KETAMINE: AN OPTION FOR YOUR PAIN MANAGEMENT TOOLBOX
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CONFlict of Interest Disclosure
• No conflicts of interest

OBJECTIVES
• Describe mechanism of action and side effects of Ketamine.
• Discuss the use of Ketamine in multi-modal strategies of pain management.
• Apply knowledge of Ketamine’s mechanism of action and benefits to case scenarios
PAIN TRANSMISSION

- Weight loss
- Inefficient glucose metabolism
- Tachycardia

- Hypercoagulation
- Increased BP, P, workload
- Decreased gastric motility and emptying
- Immune suppression

- Decreased quality of life
- Potential for chronic pain
- Depression, Anxiety
**Predictors of Persistent Post-Operative Pain (PPSP)**

- Predictors of postoperative pain intensity
  - Preoperative pain state
    - With or without medications
  - Other predictors:
    - Younger age
    - Sex (more females)
    - Type of surgery
      - Orthopedic
      - Abdominal
      - Thoracic
    - Anxiety, depression, catastrophizing
    - Substance abuse

**Development of Chronic Pain**

- Possible risk factors
  - Severity of surgical trauma
  - Psychological traits
    - Depression
    - Anxiety
    - Catastrophizing
    - Absence of coping skills
  - Concurrent/pre-existing pain
  - Guarding
    - Limping
    - Bracing
    - Flinching
  - Genetic predisposition
  - Female
  - Younger age
  - Psychosocial factors
    - Low household income
    - Unemployment
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  - Younger age
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**Non-Pharmacologic**

- Heat
- Cold
- Repositioning
- Distraction
  - Music
- Meditation
- Touch Therapy
- Active Listening
- TENS
- Referral to interdisciplinary services:
  - Chaplain,
  - Social worker,
  - Stress management,
  - Psychiatry
  - Cognitive Behavioral Therapy (CBT)

**Multi-Modal**

- **Antidepressants:**
  - Blocks reuptake of serotonin & norepinephrine at descending pain pathways:
    - Ex. nortriptyline, duloxetine
- **Alpha2-adrenergic agonists**
  - Reduces pain transmission
    - Ex. clonidine, dexmedetomidine hydrochloride, tizanidine
- **Anticonvulsants**
  - Blocks sodium & calcium channels; reducing neuron hyper excitability.
    - Ex: gabapentin, pregabalin, trileptal
- **Local Anesthetics**
  - Blocks conduction of nerve impulses by blocking sodium channels
    - Peripheral
    - Centrally (epidural)
- **Opioids**
  - PCA, oral, IV, epidural
  - Blocks prostaglandin synthesis in the central nervous system

**Acetaminophen & NSAIDS**
Epidural Analgesia

- Allows for high local concentration of drug at the desired spinal cord receptors
- Minimal amount of opioid entering the systemic circulation to reduce undesired side effects.
- Decreases sedation
- Increases mobility

Peripheral Nerve Blocks

Upper extremity
- Interscalene
- Supraventricular
- Infraclavicular

Lower extremity
- Femoral
- Saphenous
- Adductor canal
- Popliteal
KETAMINE

- Developed in 1960's
  - Initially used in animal studies
- Approved for human use in 1970's as anesthetic
- Many routes of administration available
  - IV, IM, intranasal, SQ, orally, rectal & intrathecal
- Dose dependent effects of
  - Anesthesia, amnesia, analgesia
- Antidepressant with short half-life
- Can be discontinued without withdrawal symptoms
PHARMACOKINETICS

- Metabolized in liver
- Highly lipid soluble
- Crosses blood brain barrier rapidly
- Binds to NMDA receptor
  - Inhibits glutamate from activating the NMDA
  - Creates dissociative effect between the thalamus & limbic regions of the brain
- Rapid onset
  - IV effects in 30 seconds with full effect in 1 minute
  - Duration of 60 minutes
  - Elimination half-life 2-3 hours
- Immediate effects
  - Analgesia, sedation, pupil dilation, nystagmus, lacrimation, salivation, antidepressant, and increased muscle tone

MULTI MODAL ANALGESIA

Residual Pain


COCHRANE REVIEW – OPIOIDS AND KETAMINE PERIOPERATIVE

- Perioperative ketamine (27 of 37 trials)
  - Reduced rescue analgesic requirements
  - Reduced pain intensity
  - Reduced rescue analgesia and pain intensity
  - Reduced 24 hour PCA morphine consumption
  - Reduced postoperative nausea or vomiting (PONV)
POST OPERATIVE ANALGESIA

