B et al. *JAMA*. 2019; 321(7):686-696.

Intravenous vs Oral Acetaminophen

- Argument for oral
  - Oral acetaminophen has high bioavailability (~90%)
  - Low cost compared to IV
  - No difference in pain scores or morphine equivalents
- Argument for intravenous
  - Some data suggest faster time to peak effect 10 min vs 1 hour for oral
  - Patients with severe mucositis, shock
  - Ease of administration in the ICU

- Putting cost into perspective: $0.05 vs $20
  - 20 bed ICU, 1 g Q6H for 72 hours, 20 cases per week
  - IV: $249,600
  - Oral: $624

Moller PL, et al. Br J Anaesth 94(5) May 2005

Guidelines: Acetaminophen

Society of Critical Care Medicine: Pain, Agitation, Delirium, Immobility, and Sleep Guidelines (2018)	American Pain Society: Guidelines on the Management of Postoperative Pain (2016)
Suggest using acetaminophen as an adjunct to an opioid to decrease pain intensity and opioid consumption for pain management in critically ill adults (conditional recommendation, very low quality of evidence)	Recommends acetaminophen and/or NSAIDs as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high-quality evidence)
Can be especially useful for patients at higher risk for opioid-associated safety concerns (postoperative from abdominal surgery, at risk for ileus, nausea, vomiting)	May be especially effective when used in conjunction with NSAIDs compared with each class alone

Devlin JW, et al. Crit Care Med. 2018 Sep;46(9):e825-e873.
Chou R, et al. J Pain 2016;17:131-57.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- MOA: inhibits the enzymes COX-1 and COX-2 responsible for arachidonic acid conversion to prostaglandins -> decreasing pain receptors response
- Ibuprofen
  - Dosing: 400-800 mg Q6-Q8H, limit to 2.4 g/day
  - Box Warning
    - Ulcers, leading to perforation/GI bleed
    - Elderly, history of peptic ulcer disease at greatest risk
- Ketorolac
  - 15-30 mg Q6-Q8H
  - Box Warning
    - Cardiovascular risk including myocardial infarction and stroke
    - Acute kidney injury
    - Bleeding

IV Ibuprofen for Postoperative Pain (2009)

- Multi-center, randomized, double-blind, controlled trial
- Population
  - Elective, single-site orthopedic or abdominal surgery
- Intervention
  - Morphine + Ibuprofen 400 mg q6h for 48 hrs
  - Morphine + Ibuprofen 800 mg q6h for 48 hrs
  - Morphine + Placebo for 48 hrs

	IBU 400 n = 134	IBU 800 n = 138	Placebo n = 134
Morphine req (mg)	46.3	43.8*	48.9
Pain at rest (1-24 hr) VAS-AUC	81.7	73.9*	91
Pain with movement (1-24 hr) VAS-AUC	111.9*	106.3*	123.3
Adverse Effects, (n,%)	118 (88)	124 (90)	126 (94)
*Significant difference compared to placebo			

Southworth S, et al. Clin Ther 2009;31(9):1922-1935

Additional NSAID Trials

	Population	Intervention	Results
Hynninen 2000	120 patients undergoing elective CABG procedure	Diclofenac: 75 mg x1 + 1 12 hrs later Ketoprofen: 100 mg x1 + 1 12 hrs later Indomethacin: 100 mg x1 + 1 12 hrs later Placebo **x1 given 1 hr prior to extubation	• No difference in pain scores or AEs • Diclofenac less MME compared with placebo
Oberhofer 2005	44 patients undergoing major abdominal surgery (medial laparotomy)	Ketoprofen 100 mg 1 hr and 9hrs postop Placebo Both received tramadol and methimazole as standard therapy	• Significantly lower pain scores at 3, 6 and 12 hours postop • Significantly lower tramadol requirements • No adverse effects

Hynninen MS, et al. Can J Anesth 47, 1182–1187 (2000)
Oberhofer D, et al. World J. Surg. 29, 446–449 (2005)

Prevention of Postoperative Pain

- Premedication of celecoxib and acetaminophen for otolaryngologic surgery
- Double-blind, randomized, controlled trial
- Intervention
  - Group 1: Placebo
  - Group 2: Acetaminophen 2000 mg x1
  - Group 3: Celecoxib 200 mg x1
  - Group 4: Celecoxib + Acetaminophen

After Discharge Outcomes	Placebo n = 28	Acetaminophen n = 28	Celecoxib n = 28	Combination n = 28
Max pain score	6 [3-9]	0 [0-3]	0 [0-3]	0 [0-1]*
Satisfaction with pain management (%)	11	32	46*	61*
Analgesic doses	3 ± 1	2 ± 2	2 ± 2	1 ± 1*

* $P < 0.05$ compared to placebo

Anesthesia & Analgesia 94(5):p 1188-1193, May 2002

Guidelines: NSAIDs

Society of Critical Care Medicine: Pain, Agitation, Delirium, Immobility, and Sleep Guidelines (2018)	American Pain Society: Guidelines on the Management of Postoperative Pain (2016)
Suggest not routinely using a COX-1–selective NSAID as an adjunct to opioid therapy for pain management in critically ill adults (conditional recommendation, low quality of evidence).	Recommends acetaminophen and/or NSAIDs as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high-quality evidence)
NSAID therapy most beneficial in perioperative pain management when weighing risks and benefits	Recommends a preoperative dose of oral celecoxib in adult patients without contraindications (strong recommendation, moderate-quality evidence).

Devlin JW, et al. Crit Care Med. 2018 Sep;46(9):e825-e873.
Chou R, et al. J Pain 2016;17:131-57.

Neuropathic Pain Agents: Gabapentinoids

MOA: Structurally related to but does not bind to GABA or benzo receptors.
Binds to voltage-gated calcium channels in the CNS causing inhibition of glutamate, substance P and other excitatory neurotransmitter release

Gabapentin

- Dosing: 100-300 mg q8-q24h initial, 400-600 TID tolerated by most
- Adverse effects (esp. in elderly and poor renal function)
  - Drowsiness
  - Dizziness

Pregabalin

- Dosing: 50-150 mg/day divided into 2-3 doses
- Similar AE profile to gabapentin

Pregabalin

	Population	Intervention	Results
Pesonen 2011	70 patients >75 years old undergoing cardiac surgery	Pregabalin: 150 mg preop, 75 BID for 5 days after Placebo	• Decrease in postoperative oxycodone • Less delirium POD 1 • Lower incidence of “pain during movement” 3 months postop
Joshi 2013	40 patients undergoing off-pump CABG	Pregabalin: 150 mg preop, 75 BID for 2 days after Placebo	• Lower pain scores at 6, 12, 24 and 36 h • Significantly lower tramadol use • No difference in adverse effects

- Drawbacks
  - Diverse opioids limit applicability
  - No difference in time to extubation or ICU length of stay
  - Gabapentin and pregabalin not recommended to be used together

Pesonen A, et al. Br J Anaesth. 2011 Jun;106(6):873-81
Joshi SS, et al. Ann Card Anaesth. 2013 Jul-Sep;16(3):180-5

Anticonvulsants: Carbamazepine/Oxcarbazepine

MOA: Blocking of sodium voltage gated channels decreasing hyperexcitability of neuronal membranes. Oxcarbazepine also regulates calcium voltage gated channels.

Carbamazepine: 200-400 mg/day 2-4 divided doses

- Adverse effects: Hepatotoxicity, neutropenia, thrombocytopenia (rare)
- Strong CYP3A4 inducer

Oxcarbazepine: 300-600 mg/day in 2 divided doses

- Similar AE profile to carbamazepine

<u>Box Warning:</u>

- Increased risk of developing Stevens-Johnson Syndrome in patients of Asian descent, do not initiate if positive test for HLA-B*1502

Low quality of evidence in perioperative settings, some suggest decreased opioid requirements

Adjunctive Neuropathic Pain Medications

Two post-cardiac surgery trials

- 40 pregabalin (150 mg prior to surgery then 150 mg daily)
- 60 placebo patients

Pooled data show

- Reduction in opioid consumption
- No other differences

Pesonen A, et al. *Br J Anaesth* 2011; 106:873–881.
Joshi SS, et al. *Ann Card Anaesth* 2013; 16:180–185.

Adjunctive Neuropathic Pain Medications

The 2018 SCCM PADIS guidelines

- Recommend using a neuropathic pain medication (e.g., gabapentin, carbamazepine, pregabalin) with opioids for neuropathic pain management in critically ill adults
  – Strong recommendation, moderate quality of evidence

- Suggest using a neuropathic pain medication (e.g., gabapentin, carbamazepine, pregabalin) with opioids for pain management in ICU adults after cardiovascular surgery
  – Conditional recommendation, low quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Guidelines: Neuropathic Agents

Society of Critical Care Medicine: Pain, Agitation, Delirium, Immobility, and Sleep Guidelines (2018)	American Pain Society: Guidelines on the Management of Postoperative Pain (2016)
Recommend using neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids for neuropathic pain management in critically ill adults (strong recommendation, moderate quality of evidence)	Consider gabapentin or pregabalin as a component of multimodal analgesia for patients undergoing major surgery
Suggest using a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids for pain management in ICU adults after cardiovascular surgery (conditional recommendation, low quality of evidence)	Consider gabapentin or pregabalin for postoperative patients with a history of high opioid tolerance *No mention of carbamazepine/oxcarbazepine*

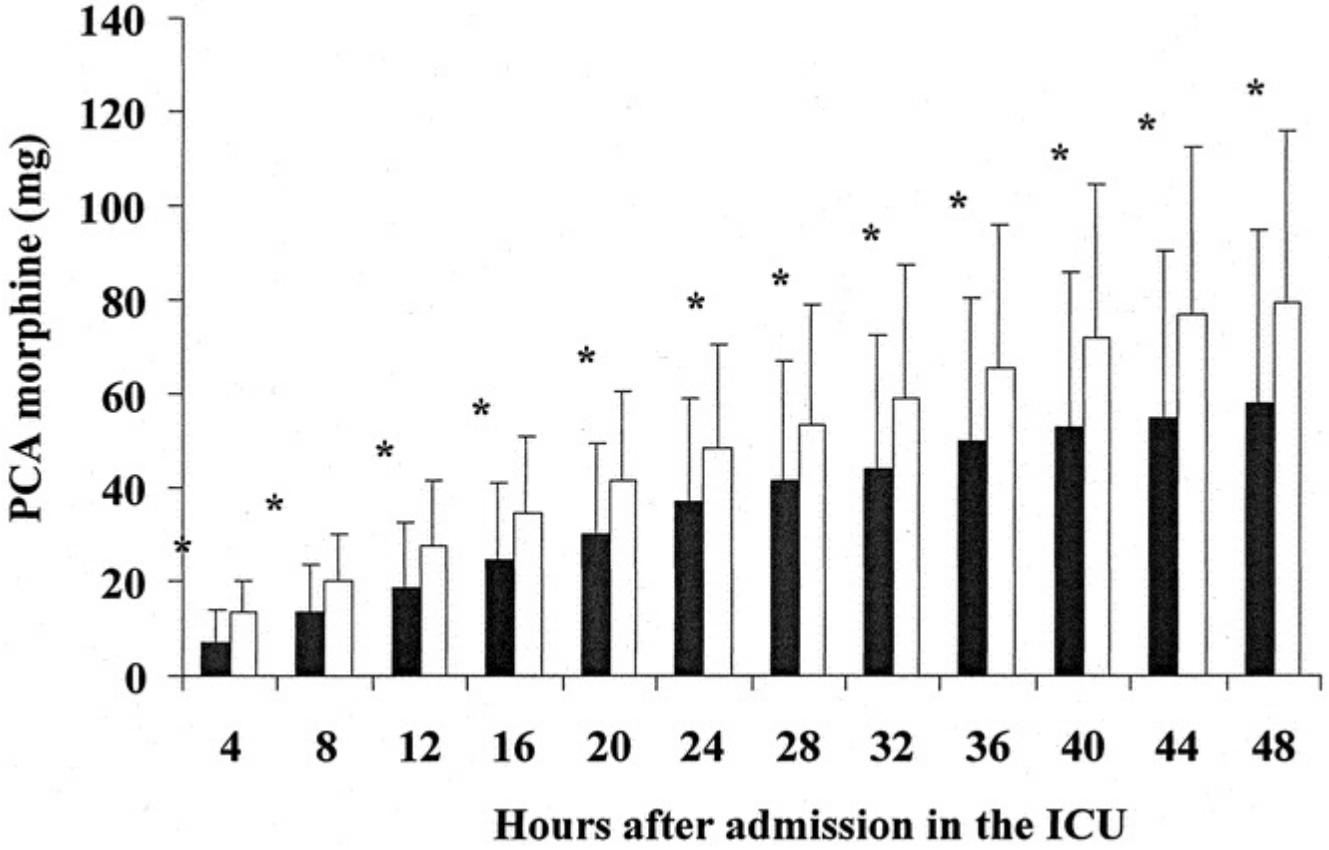
Devlin JW, et al. Crit Care Med. 2018 Sep;46(9):e825-e873.
Chou R, et al. J Pain 2016;17:131-57.

Ketamine

- Popular anesthetic that provides analgesia at subanesthetic doses
- MOA: Antagonist of the NMDA receptor therefore inhibiting glutamate release in response to pain transmission
- Dosing
  - 1-5 mcg/kg/min (0.05-0.5 mg/kg/hr) infusion
  - IV push 0.1-0.4 mg/kg
- Adverse effects
  - Hallucinations
  - Tachycardia/Hypertension
  - ICP increase? Mostly old data

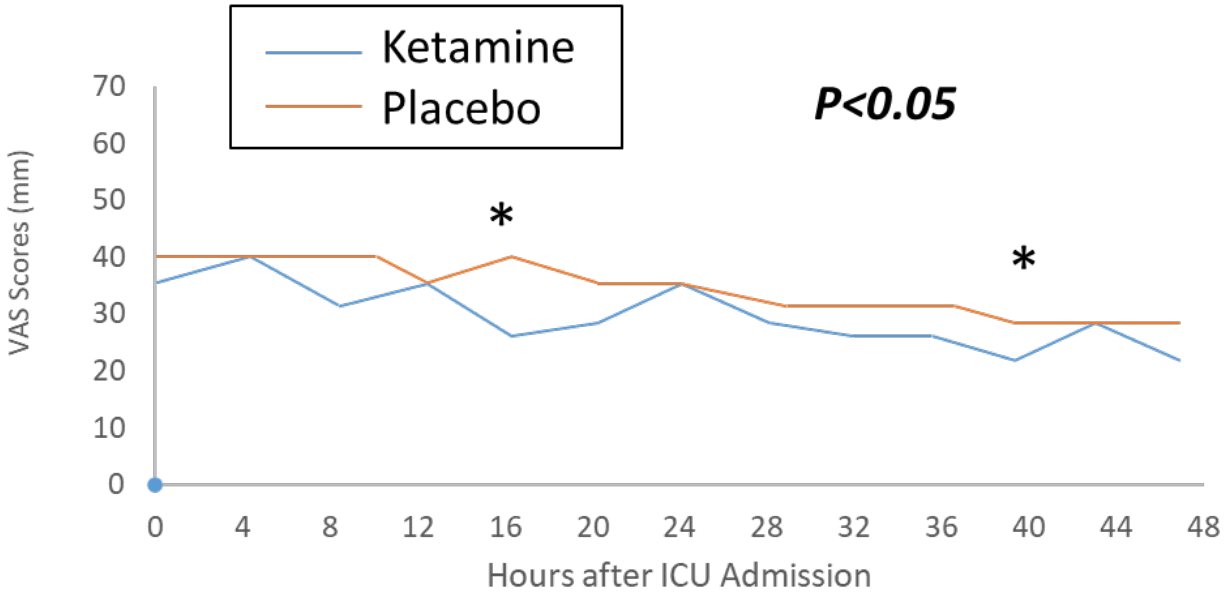
Ketamine in Abdominal Surgery (2003)

