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DUAL PURPOSED KETAMINE INFUSION THERAPY: A CASE REPORT

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Objectives

- Pharmacological review of ketamine
- Pathophysiology review of complex regional pain syndrome
- Identify potential uses for ketamine infusion therapy
- New literature
- Identify patient populations who may benefit from receiving ketamine infusions for their primary anesthetic
- Case study presentation of ketamine infusion therapy for GA
- Discussion and resources

Ketamine History and Re-emergence

History

- Introduction as a human anesthetic in the U.S. in 1970
- 1980's David Lodge identifies ketamine as a NMDA inhibitor
- Early use of ketamine: dissociative anesthesia and analgesia
  - Psychedelic effects: prevents mainstay in modern anesthetics

Re-emergence

- Wake of the current opioid crisis
- New research supporting use for psychiatric disorders
  - Depression, Bi-Polar, PTSD, Chronic Pain Syndromes
- Side effect profile reduced when combined with other anesthetics

(Mion, 2017)

Ketamine Pharmacology

- Dissociative anesthesia
  - Not generalized CNS depression
- Mechanisms of action:
  - NMDA: Non-competitive antagonism
    - Modulates glutamate
    - Excitatory activity change at the cortex and limbic systems
  - Opioid: Mu, Delta and Kappa receptors
  - Muscarinic antagonism
- Metabolism: Hepatic microsomal enzymes
  - Produce an active metabolite: norketamine
    - 20-30% reduction in activity
- Dosage
  - Induction: 1-4mg/kg IV
  - Adjunct: 0.1-0.5 mg/kg IV

Ketamine Physiological Effects

- Neurologic Effects
  - Produced dissociative and unconscious state
  - Increased cerebral blood flow, ICP and CMRO2
  - Pupil dilation and nystagmus
  - Psychiatric side effects (hallucinations)
- Respiratory Effects
  - Bronchodilation
  - Unaltered respiratory drive
- Cardiovascular Effect
  - Direct myocardial depressant
  - Indirect stimulation of SNS
  - Net effects: Increased blood pressure, heart rate and cardiac output

Precautions and Contraindications

- Cardiovascular
  - Unstable angina, poorly controlled hypertension, high-risk coronary vascular disease,
- Neurological
  - Elevated ICP, acute globe injury, glaucoma, TBI
- Endocrinological
  - Pheochromocytoma
- Hepatic
  - Severe liver disease
- Psychiatric
  - Intoxication with other substances, active substance abuse, psychosis, delirium

Proposed Uses

- Perioperative management for patients with PTSD
- Therapy Infusions
  - Chronic Pain
  - Psychiatric Disorders
- Not FDA approved
  - Treatment is not covered by insurance

Literature related to PTSD

- **Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial (2014) by Feder**
  - Randomized double-blind trial of 41 patients with PTSD
  - Outcome measures: IES-R scale (primary), Depression rating scales (secondary)
  - Conclusion: significant improvement in IES-R scores 24 hours after ketamine infusion compared with midazolam (mean difference, 12.7 [95% CI, 2.5-22.8]; P=0.02)
- **Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression (2018) by Albott**
  - Significant reduction in both the PTSD checklist for the DSM-5 score for PTSD and a significant decrease in the Montgomery-Asberg Depression Rating Scale score.
  - Remission rate for PTSD was 80%; mean time to release 41 days
  - 93.3% response rate for TRD; mean time to release was 20 days

Literature related to Chronic Pain

- **The Effect of Ketamine Infusion in the Treatment of Complex Regional Pain Syndrome: a Systemic Review and Meta-analysis (2018) by Zhao**
  - Included 15 studies and 258 patients
  - Conclusion: potential for short term (<3 months) pain relief for patient with CRPS
  - Immediate pain relief event rate of 69%
  - Follow up pain relief event rate of 58% (1-3 months)