- Randomized, double blind (n=1088)
- Evaluated effect of Ketamine & Morphine on pain intensity
- Study criteria
  - VAS > 6/10 (> 100 mcg/kg morphine in 30 mins)
- 2 Groups (< 3 doses aim of VAS <4/10)
  - Morphine 30 mcg/kg + saline
  - Morphine 15 mcg/kg + ketamine 250 mcg/kg

**KETAMINE: REDUCED ANALGESIC CONSUMPTION**

- Total Hip Arthroplasty (n=154)
  - IV ketamine before incision (0.5 mg/kg), and a 24-h infusion (2 mcg/kg/min)
  - Placebo
- Postoperative for 48 hours
  - IV acetaminophen
  - Ketoprofen
  - PCA morphine/droperidol
- Reduced total morphine consumption up to 7 days post-op


**Ketamine: Reduced Long Term Pain**

- 24-H IV INFUSION OF KETAMINE DECREASES REST PAIN BY 67% AT 6 MONTHS


**KETAMINE**

- As a singular agent→ analgesia
- With other agents
  - Synergistic
  - Dose sparing
- Minimal effect on respiratory drive
  - Bronchodilator effects
- Uses
  - Anesthesia induction
  - Sedation maintenance
  - Pre-hospital stabilization & transportation
  - Acute & chronic pain
  - Procedural sedation
CARDIOVASCULAR EFFECTS
- Sympathomimetic effect
  - Brain stem stimulation with catecholamine release
  - Blocks reuptake of catecholamines
  - Heart rate, cardiac output, blood pressure
- Direct depression of myocardium
- Increase coronary blood flow
- Heart rhythm
  - Direct anti arrhythmic
  - Indirect arrhythmogenic – catecholamines
- Acts on cholinergic, muscarinic and adenosine receptors

CENTRAL NERVOUS SYSTEM SIDE EFFECTS
- Auditory and visual hallucinations
- Paranoid ideas
- Anxious feelings (panic attacks)
- Inability to control thoughts (internal perception)
- Change in concept of time & space
- Increased awareness of sound and color (external perception)
- Intense sense of drug high or euphoria
- Nightmares or vivid dreams
- Blurred vision
- Vertigo
- Nausea/vomiting
- Dizziness
- Nystagmus
- Impaired motor function
- Memory deficits

CNS SIDE EFFECTS
- Psychedelic effects
  - Decrease rapidly after termination of ketamine administration
- Unpleasant dreams
  - Significantly increased compared with placebo for 3 nights
- Effects can be managed
  - Benzodiazepines
  - Alpha 2-adrenergic receptor agonists
SIDE EFFECTS

- Hypertension
- Tachycardia
- Hallucinations, vivid dreams
- Increased intracranial pressure
- Feeling of intoxication
- Diplopia
- Increased sedation
- Excessive salivation
- Tremors
- Nausea and vomiting

WHEN DO WE USE KETAMINE?

- Opioid tolerant patients with acute pain
- Severe pain refractory to multi-modal regimens
- Minimize total opioid requirements
  - Patient with limited respiratory reserve
- Used to reduce incidence of persistent post-operative pain
- Neuropathic pain
- Ischemic pain
- Opioid induced hyperalgesia
- CRPS
- Sickle cell crisis

Use with caution

- PTSD
- Hypertension
- Psychosis
- Schizophrenia
- Recent psychiatric hospitalization
- Absolute contraindication:
  - Head trauma, seizure, intracranial mass, MI, stroke
**MONITORING**

- Start low: 0.15-0.25 mcg/kg/hr
- Monitoring:
  - Within 60 minutes of initiation
    - Every 15 minutes for 3 hours then q 4 hours
  - Then as needed
- Opioid requirements will decrease once Ketamine initiated
  - Decrease speed by 25-50%
  - Consider low dose benzodiazepine for agitation

**MONITORING**

- Assessment:
  - Respiratory rate
  - Oxygenation saturation
  - Level of pain and sedation (using RASS)
- Notify Medical team and ordering MD if any of the following occur:
  - RASS ≤ -2 or ≥ 2
  - Psychological side effects i.e. hallucinations, vivid dreams, aggressive behavior.
  - Sustained hypertension (>20% increase in blood pressure)
  - Increased pain level or unrelieved pain

**DISCONTINUING KETAMINE**

- Limit infusion to 48-72 hours if possible
  - Risk of hemorrhagic cystitis
- Maximize multi-modal
- Avoid discontinuation of all IV pain management at the same time
- Have a plan for transition to orals
CASE STUDY #1

62 yo male admitted following traumatic BKA of right lower extremity
- History of diabetes, prior right transmetatarsal amputation, prior lumbar surgery
- Preoperative medications:
  - Gabapentin 300mg every 8 hours
  - Morphine Sulfate (MS Contin) 30 mg every 8 hours
  - Oxycodone 5-10 mg every 4 hours PRN
  - Sertraline 75 mg every morning.
- Patient reports history of PTSD