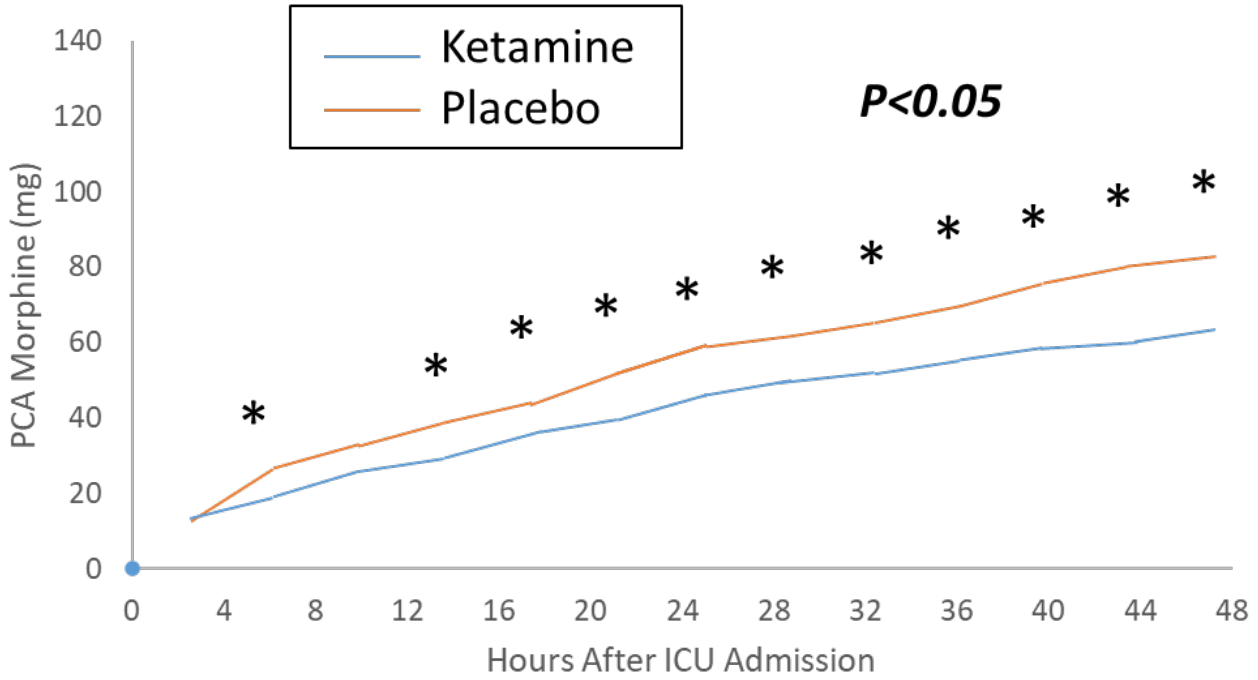
- Randomized, double blind study
- Population: 93 patients undergoing major abdominal surgery postoperative to the surgical ICU
- Intervention
  - Morphine PCA + placebo
  - Morphine PCA + ketamine 0.5 mg/kg bolus followed by 24 hours of 2 mcg/kg/min followed by 24 hours of 1 mcg/kg/min
- No significant difference in adverse effects!



Guillou N, et al. Anesthesia & Analgesia 97(3):p 843-847, September 2003.

Adjunctive Low-Dose Ketamine in Surgical ICU Patients





Single-center, prospective, randomized, double-blind trial including 93 patients scheduled to have major abdominal surgery and post-op management and ventilation in the SICU. Patients were randomized to receive morphine by patient-controlled analgesia with either placebo or ketamine (for 48 hours). Both groups were allowed as-needed morphine boluses.

Guillou N, et al. *Anesth Analg* 2003; 97:843-847.

Cochrane Systematic Review: Ketamine

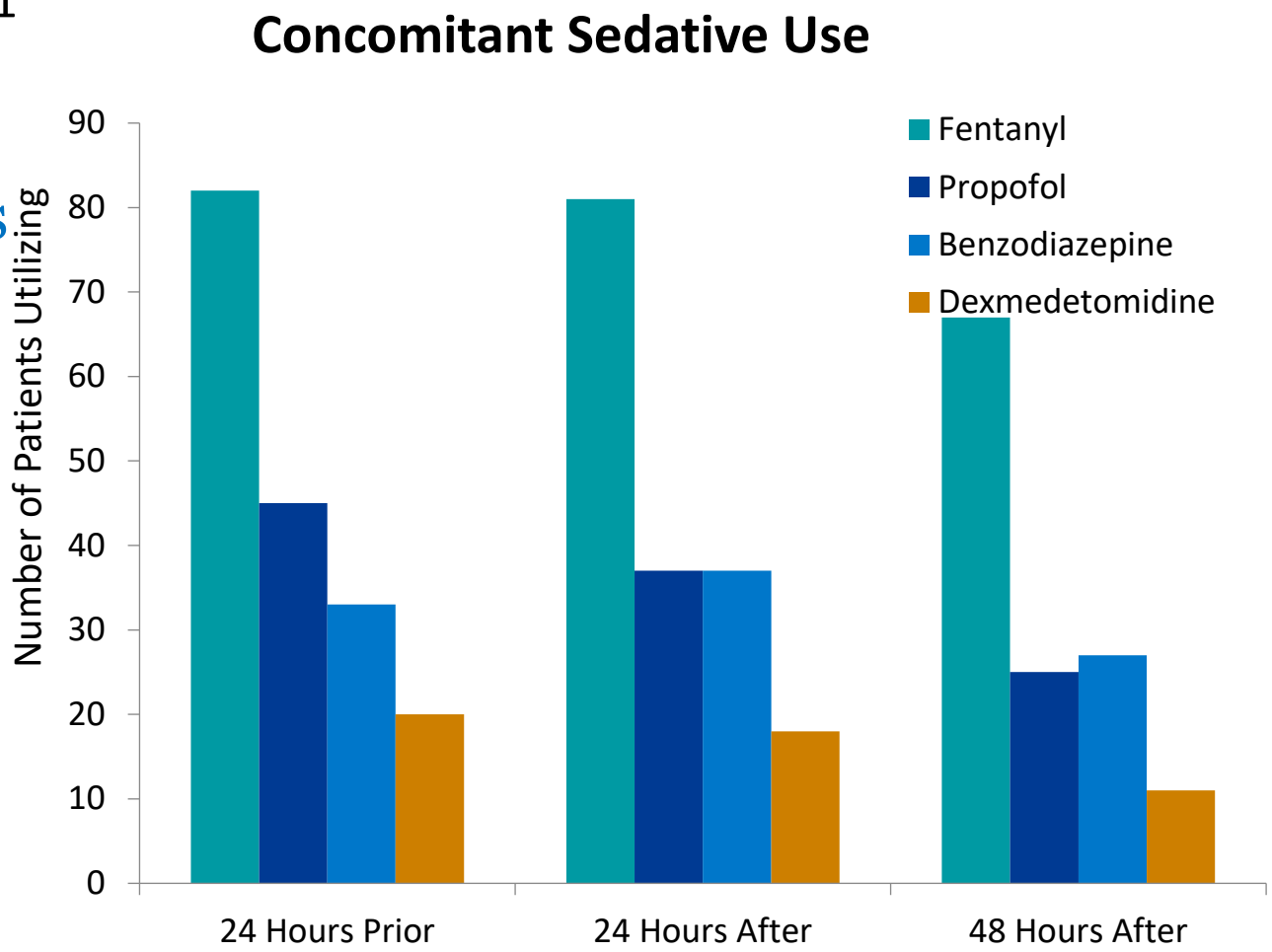
	Population	Intervention	Results
Brinck 2018	• 130 studies • 8341 patients • Postoperative surgeries including: orthopedic, cardiothoracic, abdominal, neurosurgical	Ketamine infusion: 2-5 mcg/kg/min	• Reduction in opioids required at 24 and 48 hours postoperative • Pain at rest significantly lower at 24 and 48 hours postoperative • Pain with movement significantly lower at 24 and 48 hours postoperative • Increased time until first analgesic request • Incidence of CNS adverse effects was 5% with ketamine vs 4% for placebo (NS)

Brinck ECV, et al. Cochrane Database of Systematic Reviews 2018

Ketamine for Sedation

Introduction of low-dose ketamine (median dose 0.41 mg/kg/hr) for adjunctive sedation:

- Improved time at goal Sedation-Agitation Scale in the first 24 hours
- Decreased frequency of agitation
- Allowed for reduction or discontinuation of concomitant sedatives (63% of patients)
- Relatively well tolerated (7.7% discontinuation rate)



Groetzinger LM, et al. Pharmacotherapy. 2018; 32(2): 181-188.

Ketamine in the ICU: A tale of caution

Table 1 Quantification of opioid and sedative use

	Protocol group ($n = 10$)	Control group ($n = 10$)	p value
Cumulative fentanyl equivalents from ECMO initiation to decision to achieve wakefulness, mg	15,200 (5488 to 26,981)	8275 (1363 to 20,194)	0.12
Cumulative midazolam equivalents from ECMO initiation to decision to achieve wakefulness, mg	1420 (474 to 3424)	324 (172 to 2454)	0.08
Cumulative fentanyl equivalents during duration of ICU, mg/day	6 (4 to 9)	5 (2 to 10)	0.58
Cumulative midazolam equivalents during duration of ICU, mg/day	8 (6 to 12)	6 (3 to 10)	0.32

- Indication for use is key
  - Routine surgical vs. ARDS

Dzierba AL, et al. *Intensive Care Med.* 2016 Nov;42(11):1822-1823

Guidelines: Ketamine

Society of Critical Care Medicine: Pain, Agitation, Delirium, Immobility, and Sleep Guidelines (2018)	American Pain Society: Guidelines on the Management of Postoperative Pain (2016)
Suggest low-dose ketamine (0.5 mg/kg IVP x 1 followed by 1-2 µg/kg/min infusion) as an adjunct to opioid therapy when seeking to reduce opioid consumption in postsurgical adults admitted to the ICU (conditional recommendation, very low quality of evidence)	Recommends that clinicians consider ketamine as a component of multimodal analgesia in adults (weak recommendation, moderate quality evidence)
Note that benefits must outweigh adverse effects (nausea, delirium, hallucinations, hypoventilation, pruritus, and sedation) that can be seen with ketamine	Given adverse effect profile, should be reserved for major surgeries or patients and highly opioid-tolerant patients

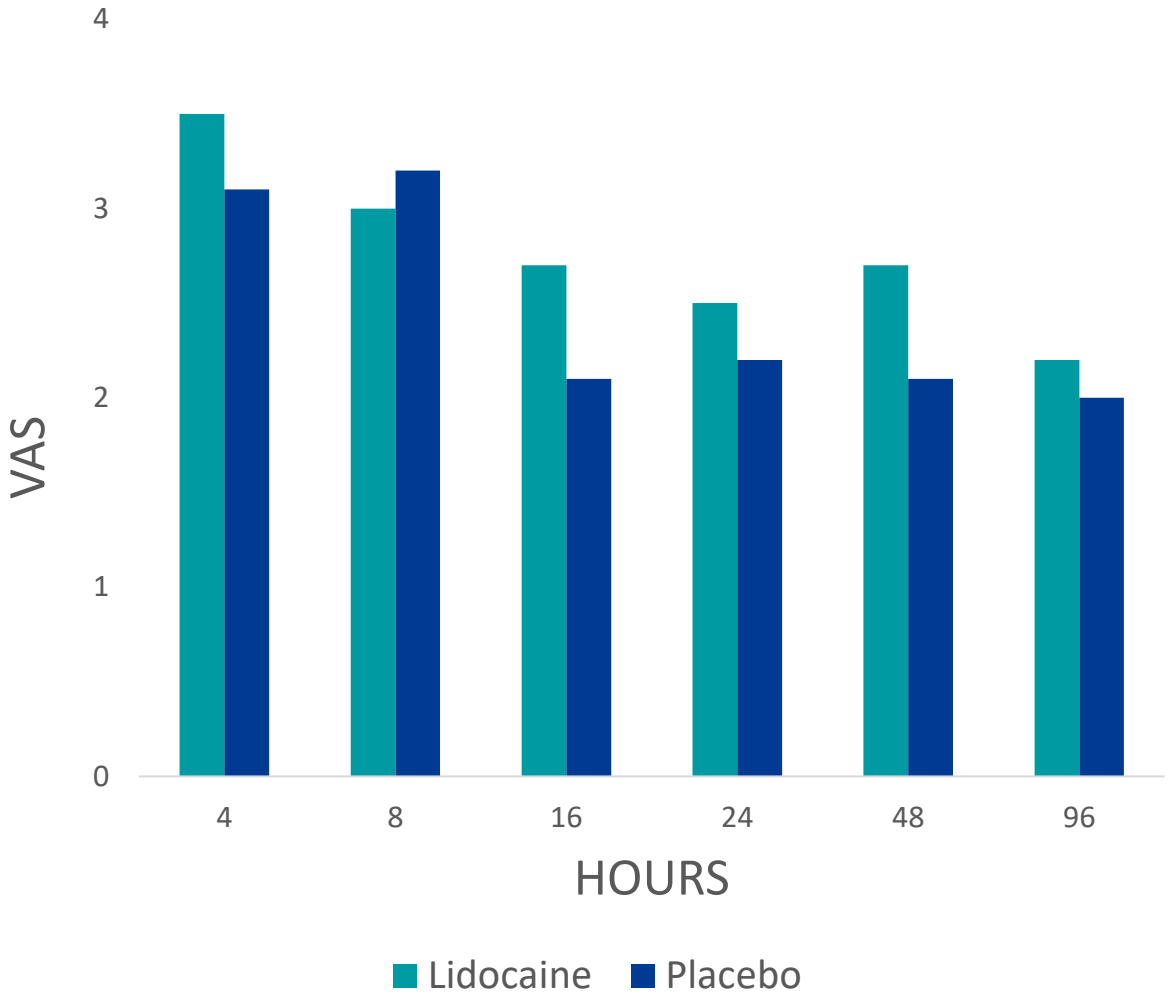
Devlin JW, et al. Crit Care Med. 2018 Sep;46(9):e825-e873.
Chou R, et al. J Pain 2016;17:131-57.

Lidocaine

- Commonly used antiarrhythmic, also with analgesic properties
- MOA: Analgesic and anti-inflammatory effects through blockade of sodium channels and NMDA receptors
- Dosing:
  - 1-2 mg/kg/hr infusion
- Adverse effects
  - Neuro- numbness, dizziness, confusion
  - GI- nausea
  - CV- bradycardia, hypotension
  - Tinnitus
- Therapeutic drug monitoring
  - Titrate to effect, target levels < 4 mcg/mL

Lidocaine for CABG (1995)

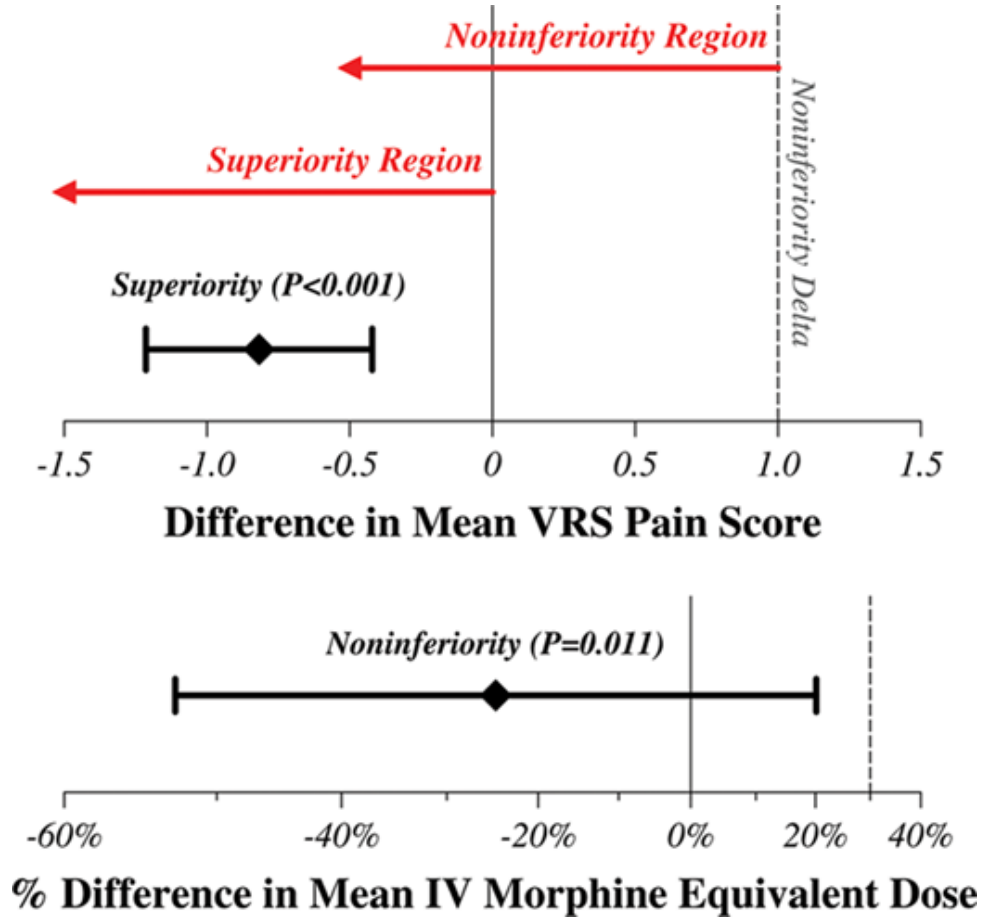
- Randomized, double blind study
- Population: 100 patients undergoing CABG
- Intervention
  - Standard of care + placebo
  - Standard of care + lidocaine 1.5 mg/kg bolus followed by 1.8 mg/kg/hr
    - Started after induction of anesthesia and continued for up to 48 hours
- No difference in opioid or benzodiazepine usage
- No difference in ICU length of stay



Insler SR, et al. Can J Anesth 2000; 47:1192

Lidocaine for Complex Spinal Surgery (2013)

- Randomized, double blind study
- Population: 100 patients undergoing complex spinal surgery
- Intervention
  - Standard of care + placebo
  - Standard of care + lidocaine 2 mg/kg/hr at induction until PACU discharge or max of 8 hours
- Superior in pain score reduction, non-inferior in opioid reduction
- Improved functionality at 1 and 3 months
- No difference in nausea or vomiting



Farag E, et al. Anesthesiology. 2013 Oct;119(4):932-40

Adjunctive Lidocaine in ICU

ICU RCT Data (1 RCT of 100 cardiac surgery patients)

- No significant differences:
  - Self reported pain
  - Opioid requirements
  - ICU LOS
  - Hospital LOS

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.
Kranke P et al. *Coch Database Syst Rev.* 2015.
Schuler BR, et al. *Clin J Pain.* 2021 Sep 1;37(9):657-663.
Insler DR et al. *Can J Anesth.* 2000; 47:1192.