Patient not meeting patient selection criteria

TAKEAWAYS FOR YOUR TOOLBOX
- Opioid requirements will decrease once Ketamine initiated
  - Decrease opioid dose by 25-50%
- Consider low dose benzo for agitation
- Maximize multimodal
  - Start low (0.15-0.25 mcg/kg/hr)

INSTITUTIONAL INITIATIVES
- Adult Roll Out
- Ketamine Lock Boxes
- Pediatric Ketamine Order Sets
Interdisciplinary team
- Attending anesthesiologist
- 3 Clinical Nurse Specialists
- 2 Nurse Clinicians
- 2 Nurse Practitioners
- Anesthesia residents
- Pain fellow
- Provide 24/7 coverage for epidural & peripheral nerve catheter patients

Consult service
- Complex pain patients
- Ketamine & Lidocaine infusions
- Intrathecal

Acute Pain Service

Ketamine Use
- Data available from 2008
  - ~70 patients first year
- Average 4-5 patients daily on Ketamine.
- Daily peak: 12 patients
- 2015: over 350 patients projected

Institutional Initiatives
- Roll out to all adult acute care areas
  - Revision of policies
  - Education for nursing staff
    - In-services
    - Just-In-Time Training
    - On-line training modules
  - Ketamine order sets
    - Consultation with Pain Service attending required
    - Bundles orders with monitoring and reporting criteria
PEDiatric ROLLOUT

- Previously only in ICU
- Pediatric Roll Out
  - Stepdown, high acuity & ICU
- Number of pediatric cases since April 2015
  - 4
- Revision of ketamine policy
- Nursing education
- Ketamine order set
  - Orders based on age
  - Convert to pediatric dosing (mcg/kg/min)

Ketamine Abuse

- Dissociative & hallucinogenic effects
- Recreational drug of abuse
- Street names
  - Special K
  - Vitamin K
  - Lady K
- K-Hole
  - Ketamine dissociative state

DUH Education Council
Ketamine Safe Handling
GO LIVE December 8th

Practice Alert: Guide tips for responsible personnel maintaining intravenous ketamine

- CRUISE
  - Ketamine can be infused with compatible solutions
  - Administered by anesthesiologist with the patient in the prone position
  - Locking the bag is recommended
- DEDICATED
  - Dedicated Ketamine pumps are kept in the Orendella
  - Ketamine syringes are separated from the DA
- TIGHTNESS
  - Use tubing and entry ports (SAP #46401) only for ketamine administration
  - Ketamine administration kept in the pharmacy
  - Do not use in the syringe
  - Use new Ketamine bags with each new bag
- TITAN
  - Clean rocking box with Cavallari between patients
  - Lock boxes can be ordered from equipment distribution
  - Keep the acrylic box door closed and locked
- TITAN
  - Administration policy, Pharmacy, Pain Team (pager 970: 84077)
**Case Studies**

**Pediatric Opioid Tolerant**

**Geriatric Addiction History**

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**CASE STUDY # 2**

**Pediatric Case Study**

- 10 yo female admitted with abdominal tumors
  - Lengthy hospitalization
  - On hydromorphone PCA
  - Opioid requirements increasing

**Management Possibilities:**

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**CASE STUDY # 3**

**Geriatric Case Study**

- 72 yo male admitted following spinal fusion; C2-T6.
  - Chronic left upper extremity shoulder & arm pain
  - Home medications:
    - Hydromorphone (Dilaudid) 2-4 mg every 4 PRN
    - Oxycodone (OxyContin) 60 mg every 12 hours
    - Clonazepam 0.5 mg twice daily PRN
    - Pregabalin 100mg twice daily

**Management Possibilities:**
CASE STUDY # 4
Sickle Cell Disease: Acute on Chronic

- 32 yo female
  - History of sickle cell disease
  - Avascular necrosis of hips
  - Admitted following total hip arthroplasty

Management Possibilities:

CASE STUDY # 5
Opioid Tolerant

- 30 yo male with metastatic cancer
  - Requiring thoracotomy
  - Home medications:
    - Morphine Sulfate (MS Contin) 60 mg every 12 hours
    - 10/10 post-operative pain

Management Possibilities:

CASE STUDY # 6
Substance Abuse History

- 35 yo female
  - MVC
    - Traumatic amputation of left lower extremity below the knee
  - Drug screen positive
    - Cocaine, opiates, THC

Management Possibilities:
REFERENCES

- De Kock, M., Lavand'homme, P., & Waterloos, H., (2001), Balanced analgesia in the perioperative period: is there a place for ketamine?. Pain, 92 (3) 373-80.

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