IV Lidocaine: Abdominal Surgery Meta-Analysis – non-ICU

Intravenous lidocaine administration

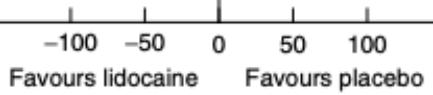
- Decreased the duration of ileus
- Length of hospital stay
- Postoperative pain intensity at 24 h after operation
- Incidence of nausea and vomiting

Marret E, et al. *Br J Surg.* 2008 Nov;95(11):1331-8.

Meta-analysis Lidocaine in Abdominal Surgery (2008)

- 8 RCTs from 1985-2007, included open & laparoscopic
- 161 received lidocaine vs 159 placebo

Reference	Lidocaine		Placebo		WMD (random)	Weight (%)	WMD (random)
	n	Ileus (h)*	*n*	Ileus (h)*			
Groudine *et al.*[12]	20	28·50 (13·40)	20	42·10 (16·00)		11·12	−13·60 (−22·75, −4·45)
Herroeder *et al.*[8]	31	66·60 (26·40)	29	82·10 (33·80)		6·67	−15·50 (−30·92, −0·08)
Kaba *et al.*[7]	20	18·00 (9·10)	20	31·30 (11·50)		14·80	−13·30 (−19·73, −6·87)
Koppert *et al.*[13]	20	79·00 (13·34)	20	85·00 (20·76)		10·07	−6·00 (−16·81, 4·81)
Kuo *et al.*[14]	20	60·20 (5·80)	20	71·70 (4·70)		18·26	−11·50 (−14·77, −8·23)
Rimback *et al.*[15]	15	37·60 (2·40)	15	42·40 (4·80)		18·74	−4·80 (−7·52, −2·08)
Wu *et al.*[16]	25	22·10 (1·60)	25	22·90 (1·80)		19·74	−0·80 (−1·74, 0·14)
Total	151		149			100·00	−8·36 (−13·24, −3·47)
Test for heterogeneity: $\chi^2 = 63{\cdot}71$, 6 d.f., $P < 0{\cdot}001$, $I^2 = 90{\cdot}6\%$							
Test for overall effect: $Z = 3{\cdot}35$, $P < 0{\cdot}001$							



Duration of postoperative ileus

- Significant reductions in length of stay, postoperative pain at 24 hours, and postoperative nausea and vomiting
- Only 25% continued lidocaine > 4 hours after closure
- “Intravenous lidocaine is devoid of side-effects”

Marret E, et al. Br J Surg. 2008 Nov;95(11):1331-8

Safety of IV Lidocaine for Postoperative Pain

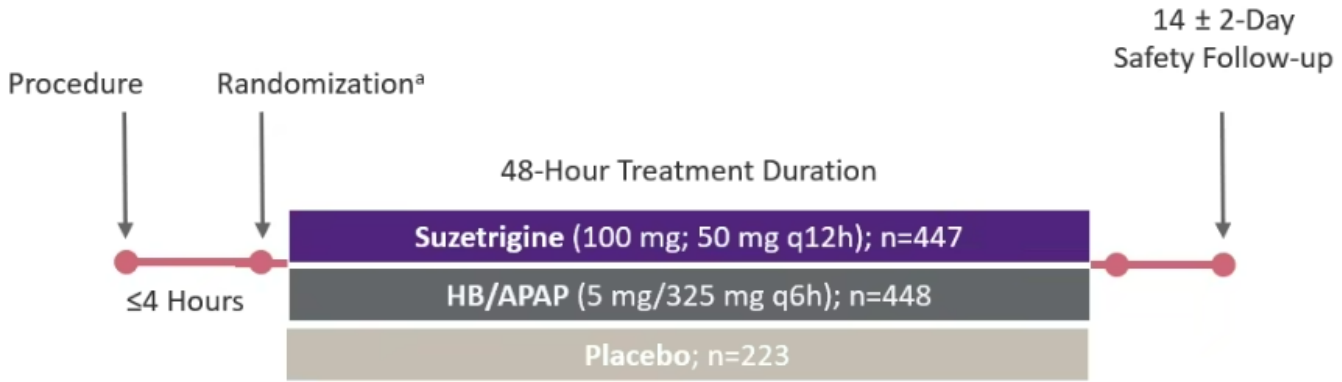
- Single-center, retrospective, single arm study
- Approximately 300 patients receiving lidocaine infusions for pain
- Duration: 34 [20:48] hours with a median initial and maintenance rate of 1 mg/kg/h
- Neurologic AEs: 32.2%
- Cardiovascular AEs: 22.8%
- Gastrointestinal AEs: 24.8%
- Resulted in discontinuation? **12.8%**

Variable	**Lido > 4** Occurred During Lidocaine Infusion n = 96	**Lido ≤ 4** Occurred During Lidocaine Infusion n = 202	**P value**	**Lido > 4** Cause of Lidocaine Discontinuation n = 96	**Lido ≤ 4** Cause of Lidocaine Discontinuation n = 202	**P value**
Any Adverse Effect[α] Neurologic Cardiac Gastrointestinal	59 (61.5) 32 (33.3) 21 (21.9) 26 (27.1)	115 (56.9) 64 (31.6) 47 (23.3) 48 (23.8)	0.459 0.775 0.789 0.535	11 (11.5) 11 (11.5) 0 (0) 0 (0)	27 (13.4) 22 (10.9) 2 (1.0) 3 (1.5)	0.644 0.884 N/A N/A
α presented as n (%)						

Schuler BR, Szumita PM et al. Clin J Pain. 2021 Sep 1;37(9):657-663

VX22-548-105: STUDY DESIGN[1,2]

Phase 3, randomized, double-blind, placebo-controlled study in adults with moderate-to-severe acute pain after an abdominoplasty (ABD)



Primary Endpoint

- Time-weighted SPID as recorded on the NPRS from 0 to 48 hours (SPID48) compared with placebo

Key Secondary Endpoints

- SPID48 compared with HB/APAP
- Time to ≥2-point reduction in Numeric Pain Rating Scale (NPRS) from baseline compared with placebo

Key Inclusion Criteria

- Aged 18 to 80 years
- Before Surgery
  - Scheduled to undergo a standard ("full") ABD
- After Surgery
  - Lucid and able to follow commands and able to swallow oral medications
  - All analgesic guidelines were followed during and after the ABD
  - ABD procedure duration ≤3 hours
- Moderate to severe pain and ≥4 on the NPRS

Key Exclusion Criteria

- Before Surgery
  - Prior history of ABD
  - History of intra-abdominal and/or pelvic surgery that resulted in complications
  - History of cardiac dysrhythmias within the last 2 years requiring anti-arrhythmia treatment(s)
  - Any prior surgery within 1 month before the first study drug dose
- After Surgery
  - Non-standard ABD, collateral procedures during the ABD or any surgical complications during the ABD
  - Medical complication during ABD that, in the opinion of the investigator, should preclude randomization

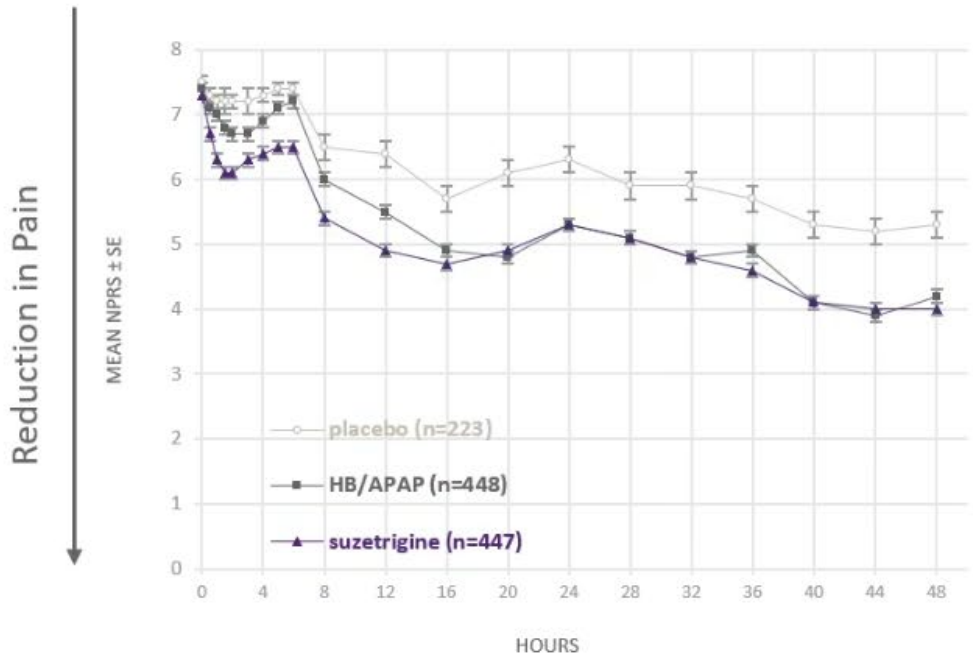
[a] Participants were randomized in a 2:2:1 ratio to receive suzetrigine, HB/APAP, or placebo.

HB/APAP, hydrocodone bitartrate/acetaminophen; q6h, every 6 hours; q12h, every 12 hours.

1. Data on file. Vertex Pharmaceuticals Incorporated, Boston, MA. 2. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05558410. Accessed June 3, 2024.

VX22-548-105 – ABDOMINOPLASTY: MEAN NPRS SCORES

Mean NPRS Scores Over the Treatment Period



NPRS Reductions From Baseline at 48 Hours

	Placebo n=223	**HB/APAP** 5 mg/325 mg q6h n=448	**Suzetrigine** 100 mg; 50 mg q12h n=447
Baseline NPRS, Mean	7.5	7.4	7.3
Change From Baseline in NPRS at 48 Hours, Mean	-2.3	-3.2	-3.4
% Reduction From Baseline in Mean NPRS at 48 Hours	31%	43%	47%

HB/APAP, hydrocodone bitartrate/acetaminophen; NPRS, Numeric Pain Rating Scale; q6h, every 6 hours; q12h, every 12 hours.

Data on file. Vertex Pharmaceuticals Incorporated, Boston, MA.

Guidelines: Lidocaine

Society of Critical Care Medicine: Pain, Agitation, Delirium, Immobility, and Sleep Guidelines (2018)	American Pain Society: Guidelines on the Management of Postoperative Pain (2016)
Suggest not routinely using IV lidocaine as an adjunct to opioid therapy for pain management in critically ill adults (conditional recommendation, low quality of evidence)	Recommends in adults who undergo open and laparoscopic abdominal surgery who do not have contraindications (weak recommendation, moderate-quality evidence)
Individual patients and surgical populations may benefit from use **Lack of safety data**	Clinical experience: recommend 1.5 mg/kg bolus followed by 2 mg/kg/hr intra-operatively **Lack of data in postoperative setting**

Devlin JW, et al. Crit Care Med. 2018 Sep;46(9):e825-e873.
Chou R, et al. J Pain 2016;17:131-57.

Dexmedetomidine

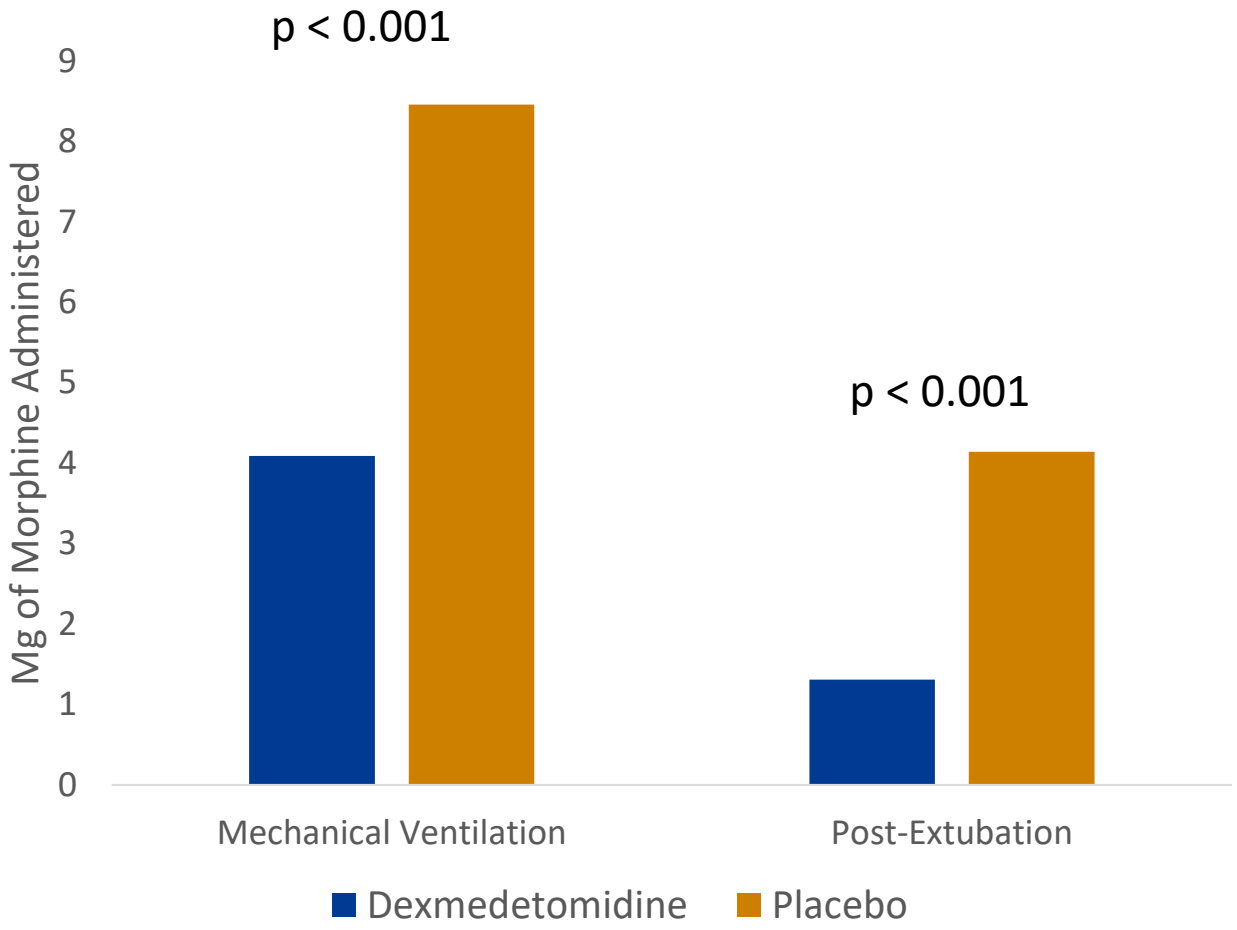
- Light sedative in the ICU (does not suppress respiratory drive)
- MOA: alpha-2 agonist
- Dosing:
  - 0.2-1.5 mcg/kg/hr infusion
- Adverse effects
  - Bradycardia (rare reports of cardiac arrest)
  - Hypotension
  - Drowsiness
  - Drug fever*
- Can be used in mechanical ventilation and non-ventilated patients
- Withdrawal can occur if abruptly discontinued after prolonged durations of use

Is dexmedetomidine opioid sparing?

- Depends
  - Pure surgical trial = maybe
  - Mixed medical/surgical = likely not
    - No difference in SEDCOM, PRO/DEX, MID/DEX, SPICE III
    - MENDS – over 3X more opioid consumption in the dexmedetomidine arm

Dexmedetomidine Trial

- Randomized, double blind, multicenter study
- Population: 400 patients requiring MV ≥ 6 hours after surgery
- Intervention
  - Dexmedetomidine 0.2-0.7 mcg/kg/hr to maintain light sedation
  - Placebo
- Results
  - Decreased morphine requirements in treatment group
  - Fewer patients reported remembering pain/discomfort



Martin E, et al. J. Intensive Care Med. 2003;18(1):29-41

Dexmedetomidine vs Lorazepam: MENDS TRIAL

	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*p* Value
Lorazepam mg/hr (mean)		**3**	
Fentanyl mcg/day (mean)	575	150	$p = 0.006$
Sedated deeper than nurse goal RASS score, Days %	15	33	$p = 0.01$

Pandharipande PP, et al. *JAMA*. 2007 Dec 12; 298(22) :2644-53.

Muscle Relaxants

- Helpful for spasticity in brain or spinal cord injury, muscle spasms
- Methocarbamol
  – Dosing: 300 – 1500 mg 3 or 4 times daily
- Cyclobenzaprine
  – Dosing: 5 – 10 mg 3 times daily
- Baclofen
  – Dosing: 5 – 10 mg 3 times daily
  – Dose reduction needed in renal dysfunction
- Tizanidine
  – Dosing: 2 – 4 mg 3 to 4 times daily
  – Dose reduction needed in renal dysfunction

Risk of respiratory depression and withdrawal

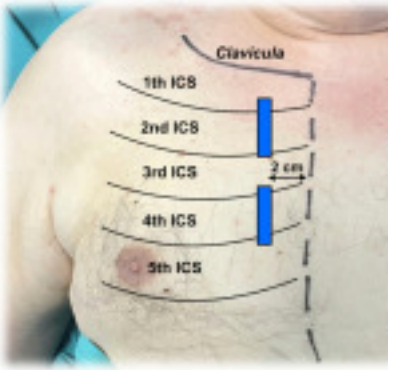
Regional Anesthesia

- Peripheral nerve blocks can be used to inhibit impulse transmission at the nerve site to block the pain sensation from being received
- Has been shown to decrease pain scores and rescue opioid requirements
- Strongly recommended by the American Pain Society when appropriate, especially in patients at risk for cardiac and pulmonary complications
- Adverse effects:
  - Nerve injury
  - Hematoma
  - Hypotension

Timing ("When?"):
pre-op or post-op block ?

similar effects,
no significant differences

pre-op block might reduce intraoperative opioid use and provide greater anesthesiologic stability during surgery



Local anesthetic ("What?"):
levobupivacaine 0.5% 20 mL
or
ropivacaine 2 mg/mL 20 mL ?

similar effects,
no significant differences

both long lasting (24h), slightly different onset, levobupivacaine more permeable in tissues

Schiavoni L, et al. JCVA. 2022;36(11):4173-82

Topical Options

- Lidocaine
  - Patches, ointments
  - Patches can be cut to fit to size
- Diclofenac
  - NSAID ointment
  - Dosing: 4 g four times daily
  - Comes with card for measuring dosing grams
- Capsaicin
  - TRPV1 agonist
  - Causes nociceptor defunctionalization at the topical site

Multimodal Pain Management: A LOT to Choose From but Limited Data

2018 PADIS endorsed

- Acetaminophen
- NMDA receptor antagonists
  - Ketamine
- Anticonvulsants
  - Gabapentin/Pregabalin
- Non-pharmacological

Other Options

- NSAIDs
- COX-2 inhibitors
- α-2 agonists
  - Clonidine & Dexmedetomidine
- Corticosteroids
- Local Anesthetics
  - Systemic, regional & local techniques

Choice of agent, route, dosing, and monitoring is often patient-specific and limited by resources available

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.
Buvanendran A, et al. *Curr Opin Anaesthesiol*. 2009 Oct;22(5):588-93.
Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Adverse Drug Reactions for Select "Multimodals"

APAP	NSAIDS/COX II	Local anesthetics	Alpha-2 agonists	NMDA antagonists	Anticonvulsants
Liver toxicity/failure	GI toxicity	Hypotension	Hypotension	Hallucinations	Hallucinations
Nausea and Vomiting	Renal failure	Bradycardia	Bradycardia	Tachycardia	Withdrawal
Hypotension (IV)	Bleeding	Urinary retention*	Tachycardia		Seizures
	CV events	Epidural hematomas*			Excess sedation
	Nausea and Vomiting	Neurotoxicity			

Anticonvulsants: gabapentin/pregabalin

*Associated with epidural administration

Riker RR, Fraser GL. Pharmacotherapy. 2005 May;25(5 Pt 2):8S-18S
Devlin JW, et al. Crit Care Med. 2010 Jun;38(6 Suppl):S231-43.
Devlin JW, et al. Crit Care Med. 2018 Sep;46(9):e825-e873.
Schuler BR, et al. *Clin J Pain*. 2021 Sep 1;37(9):657-663.

Multimodal is more than medications

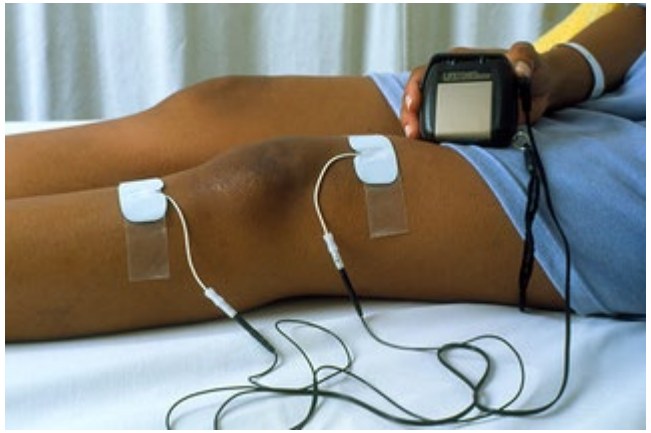
The 2018 SCCM PADIS guidelines

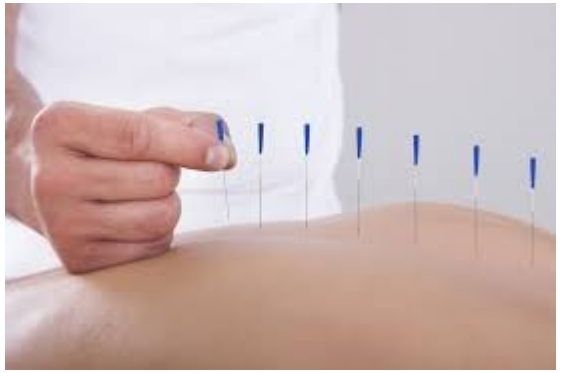
- Suggest cold therapy for procedural pain management in critically ill adults
  – Conditional recommendation, low quality of evidence
- Suggest offering relaxation techniques for procedural pain management in critically ill adults
  – Conditional recommendation, very low quality of evidence
- Suggest offering massage for pain management in critically ill adults
  – Conditional recommendation, low quality of evidence
- Suggest offering music therapy to relieve both non-procedural and procedural pain in critically ill adults
  – Conditional recommendation, low quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Non-Pharmacologic Pain Relievers

- Low evidence for efficacy, low risk
- Cognitive behavioral therapy
  - Has shown to reduce perioperative anxiety but not long-term pain scores
  - Some benefit may be seen in acute setting, however lack of standardization of interventions
- Transcutaneous electrical nerve stimulation
- Acupuncture
- Music therapy





Nadinda PG, et al. Pain. 2022 Jul 1;163(7):1254-1273
Buvanendran A, et al. Reg Anesth Pain Med. 2021 Apr;46(4):313-321

Best Practices in Analgesic Therapy

- Assess Assess Assess
  - Is pain well controlled?
    - If not, what receptors have we not yet targeted
      - NSAIDs, gabapentinoids, lidocaine, ketamine
    - If so, what can we peel back to remove the risk of adverse effects
      - Still need 1g Q6 of acetaminophen?
- Factoring in patient history
  - Home medications? Chronic pain? Opioid use disorder?
- Multimodal analgesia
  - Using multiple mechanisms of action to your advantage
  - Overall can limit adverse effects of a singular agent by targeting multiple receptors
- Non-pharmacologic therapies

Patient Case CC

- 55 YO male who presents for invasive oral surgery requiring inpatient stay
- Past medical history
  - Type 2 Diabetes
  - Atrial fibrillation
  - Hyperlipidemia
- Past surgical history: prior coronary artery disease with PCI (2021)

Patient Case CC

- Postoperative day (POD) 0
- Neuro
  - Pain scores ranging from 5-8
  - Hydromorphone: 0.5 mg x 11 doses
  - Oxycodone: 10 mg x4 doses
  - No additional analgesia ordered

Home Meds	Restarted POD0?
Apixaban 5 mg BID	No
Atorvastatin 80 mg QD	Yes
Gabapentin 800 mg TID	No
Metformin 500 mg BID	No
Metoprolol XR 50 mg QD	No

Labs	Pre-op	POD1
Na (mmol/L)	143	140
K (mmol/L)	4.4	4.3
Cl (mmol/L)	101	98
SCr (mg/dL)	0.78	1.51
Glu (mg/dL)	101	115

How can we best optimize CC's pain regimen?

a) Restart home gabapentin 800 mg 3 times daily

b) Start ketamine infusion at 10 mcg/kg/min

c) Start acetaminophen 1000 mg every 8 hours

d) Consult post-operative pain service for a hydromorphone patient-controlled analgesia (PCA)

How can we best optimize CC's pain regimen?

a) Restart home gabapentin 800 mg 3 times daily

b) Start ketamine infusion at 10 mcg/kg/min

c) Start acetaminophen 1000 mg every 8 hours

d) Consult post-operative pain service for a hydromorphone patient-controlled analgesia (PCA)

Perioperative Management of Opioid Use Disorder

Patient Case SB

- 40 YO female who presents following a high-speed motor vehicle collision
- Past medical history
  - Atrial fibrillation
  - Opioid use disorder (On buprenorphine 16 mg QD)
- Past surgical history: none
- Patient intubated and sedated on propofol 45 mcg/kg/min and fentanyl 200 mcg/hr. Overnight resident suggested adding APAP 1g Q6H for pain
- Assessment
  - major maxillofacial surgery
  - RASS: +2
  - VAS: 9

How can we best optimize SB's pain regimen?

a) Transition fentanyl to morphine infusion

b) Increase propofol to 65 mcg/kg/min for RASS goal -2 to -3

c) Ketamine 0.5 mg/kg bolus, followed by 0.5 mg/kg/hr infusion

d) Gabapentin 800 mg 4 times daily

e) Divide buprenorphine to 8 mg BID

Buprenorphine

- MOA: partial mu-agonist, has high affinity but low activity
- Indicated for chronic pain and often paired with naloxone for opioid use disorder (dissuade injection)
- Dosing
  - Chronic pain: 75 mcg QD or BID, slow titration as tolerated
  - Opioid use disorder: 2-4 mg, can titrate up more rapidly
  - Patch can be used for chronic pain, ER injections for opioid use disorder
- Adverse effects
  - Rapid transition after high dose opioids may precipitate withdrawal symptoms and/or severe pain
  - Otherwise well tolerated

Buprenorphine Peri-operative Management

- Preoperative
  - Recommended to continue buprenorphine preoperatively as for most patient's pain can be effectively treated
  - Risk of a patient using illicit drugs during preoperative period outweighs the benefit
  - Data suggest continuation is preferred even in high buprenorphine requirements
  - Tapering:
    - Lack of consensus
    - Experts suggest tapering over several days if buprenorphine doses >16 mg/day to 12-16 mg/day if severely painful surgery expected
    - Risk/benefit conversation taking into account relapse risk

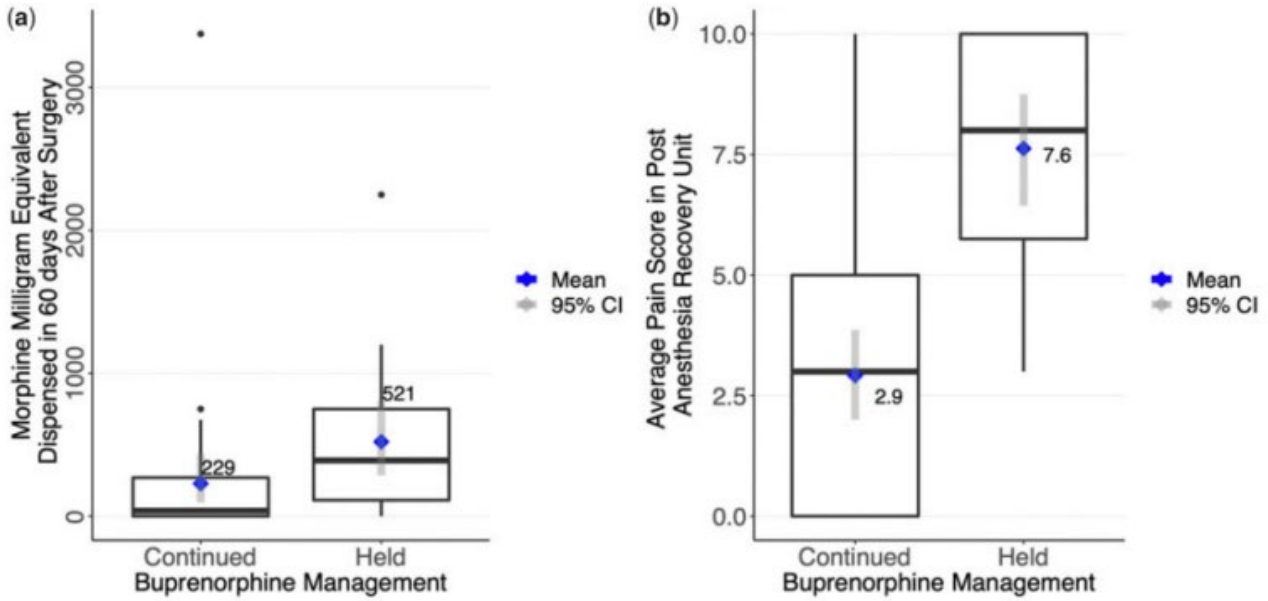
Quaye A, et al. Pain Med. 2019;20(7):1395
Lembke A, et al. Pain Med. 2019;20(3):425

Buprenorphine Perioperative Management (2020)

- Retrospective observational study, post guideline implementation
  - Hospital guideline: Continue buprenorphine, taper to 16 mg if home dose >16 mg
- Population
  - 55 patients undergoing elective major surgery
    - 50% orthopedic, 20% abdominal, 10% cardiothoracic
- Intervention
  - 38 followed guideline and continued
  - 17 held prior to surgery
- No difference in median home buprenorphine dose or baseline characteristics

Quaye A, et al. Pain Med. 2020 Sep 1;21(9):1955-1960

Buprenorphine Perioperative Management (2020)



- Results
  - Significant increase in MME dispensed at 60 days after surgery in buprenorphine held group
  - Significant increase in pain scores
  - Significant increase in opioid prescriptions filled
- Continuing buprenorphine through surgery is safe and effective

Quaye A, et al. Pain Med. 2020 Sep 1;21(9):1955-1960

Buprenorphine Postoperative Management

- Immediate postoperative
  - Pain treatment stratified based on severity
    - Mild
      - Continue home buprenorphine dosing
      - Avoid opioids if possible, otherwise short acting
    - Moderate
      - Home buprenorphine dosing, **consider** dividing to Q8 to maximize pain control
      - Add opioids as necessary, keeping in mind higher requirements most likely needed
    - Severe
      - Home buprenorphine, **suggest** dividing to Q8
      - Opioids as needed, keeping in mind higher requirements needed

Kohan L, et al. Reg Anesth Pain Med. 2021;46(10):840

BWH Perioperative Buprenorphine Protocol

Anticipated postoperative opioid requirement	Before surgery	On day of surgery and throughout hospital stay	Preparing for discharge
Moderate to High Opioid Requirements	IF HOME DOSE > 16 MG • Consider tapering so that on the day before surgery, total buprenorphine dose is 16 mg daily • May consider continuing home dose if reliable continuous regional anesthesia techniques are available or based on patient and clinician preference	• Consider decreasing to buprenorphine 8 mg per day on day of surgery (preferably 4 mg BID vs. 8 mg daily) • Anticipate need for higher opioid agonist dose requirement, similar to opioid tolerant patients maintained on methadone • Use additional opioid agonists as needed	• Provide a post-discharge taper plan for full agonist opioids • Ideally, increase back to buprenorphine home dose at time of discharge • Transition care back to patient's outpatient buprenorphine prescriber for ongoing care with plan to increase back to original home buprenorphine dose
	IF HOME DOSE $\leq$ 16 MG: consider continuing home dose if reliable continuous regional anesthesia techniques are available or based on patient and clinician preference		
Low Opioid Requirements	Continue home regimen (do not discontinue prior to surgery and continue home dose throughout the perioperative period)		

Methadone Peri-operative Management

- Methadone should be continued preoperatively and postoperatively minimizing chance of missed doses
- Patients receiving methadone outpatient likely will need higher doses of opioids than opioid naïve patients
- Non-opioid analgesic infusions such as ketamine and lidocaine have shown great benefit in these patient populations
- Patients receiving methadone daily dosing for OUD, consider dividing dose to Q8 or Q12 to maximize the duration of pain coverage

Taveros MC, et al. BMJ Support Palliat Care. 2017;7(4):38
Faculty of Pain Medicine of the Royal College of Anaesthetists
Chou R, et al. J Pain 2016;17:131-57.

Patient Case SB

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  - Opioid use disorder (On buprenorphine 16 mg QD)
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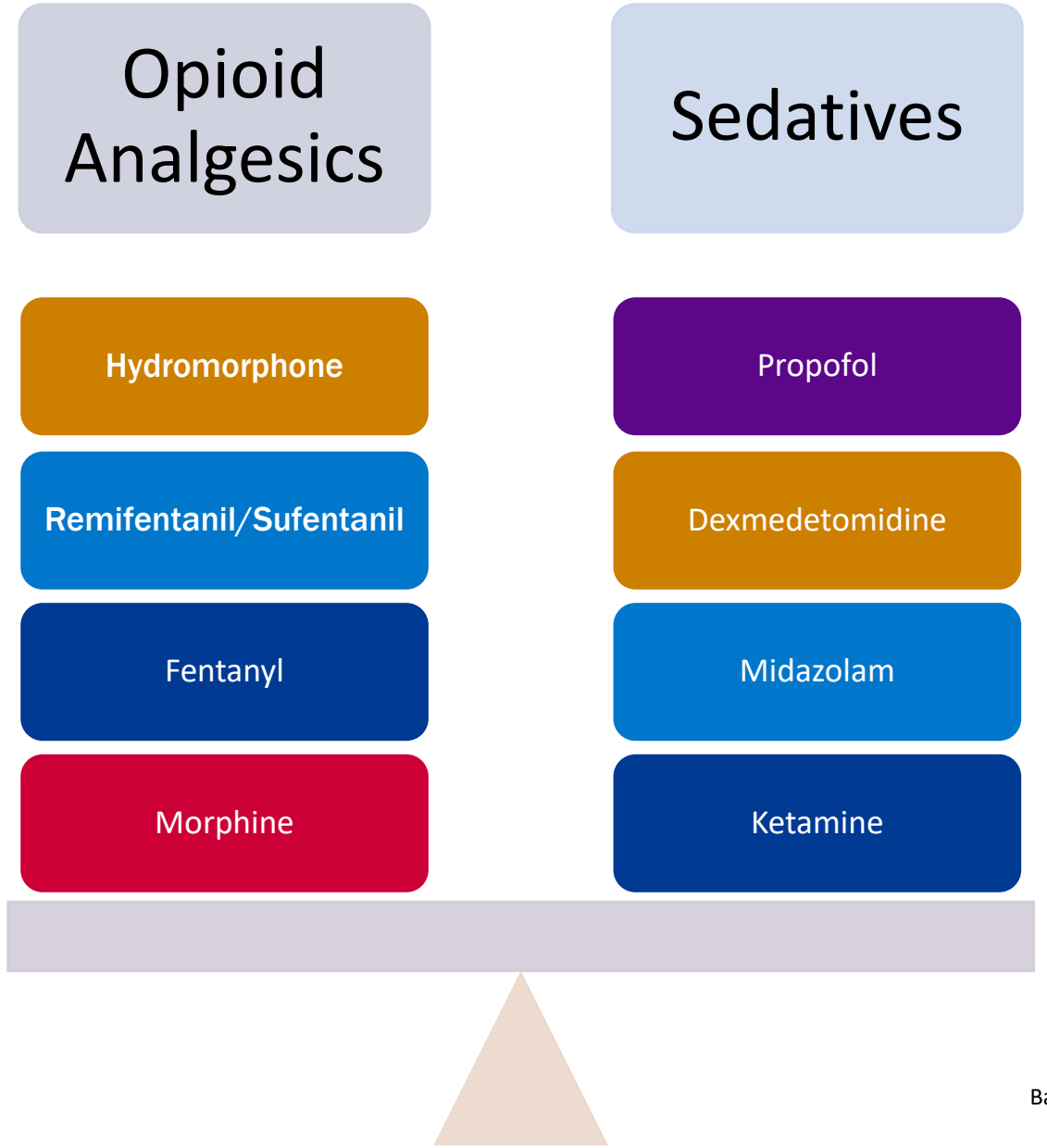
Pharmacotherapy Options



Baker SN, et al. *J Pharm Pract*. 2011;24(2):189-195.

Sedatives

Dexmedetomidine

Midazolam

Ketamine

Propofol

“Ketofol”

Preprocedure Benzodiazepines

- Recovery reactions in adults relative to pediatrics who receive ketamine
- Trials have found that midazolam pretreatment (0.03 mg/kg IV) significantly reduced the incidence of recovery agitation by 17% (number needed to benefit = 6)
  - Study does not characterize the nature or severity of these reactions
  - Unclear how many of the events were clinically important
- According to ACEP, midazolam prophylaxis is reasonable but nonmandatory option for adults

Kern J, et al. *Emerg Med Pract*. 2022;24(6):1-24.
Sener S, et al. *Ann Emerg Med.* 2011;57:109-114.e2.

Midazolam

Benzodiazepine

Initial Dose

- Adult: 0.05-0.1 mg/kg IV
- Pediatric: 0.025-0.1 mg/kg IV

Titration: initial dose every 3-5 min

Pharmacokinetics

- Onset: 1-3 min
- Duration: 30-80 min

Adverse Effects

- Respiratory depression
- Hypotension
- Bradycardia

Pearls

- Short duration of action limits makes this optimal for most procedures
- Rarely used as first-line
- Midazolam as a sole agent or in combination with opioids carries the highest risk of apnea

Baker SN, et al. *J Pharm Pract*. 2011;24(2): 189-195.
Bellolio MF, et al. *BMJ Open.* 2016;6(6):e011384.
Bellolio MF, et al. *Acad Emerg Med.* 2016;23(2):119-134.

Benzodiazepine Pearls

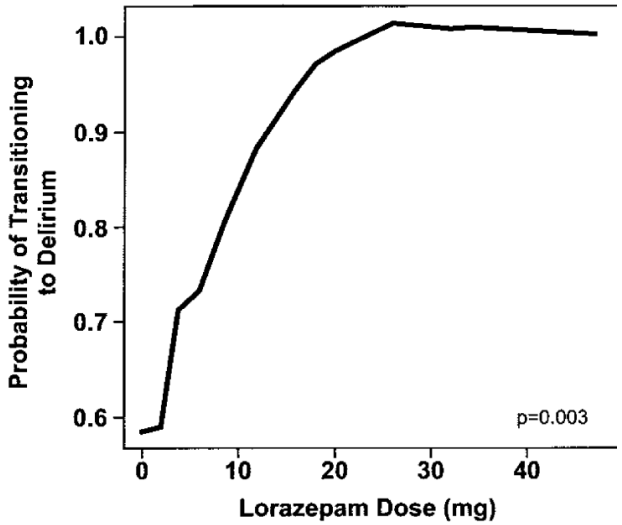
Drugs

- Midazolam (fast onset)
  - Metabolite accumulation
- Lorazepam (slower onset, longer duration)
  - Vehicle- propylene glycol
- Diazepam (fast onset and long duration)
  - Long acting
- Metabolites accumulation

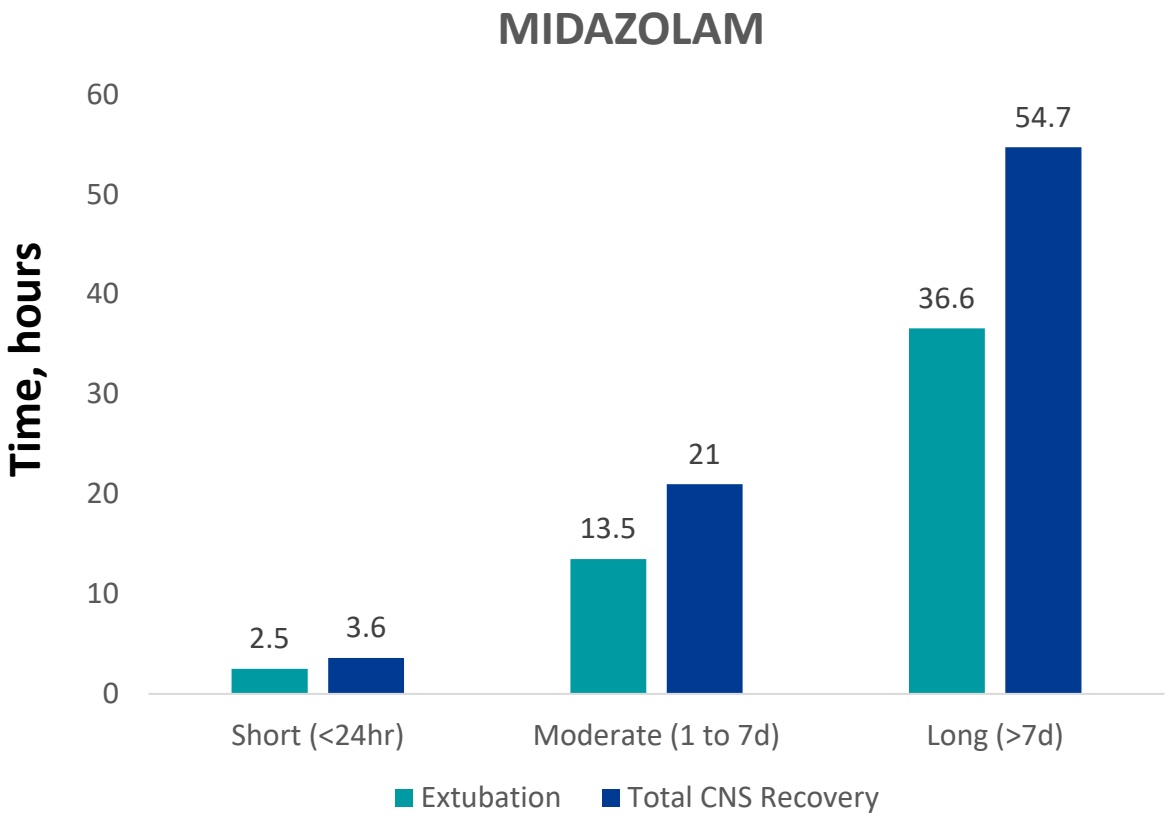
Potential Roles

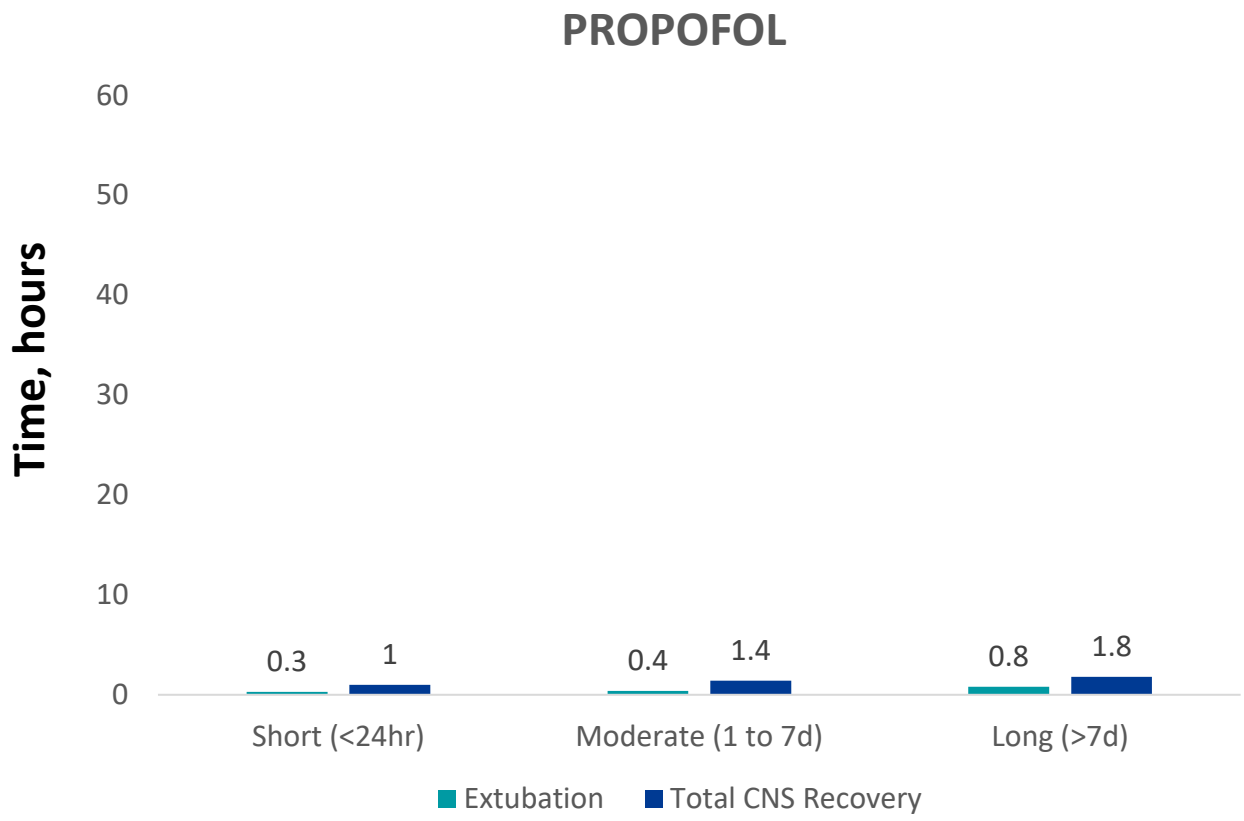
- Deep sedation and when amnesia is the goal (NMB)
- Sedation in the setting of hemodynamic instability
- Ethanol withdrawal (plus or minus other agents)
- Anxiety/agitation with PRN bolus
- Neuro indications
  - Seizures
  - ICP

Dose & Delirium Association



Propofol vs. Midazolam in short-, medium-, and long-term sedation





Carrasco G, Molina R, Costa J, Soler JM, Cabré L. Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients. A cost-benefit analysis. Chest. 1993 Feb;103(2):557-64

Propofol

Sedative hypnotic

Initial Dose

- Adult: 0.5-1 mg/kg IV
- Pediatric:
  - ≤3 yr: 2 mg/kg IV
  - Children and teenagers: 1.5 mg/kg IV

Titration

- Adult: 0.25-0.5 mg/kg every 1-3 min
- Pediatric: 0.5-1 mg/kg every 1-3 min

Pharmacokinetics

- Onset: < 1 min
- Duration: 5-10 min

Adverse Effects

- Pain at injection site
- Hypotension and bradycardia
- Respiratory depression and hypoxia (1%-12%)

Pearls

- Most commonly used agent
- Administer in same line as fluids to decrease injection site pain

Baker SN, et al. *J Pharm Pract*. 2011;24(2): 189-195.
Miller KA, et al. *Ann Emerg Med*. 2019;73(5):470-480.

Propofol

Pearls

White magic

- Short duration
- Fast onset

Nitroprusside of sedation

- Titratable

Reasonable option for sedating the renal patient

- Minimal accumulation

Any downside?

Adverse Effects

Bradycardia

Hypotension

Increased lipids

- Pancreatitis

Infection

- Suppress T-cell function
- Culture media for bacteria

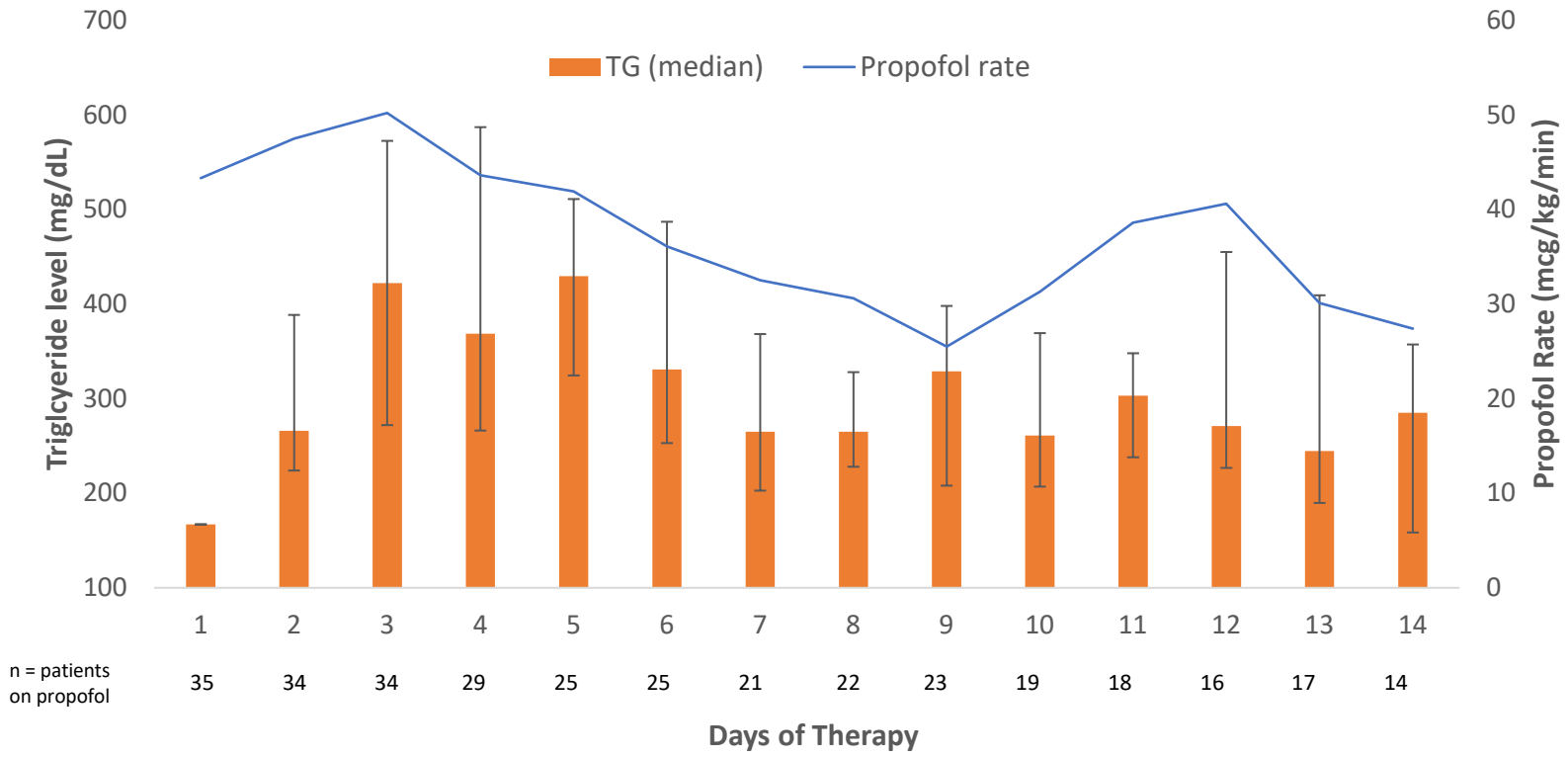
Propofol Infusion Syndrome

- Progressive myocardial failure
- Dysrhythmia
- Rhabdomyolysis with cardiac involvement
- Metabolic acidosis
- Hyperkalemia

Roberts RJ, Szumita PM, et al.. Crit Care. 2009;13(5):R169.
Kovacevic MP, Dube KM, Lupi KE, Szumita PM, DeGrado JR. Crit Care Explor. 2021 Jan 11;3(1):e0330.
Corrado MJ, Kovacevic MP, Dube KM, Lupi KE, Szumita PM, DeGrado JR. Crit Care Explor. 2020 Nov 30;2(12):e0282.

Dube KM, Szumita PM, Rocchio MA, Lee PS, Anger KE. Am J Ther. 2019 Jan/Feb;26(1):e103-e109.

Propofol and Triglycerides



Kovacevic MP, Dube KM, Lupi KE, Szumita PM, DeGrado JR. Crit Care Explor. 2021 Jan 11;3(1):e0330.
Corrado MJ, Kovacevic MP, Dube KM, Lupi KE, Szumita PM, DeGrado JR. Crit Care Explor. 2020 Nov 30;2(12):e0282.
Dube KM, Szumita PM, Rocchio MA, Lee PS, Anger KE. Am J Ther. 2019 Jan/Feb;26(1):e103-e109.

Target-Controlled Propofol Infusion

Bolus administration of propofol is commonly associated with side effects, including airway compromise and cardiovascular depression

- Target-controlled IV infusion of propofol may be a safer alternative
- Theoretically, it provides a more consistent drug concentration within the therapeutic range in brain tissues compared with intermittent IV boluses

Systematic review found fewer respiratory and cardiovascular adverse outcomes in three of seven studies

Burton FM, et al. *Eur J Emerg Med.* 2020;27(4):253-259.

Analgosedation – replacing benzodiazepine infusions (largely) with opioid infusions

- Patients: Typically, short duration of mechanical ventilation
- Intervention: Typically, remifentanil infusion +/- propofol infusion
- Comparator: Typically, Midazolam infusion +/- opioid infusion
- Outcomes: More likely to be achieve light sedation and faster time to extubation in the opioid group

- Newer feasibility study supports the feasibility vs. more contemporary comparator regimens
  - Need outcomes data to support widespread use of this strategy

- However, what about no sedation strategies?
  - Is that analgosedation?
  - Is it feasible?
  - Is it beneficial?

Breen D, et al. *Crit Care* 2005; 9:R200–R210.
Karabinis A, et al. *Crit Care* 2004; 8:R268–R280.
Rozendaal FW, et al. *Intensive Care Med* 2009; 35:291–298.
Muller L, et al. *Ann Fr Anesth Reanim* 2008; 27:481.e1–481.e8.
Bugedo G, et al. *Rev Bras Ter Intensiva.* 2013; 25:188–196.
Tanios M, et al. *J Crit Care*. 2019 Oct;53:107-113.

Patient Case

You are preparing to perform procedural sedation on the following patient:

- 82 year-old, 80-kg male for a short painful procedure
- PMH: hypertension
- Vital signs: blood pressure 153/95 mm Hg, heart rate 82 bpm, respiratory rate 12 breaths/min

You would like to use propofol bolus and fentanyl bolus for the procedure. Based on what you know about the patient, what dose adjustment is recommended for propofol?

Age Limits: Do They Exist?

Pediatric

Augmented drug metabolism or clearance

Volume of distribution considerations

Elderly

Perceived increased risk for undergoing PSAA

Suggest evaluate for increased sensitivity to sedating medications

- Review medication history
- Review past medical history

Kern J, et al. Emerg Med Pract. 2022;24(6):1-24.

Miller MA, et al. *Emerg Med Clin North Am.* 2005;23(2):551-572.

Green SM, et al. *Ann Emerg Med*. 2011;57(5):449-461.

Miller KA, et al. *Ann Emerg Med*. 2019;73(5):470-480.

Age Matters

≥65 yr compared with patients 18-40 yr

- Required less weight-based propofol for induction (p<0.001)
- Required less weight-based propofol for the entire procedure (p<0.001)
- Patient age was negatively predictive of:
  - Induction dose (coefficient -0.011, 95% CI, -0.017 to -0.005)
  - Total dose (coefficient -0.014, 95% CI, -0.022 to -0.007)

≥65 yr compared with patients 18-64 yr required:

- Less total weight-based propofol requirements (p=0.024)
- Less total propofol dose for sedation (p=0.007)
- Fewer repeat doses during the procedure (p=0.043)

Patanwala AE, et al. *J Emerg Med.* 2013;44(4):823-828.
Wells ME, et al. *Adv Emerg Nurs J.* 2021;43(4):255-264.

Additional Considerations

- Asthma or upper respiratory tract infections
- Cardiac disease
- Obesity

Tolerance to opioids or sedatives
- Chronic home therapies
- Substance use disorder

Presently intoxicated

Volume status

Kern J, et al. *Emerg Med Pract*. 2022;24(6):1-24.
Miller MA, et al. *Emerg Med Clin North Am*. 2005;23(2):551-572.
Green SM, et al. *Ann Emerg Med*. 2011;57(5):449-461.
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Based on what you know about the patient, what dose adjustment regarding is recommended for propofol?

Based on the patient’s age, a dose reduction is recommended

Weight Matters

Clinical Practice Guideline for Emergency Department Procedural Sedation with Propofol: 2018 Update

- *"Because propofol should be dosed on lean body mass, obese patients require lower total body-weight-dosing"*

A study of 1976 patients 2-21 yr who underwent sedation with propofol:

- Those who had a BMI >85% compared with those who were considered normal weight used less propofol ($p<0.01$)
- Those who had a higher BMI had a higher proportion of adverse events compared with those who were normal weight ($p<0.001$)

Miller KA, et al. *Ann Emerg Med*. 2019;73(5):470-480.

Rogerson CM, et al. *Hosp Pediatr*. 2017;7(9):542-546.

Etomidate

Nonbarbiturate, sedative hypnotic

Initial Dose

- Adult: 0.1-0.15 mg/kg IV
- Pediatric: 0.1 mg/kg IV

Titration: 1-2 mg every 10 min

Pharmacokinetics

- Onset: ~1 min
- Duration: 5-15 min

Adverse Effects

- Emergence nausea and vomiting
- Myoclonus
- Adrenal suppression

Pearls

- Ideal agent for cardioversion
- Unclear whether combination with analgesics provides any benefit

Baker SN, et al. *J Pharm Pract*. 2011;24(2):189-195.

Ketamine

Inhibits N-methyl-D-aspartate receptor
- Also binds to opiate, norepinephrine, serotonin, and muscarinic receptors

Initial Dose
- Adult: 1-2 mg/kg IV
- Pediatric: 1.5-2 mg/kg IV

Titration: 0.5-0.1 mg/kg every 10 min

Pharmacokinetics
- Onset: 30 sec
- Duration: 10-20 min

Adverse Effects
- Emergence delirium
- Laryngospasm
- Hypersalivation
- Increased intraocular pressure

Pearls
- Very commonly used agent for all procedures
- Does not always exhibit a dose-response relationship
- Peak pain reduction scores similar to IV morphine

Strayer RJ, et al. *Am J Emerg Med*. 2008;26:985-1028.; Miner JR, et al. *Acad Emerg Med*. 2010;17:604-611.; Baker SN, et al. *J Pharm Pract*. 2011;24(2): 189-195.

Clinical Practice Guideline for ED Ketamine Dissociative Sedation

"The literature is strongly supportive of the safety and efficacy of ED dissociative sedation for a variety of brief or emotionally disturbing procedures in both children and adults (e.g., fracture reduction, laceration repair, abscess drainage)."

Absolute contraindications:

- Age younger than 3 months
  - Higher risk of airway complications, including apnea and laryngospasm
- Known or suspected schizophrenia, even if currently stable or controlled with medications
  - Can exacerbate condition

Green SM, et al. *Ann Emerg Med*. 2011;57(5):449-461.

Subdissociative Ketamine

- Doses < 0.5 mg/kg IV or < 3 mg/kg IM
- Produces analgesia, disorientation, and obtundation rather than dissociation
- Does the procedure require dissociation or can satisfactory conditions be achieved with adjunctive local anesthesia?
- Further research is needed to identify which indications are appropriate as well as to quantify the relative advantages and disadvantages of each dosing strategy

McGlone RG, et al. *Emerg Med J.* 2004;21:290- 295.
Green SM, et al. *Ann Emerg Med*. 2011;57(5):449-461.

Teamwork Makes the Dream Work: Ketamine ED Guidance Example

APPENDIX A: Implementation Specifics

Indication	Adult Dosing	Pediatric Dosing	How to order in Epic?
Procedural Sedation (monotherapy)	IV: Administer incremental doses of 0.5-1 mg/kg slow push over 1-2 minutes • Typical total dose of 1-5 mg/kg. IM: 4-5 mg/kg; repeat half to full dose after 5-10 mins for insufficient conditions	IV: Administer incremental doses of 0.5-1 mg/kg slow IV push over 1-2 minutes. • Typical total dose of 1-5 mg/kg. IM: 4-5 mg/kg; repeat half to full dose after 5-10 mins for insufficient conditions	• Ketamine Injection 10 mg/mL
Procedural Sedation (in combination with propofol)	IV: Administer ketamine in incremental doses of 0.5-1 mg/kg slow push over 1-2 minutes Administer propofol in incremental doses of 0.5-1 mg/kg slow push over 1-2 mins *The addition of ketamine is intended to reduce the total amount of propofol necessary*	IV: Administer ketamine in incremental doses of 0.5-1 mg/kg slow IV push over 1-2 minutes. Administer propofol in incremental doses of 0.5-1 mg/kg slow push over 1-2 mins *The addition of propofol is intended to reduce the total amount of ketamine necessary*	• Ketamine Injection 10 mg/mL • Propofol injection 10 mg/mL

Ketamine example

Side effect Management

Hypersalivation	Atropine	0.01-0.03 mg/kg IV (Adult Max: 0.1-0.3 mg IV)
	Glycopyrrolate	>16 yo: 0.2 mg IV
Emergence Reaction	Midazolam	0.025-0.1 mg/kg IV (Adult Max: 1-2 mg IV) 0.1-0.15 mg/kg IM (Adult Max: 5 mg IM)

Notes:
In adults, pretreatment with midazolam (versed) 2-4 mg can reduce the incidence of psychosis by >50%. The incidence of recovery agitation in patients receiving intravenous ketamine with or without midazolam was 7% and 22%, respectively (NNT 6). This does not appear to result in any increase in respiratory or cardiovascular effect or impair recovery time.

The pediatric literature does not advocate for the use of midazolam as pre-treatment to the same level as it is supported in the adult literature.

Ketamine-Propofol - “Ketofol”

Premade mixture of ketamine and propofol in the same syringe

Combination of the two components provides complementary effects and overcomes shortcomings of each agent

Ratio

- 1:1 mixture of ketamine and propofol most common
- 1:3 and 1:4 are described

Dosed with the same mL/kg dosing as single-agent propofol

- Repeat doses of single-agent propofol can be used after the combination, as needed

Recovery time typically is prolonged compared with propofol alone

- 8 min vs. 6 min

Propofol

- Hypotension
- Bradycardia
- Antiemetic
- No analgesic properties

Ketamine

- Hypertension
- Tachycardia
- Emesis
- Analgesia

Miller KA, et al. *Ann Emerg Med*. 2019;73(5):470-480.

Need more robust data on the following (and more)

- Will certain patient populations benefit from different strategies?
  - What medication for what type of patient?
- Multimodal pain management outcomes trials
  - Combination of therapies
- What outcomes in the PICO questions should be prioritized?
- Will multimodal pain management lead to less chronic pain?
- Data/recommendations for regional/neuraxial techniques?

Key Takeaways

- Many pharmacological options for the management of PSAA in dental surgery
- Dexmedetomidine is an emerging medication for use in dental surgery
  - Efficacy must be balanced with preferred outcome, possible adverse effects, and cost of care
  - Tremendous heterogeneity in PSAA literature
    - IV (bolus, no bolus, CI, no CI, high dose, low dose, timing)
    - IN
    - Local
- Opioids have vastly different pharmacokinetics and pharmacodynamics
  - Not one size fits all
- Medication selection and dosing for PSAA is patient defendant

Additional slides to use PRN

Dexmedetomidine Role

Focus on 2 major things

- Outcome data
- Study design

The next few slides do NOT mean I'm pro benzo… I am NOT pro benzo…
Just thought provoking

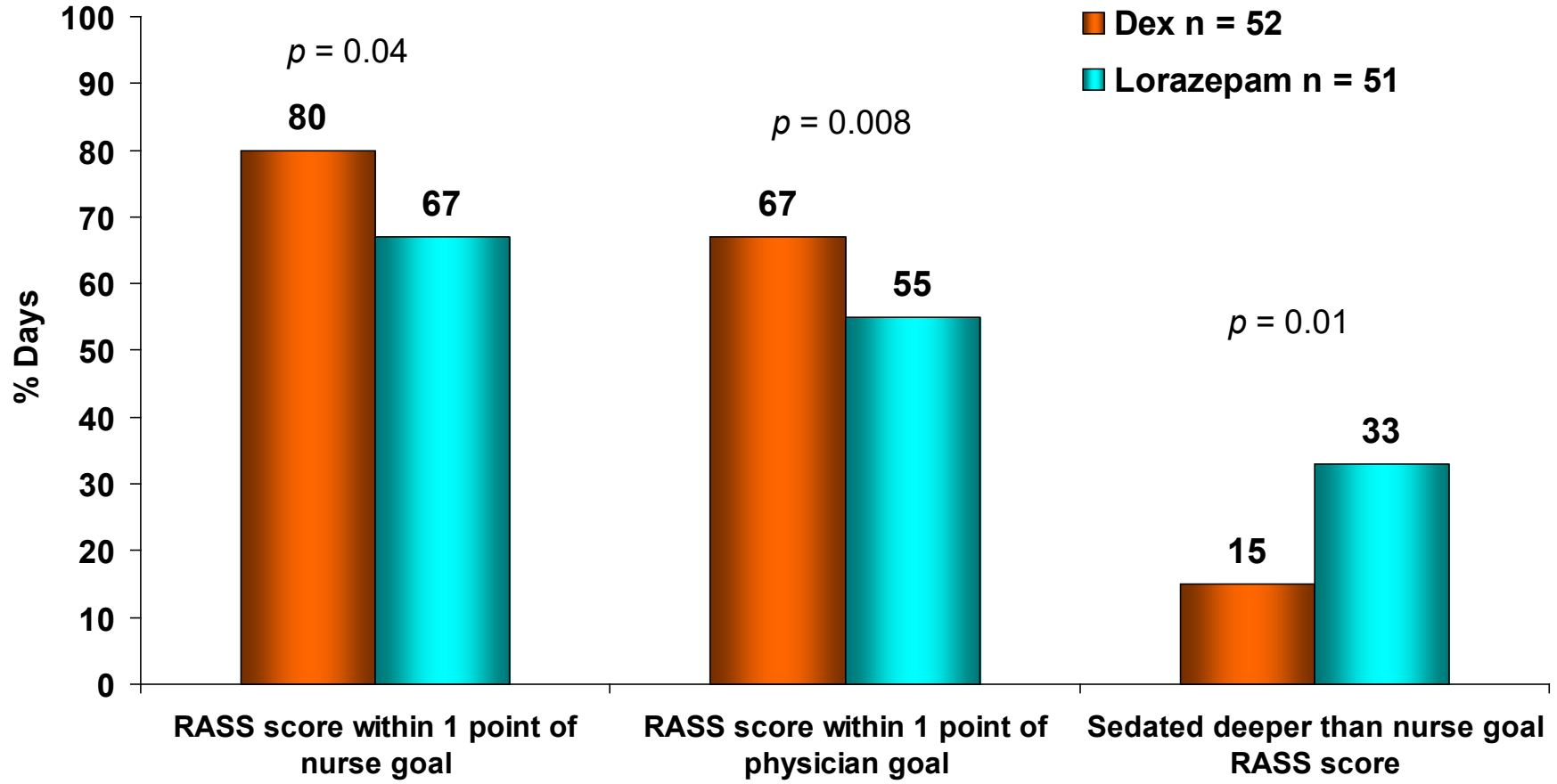
I'm not a vigilante against dexmedetomidine….

Goals of care: General Principals we can all agree on

Minimize mortality
Minimize ICU LOS
Minimize hospital LOS
Facilitate MV
Minimize length of MV
Minimize delirium
Minimize agitation
M
M
M

Question – Is dexmedetomidine better compared to optimized protocolized therapy?

Dexmedetomidine provides lighter sedation than lorazepam: MENDS



Two center, double-blind, trial in adult ICU patients randomizing patients to dexmedetomidine (0.15 µg/kg/hr to 1.5 µg/kg/hr) or lorazepam (1mg/hr to 10 mg/hr) infusions titrated to local sedation goal

K

Pandharipande PP, et al. *JAMA.* 2007;298:2644-2653.

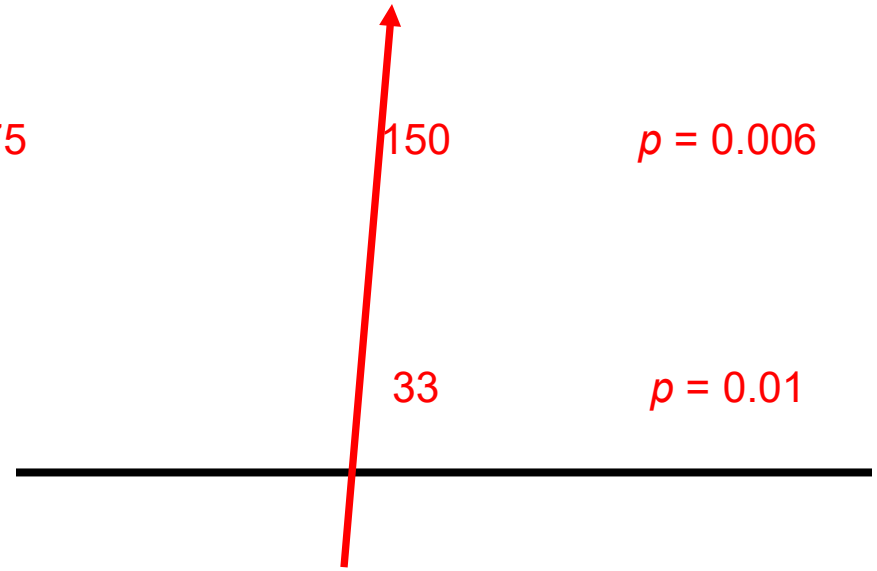
Dexmedetomidine vs Lorazepam: *MENDS TRIAL;*

	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*p* Value
Delirium, No(%)	41 (79)	42 (82)	*p* = 0.65
Duration of Delirium, days	2.5 (1-5)	4 (1-5)	*p* = 0.71
Ventilator-free, days	22 (0-24)	18 (0-23)	*p* = 0.22
ICU LOS, days	7.5 (5-19)	9 (6-15)	*p* = 0.92
28 day all-cause mortality, No(%)	9 (17)	14 (27)	*p* = 0.18
Hospital LOS	not reported		

Pandharipande PP, et al. *JAMA*. 2007 Dec 12; 298(22) :2644-53.

Dexmedetomidine vs Lorazepam: *MENDS TRIAL; Key Critiques*

	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*p* Value
Lorazepam mg/hr (mean)		3	
Fentanyl mcg/day (mean)	575	150	*p* = 0.006
Sedated deeper RASS score, Da		33	*p* = 0.01



3 mg/hr yikes!

A bottle of tequila or a glass of wine?

Pandharipande PP, et al. *JAMA*. 2007 Dec 12; 298(22) :2644-53.

JAMA 2012 PRODEX-MIDEX

CARING FOR THE CRITICALLY ILL PATIENT

Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation

Two Randomized Controlled Trials

Stephan M. Jakob, MD, PhD
Esko Ruokonen, MD, PhD
R. Michael Grounds, MBBS, FRCA, MD
Toni Sarapohja, MSc
Chris Garratt, MBChB, FFPM
Stuart J. Pocock, PhD
J. Raymond Bratty, BSc, MB, BCh, FFPM
Jukka Takala, MD, PhD
for the Dexmedetomidine for Long-Term Sedation Investigators

Context Long-term sedation with midazolam or propofol in intensive care units (ICUs) has serious adverse effects. Dexmedetomidine, an α_2-agonist available for ICU sedation, may reduce the duration of mechanical ventilation and enhance patient comfort.

Objective To determine the efficacy of dexmedetomidine vs midazolam or propofol (preferred usual care) in maintaining sedation; reducing duration of mechanical ventilation; and improving patients' interaction with nursing care.

Design, Setting, and Patients Two phase 3 multicenter, randomized, double-blind trials carried out from 2007 to 2010. The MIDEX trial compared midazolam with dexmedetomidine in ICUs of 44 centers in 9 European countries; the PRODEX trial compared propofol with dexmedetomidine in 31 centers in 6 European countries and 2 centers in Russia. Included were adult ICU patients receiving mechanical ventilation who needed light to moderate sedation for more than 24 hours (midazolam, n=251, vs dexmedetomidine, n=249; propofol, n=247, vs dexmedetomidine, n=251).

EDATION IN INTENSIVE CARE PA-

Jakob SM, et al. JAMA. 2012 Mar 21;307(11):1151-60.

PRODEX MIDEX; JAMA 2012

Midaz vs dex

- Primary outcome (no difference – time in sedation score)
- Dex less time on MV
- No differnence
  - Mortality
  - Length of stay
- Not assessed delirium

Propofol vs dex

- No difference
  - Primary outcome of time in sedation score
  - Time of MV
  - LOS
  - Mortality
- Dex arm more likely to answer to VAS

Jakob SM, et al. JAMA. 2012 Mar 21;307(11):1151-60.

Dexmedetomidine vs Midazolam: *MIDEX; Key Critiques JAMA 2012*

Excluded 7800 pt to get 501… selection bias
Pain 1st
- No

Delirium assessment
- No

RASS awake and alert
- 0 to -3
  - (4 to -5)

Dose equivalence
- Six dose levels of each study drug covered the full dose range
  - dexmedetomidine, 0.2-1.4 μg/kg per hour;
  - midazolam, 0.03-0.2 mg/kg per hour;
  - propofol, 0.3-4.0 mg/kg per hour)

Blinded… SEDCOM all over again…
Minimum rescue data
No antipych data

Jakob SM, et al. JAMA. 2012 Mar 21;307(11):1151-60.

Dexmedetomidine vs Midazolam: *MIDEX; Key Critiques JAMA 2012*

	Dexmedetomidine (n = 244)	Midazolam (n = 122)	*p* Value
Time in target sedation range*	60.7	56.6	$p = 0.15$
Median Dose	0.83 mg/kg/hr	0.062 mg/kg/hr	

*Value expressed as mean %

A bottle of tequila or a glass of wine?

MORE than SEDCOM…. 80 KG is about 5 mg/hr

Jakob SM, et al. JAMA. 2012 Mar 21;307(11):1151-60.

Take home from PRODEX MIDEX

Propofol and dex essentially equivalent

MIDEX

- SEDCOM all over again, so however you felt about SEDCOM you will probably feel the same about MIDEX (minus the delirum data)

Jakob SM, et al. JAMA. 2012 Mar 21;307(11):1151-60.

Dex Stew

Research Report

Annals of Pharmacotherapy
47(11) 1400–1405

DOI: 10.1177/1060028013504086
aop.sagepub.com
SAGE

Implementation of a Dexmedetomidine Stewardship Program at a Tertiary Academic Medical Center

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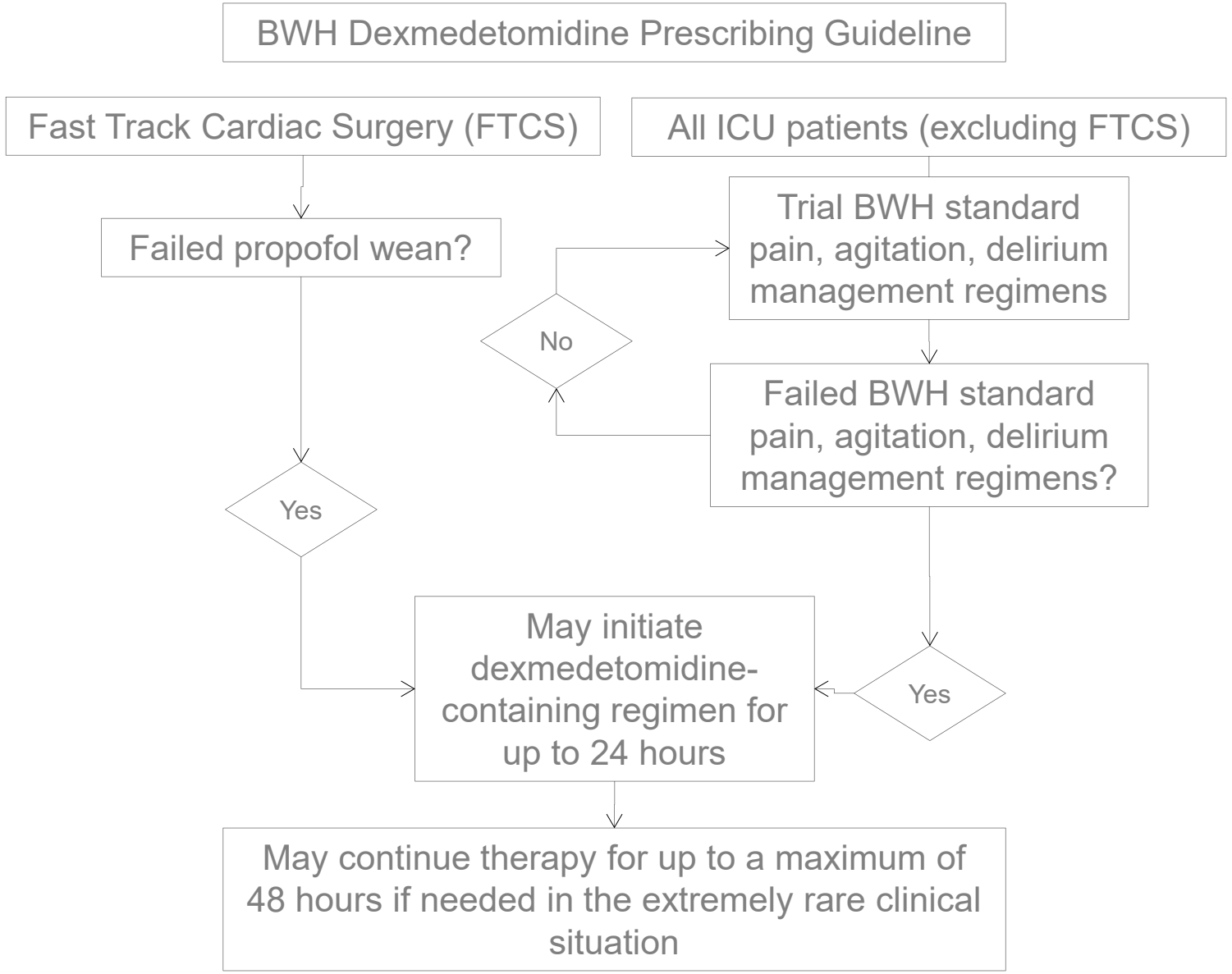
Abstract

Background: Brigham and Women's Hospital implemented a dexmedetomidine stewardship program in October 2010 beginning with an institution-specific prescribing guideline. To ensure continued adherence to the prescribing guideline, a pharmacist-driven quality assurance program was implemented in November 2011. **Objective:** The primary objective of this study is to describe the role and impact of a dexmedetomidine stewardship program on dexmedetomidine use at a tertiary academic medical center. **Methods:** This is a prospective descriptive analysis of a dexmedetomidine stewardship program. Dexmedetomidine stewardship data were collected prospectively from January 2012 through June 2012, in all intensive care units (ICUs) at a single academic medical center. Adult patients (>18 years old) receiving dexmedetomidine therapy continuously for sedation and in the ICU were included in the analysis. **Results:** A total of 99 patients were identified during the study time frame, during which 71 (71.7%) were identified as compliant with the institutional guideline. The total number of patients receiving dexmedetomidine for greater than 24 hours was 13 (13.1%), of whom 10 (76.9%)

Blum RM, Stevens CA, Carter DM, et al. Ann Pharmacother. 2013 Nov;47(11):1400-5.

BWH Prescribing Guideline – Simplified



Blum RM, Stevens CA, Carter DM, et al. Ann Pharmacother. 2013 Nov;47(11):1400-5.

Utilization - 6 month Snapshot

Variable	Total N=99
Indication, n (%)	
Extubation facilitation	39 (39.4)
Fast track cardiac surgery, extubation	33 (33.3)
Non-intubated/agitation	17 (17.2)
Other	10 (10.1)
Identified as compliant to guideline	71 (71.7)
Service, n (%)	
Cardiothoracic Surgery ICU	64 (64.6)
Thoracic Surgery ICU	12 (12.1)
Burn/Trauma and Surgical ICU	16 (16.2)
Medical ICU	5 (5.1)
Neuroscience ICU	2 (2)

Blum RM, Stevens CA, Carter DM, et al. Ann Pharmacother. 2013 Nov;47(11):1400-5.

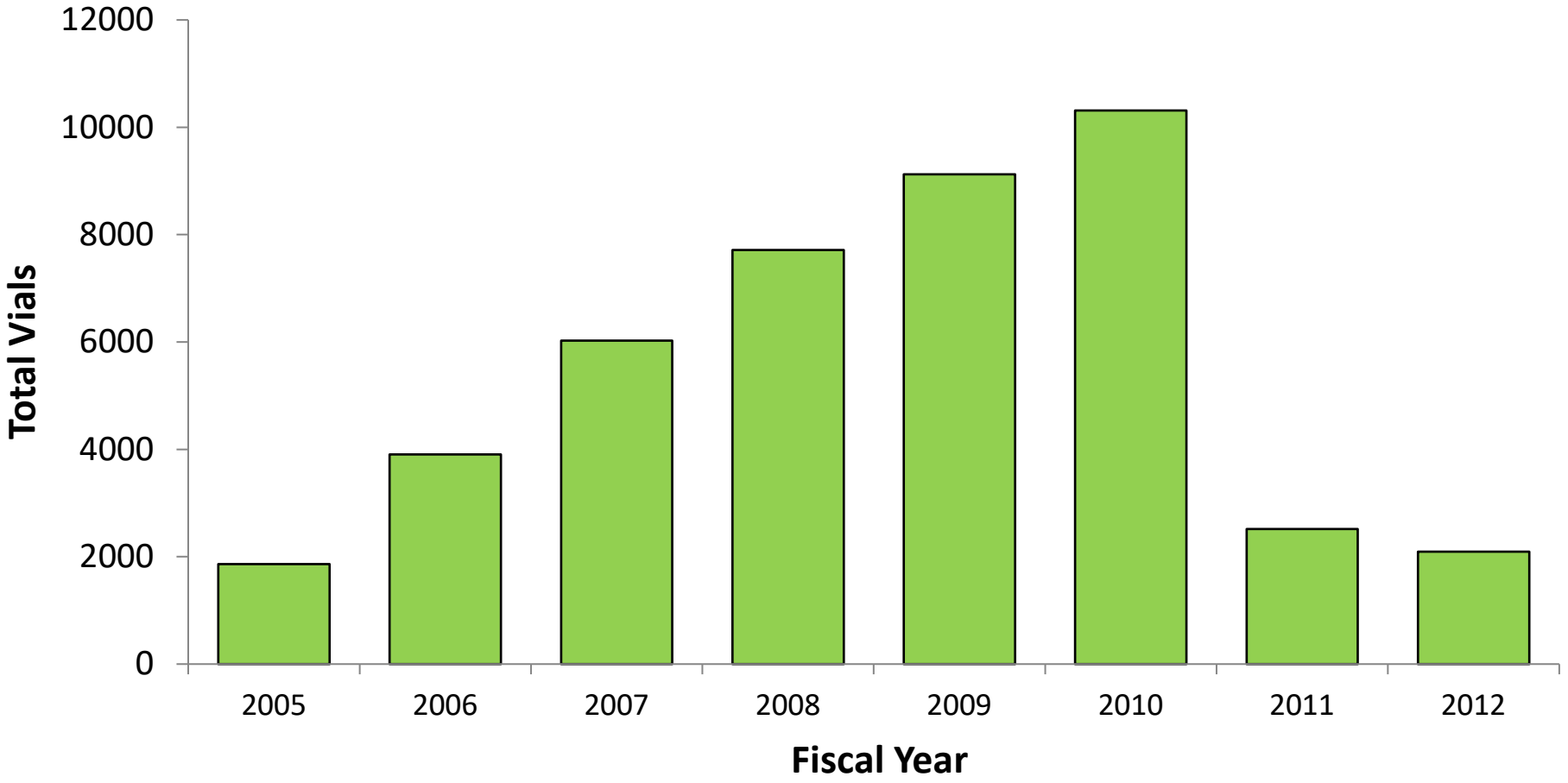
6 Month Snapshot of Utilization

Variable	Total N=99
Dexmedetomidine <24H, n (%)	86 (86.9)
Dexmedetomidine 24H to 48H, n (%)	12 (12.1)
Dexmedetomidine >48H, n (%)	1 (1)
Number of targeted interventions, n (%)	15 (15.2)
Infusion	
Total duration evaluated (H)	1564
Median duration (H)	12
IQR (H)	10 – 24

H = hours, IQR = interquartile range

Blum RM, Stevens CA, Carter DM, et al. Ann Pharmacother. 2013 Nov;47(11):1400-5.

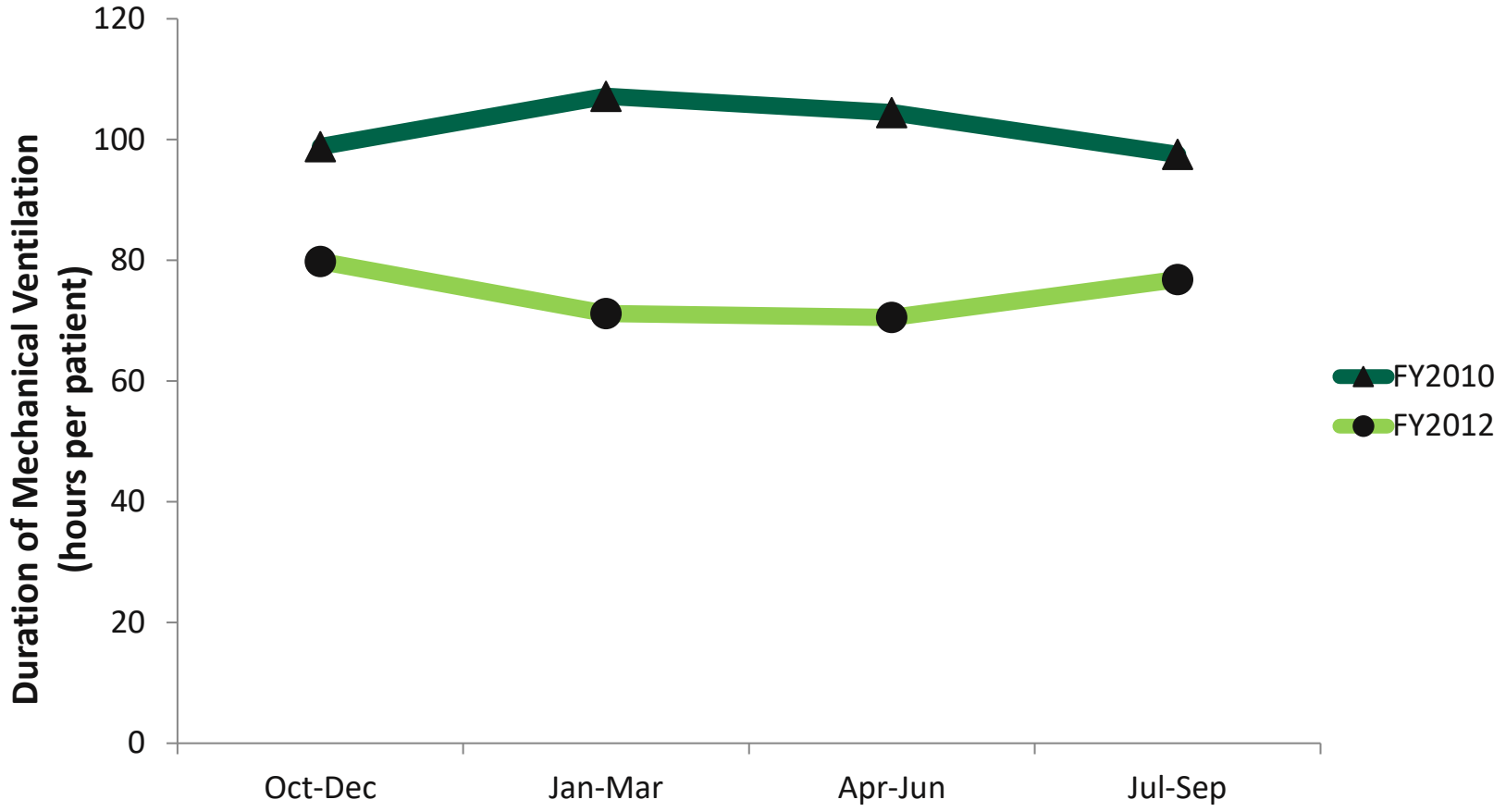
BWH Dexmedetomidine Utilization



FY 13 ~ 2000
Halfway through FY14 ~ projected at about 2500

Blum RM, Stevens CA, Carter DM, et al. Ann Pharmacother. 2013 Nov;47(11):1400-5.

Duration of MV



Blum RM, Stevens CA, Carter DM, et al. Ann Pharmacother. 2013 Nov;47(11):1400-5.

Dexmedetomidine Stewardship Tips

Created/edited policy/guideline with key leaders from all areas with a vested interest
Approved at the highest level of hospital clinical leadership
Not a pharmacy policy - it is a hospital policy or it will not work
Promotion of best practices
Not a policy to limit use; a policy to promte use in the proper hospital approved setting
Continuous daily monitoring of use and feedback to key leaders – both positive and not so positive (I'm happy to help whomever is left with that task)

XYZ Health Center use of dex through 6 month of FY '15 ~ $???

Dexmedetomidine – Intensive Care Medicine Rapid Practice Guideline

P – Invasively mechanically ventilated patients in the ICU
I – Intravenous dexmedetomidine
C – Other forms of sedation
O – mortality, delirium, duration MV, ADEs, ICU LOS

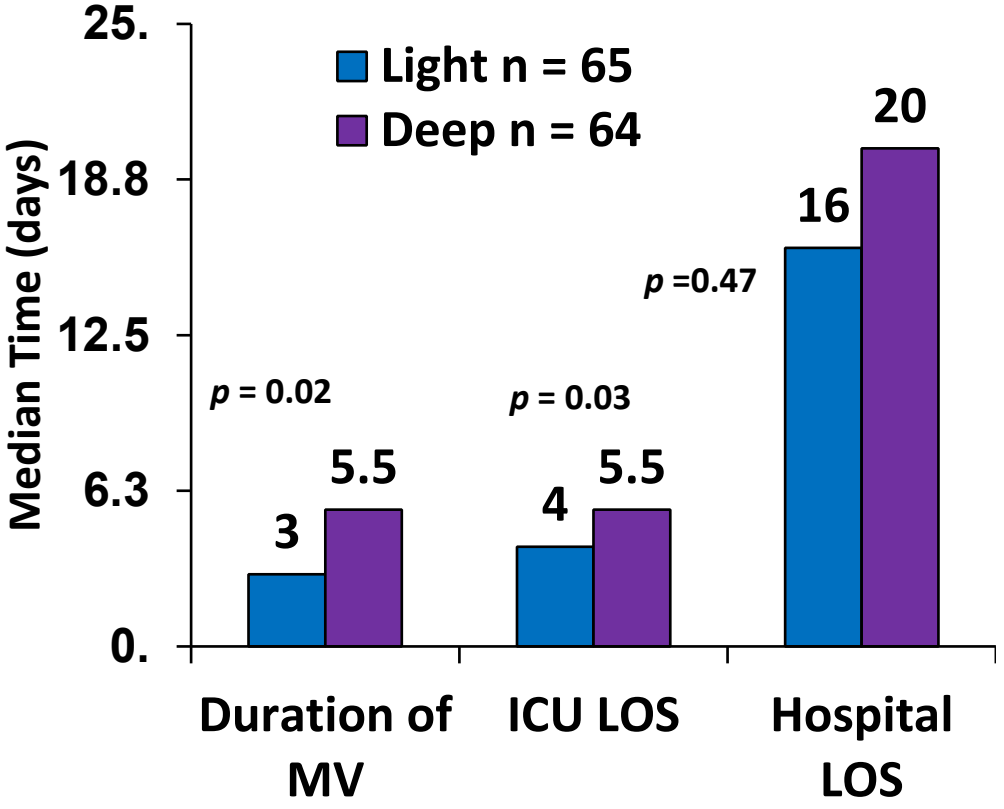
“In invasively mechanically ventilated adult ICU patients, we suggest using dexmedetomidine over other sedative agents, if the desirable effects including a reduction in delirium are valued over the undesirable effects including an increase in hypotension and bradycardia”

Moller MH, et al. Intensive Care Med 2022;48(7):801-810

Dose Minimization Strategies

1. Set a clear goal, and have all involved in the care aware of the goal
2. Assessment, Assessment, Assessment; and discussion of assessment
3. Non-pharm strategies (vent adjustments etc)
4. Awake and alert (RASS 0)
5. Symptom triggered/preemptive bolus only
6. Sedation Holiday
7. Analgosedation or no sedation
8. Patient specific pharmacotherapy
9. Rotation of medication (avoid accumulation)

Light vs. Deep Sedation on Clinical Outcomes and Mental Health after Critical Illness



Significant patient characteristics/metrics/outcomes

	Light	Deep	P value
PTSD score ICU discharge*	52	57	0.39
PTSD score 4wks post ICU*	46	56	0.07

*Data presented as mean

PTSD = Posttraumatic stress disorder

Single center, prospective, open label trial of 137 ICU patients requiring mechanical ventilation randomized to light (Ramsey 1-2) or deep (Ramsey 3-4) sedation at Geneva Hospital Switzerland. Extensive exclusion criteria, removing high risk patients and those with baseline cognitive dysfunction.

Treggiari MM et al. *Crit Care Med*. 2009; 37(9):2527-34.

Opioid Use in the United States

- Prescription Opioids are Misused
- Prescription Opioid Misuse Leads to Heroin Use
- Opioid overdose is a societal issue
- Post ICU:
    - Mean opioid consumptions continuously declined 24 month after ICU stay, but did not return to baseline (pre-ICU)
    - Patients with chronic opioid use, mortality was increased 6-18 months after ICU admission
    - Chronic opioid use after discharge from ICU is complex and multifactorial

https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis#one

von Oelreich E, et al. *Crit Care Med.* 2021 Mar 1;49(3):462-471.

Transitions of Care Considerations in the ICU (and pre transition)

- Multimodal therapy while in the ICU may be beneficial, including reducing the development of tolerance and dependence on opioids while in the ICU
- Weaning of opioids from patients who have required high doses and/or prolonged durations
- Medications initiated during ICU stay are often continued post-ICU
  - Antipsychotics
  - Opioids
  - Sedatives
  - Stress ulcer prophylaxis and many more
- Efforts to align indications for use of medications with the active problem list at transition of care are warranted
  - ICU to the ward
  - Ward to home/rehabilitation facility

Hanidziar D, et al. *Anesth Analg*. 2020 Jul;131(1):e40-e41.

Terry K, et al. *SAGE Open Med*. 2015;3:32050312115621767.

Farrokh S, et al. *J Pharm Pract*. 2017 Jun;30(3):342-346.

Marshall J, et al. *J Crit Care*. 2016 Jun;33:119-24.