Literature related to Psychiatric Disorders

- **Ketamine Administration in Depressive Disorders: A Systematic Review and Meta-analysis (2014) by Fond**
  - Included 9 randomized control trials
  - 192 patient with major depressive disorder and 34 patients with bipolar
  - Cite a significantly improved depression scores in patients receiving ketamine compared to controls (SMD = -0.99; 95 % CI -1.23, -0.75; $p < 0.01$)
- **Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression (2018) by Zheng**
  - 97 participants with bipolar received 6 repeated ketamine infusions (0.5mg/kg IV over 40 mins)
  - Outcome measures included: Montgomery-Asberg Depression Rating Scale, Scale for Suicidal Ideation, Hamilton Anxiety Scale, Clinician Administered Dissociative States Scale, and the Brief Psychiatric Rating Scale
  - Measured at baseline, 4hr, 24hr, Days 3-13 and Day 26
  - Results: Significantly and sustained decreases in the MADRS, HAMA, and SSI-part 1
  - Response Rate 68.0% Remission Rate 50.5%
  - Rapid Response Rate within 24 hours of first infusion

Complex Regional Pain Syndrome

- Types
  - CPRS-I: unconfirmed nerve injury
  - CRPS-II: confirmed nerve injury
- Chronic pain syndrome after acute trauma
  - Improper management of acute pain
  - Neuroplasticity of affected limb
- Maladaptive efferent and afferent impulses
  - Trigger chronic inflammation and vascular responses
  - Leads to arteriole demise, hyperalgesia and allodynia
- Associated with higher onset of psychiatric disorders

Case Report: Patient History

- HPI: 33 y/o patient with a history of CPRS presenting for spinal cord stimulator hardware removal
- PMH: CRPS r/t right ankle fracture, depression, PTSD, hypertension, hyperlipidemia, DM II, GERD, OSA, obesity, right sided upper and lower extremity allodynia, systemic hyperalgesia
- PSH: Spinal cord stimulator implantation 2001
- Medications: P.O. morphine 105 mg qday (4 doses), omeprazole, atorvastatin, lisinopril, PRN alprazolam, bi-monthly 500mg ketamine infusions

Case Report: Pre-Op

- Private, low stimulating pre-operative holding area
- PO premedication
  - 20 mg omeprazole, 300 mg gabapentin, 30 mg morphine, 4 mg perphenazine
- IV: inserted under local anesthesia with ultrasound
- IV premedication
  - 2 mg IV midazolam and 12 mcg IV dexmedetomidine

Case Report: Operative Management

- Induction
  - Preoxygenation
  - Lidocaine 100 mg IV , propofol 200 mg IV, rocuronium 40mg IV
  - Endotracheal tube intubation
- Maintenance
  - Ketamine infusion 150mg/hr, propofol infusion 75-125 mcg/kg/min, Esmolol infusion 100-125 mcg/kg/min
  - Surgical Time 75 minutes
- Emergence:
  - Discontinued Propofol and Esmolol
  - Muscle relaxant reversal: neostigmine 5mg IV and glycopyrrolate 0.8 mg IV
- Extubation:
  - Stage III
  - Placement of nasal airway
  - Extubated: respiratory rate of 12 and 300 ml consistent tidal volumes.

PACU Management

- Transport
  - Patient remained somnolent throughout transfer to PACU
- Setting
  - Private, low stimulation PACU bed
- Medication
  - Ketamine infusion; resume propofol infusion at 20mcg/kg/min
- Post infusion assessment
  - Vital signs stable, calm demeanor, pain free, described a state of euphoria
- Discharge
  - To home four hours post-op

Discussion

- Prime Patient
  - PTSD, Depression, CRPS, Chronic Opioid Use
- Esmolol rational: MAC reduction, antinociceptive properties, decreases SNS response
  - Initial RCTs and Literature Reviews conclude perioperative esmolol to reduce post-operative and perioperative opioid consumption, decrease PONV, and reduce anesthetic depth requirements (Harless, 2015; Watts 2017).
- Opioid-sparing management
- Effective post operative pain management
- Effective PTSD management
  - Avoidance of post-op delirium
  - Patient specific: post-op propofol infusion

ASA Consensus Guidelines on Ketamine Infusions

- Acute Pain
  - Adjunct to therapy reduces pain scores and opioid consumption up to 48 hours post operatively
  - Opioid-tolerant and dependent patients reported improved post operative pain scores
- Chronic Pain
  - Moderate evidence to support improvement in CRPS for up to 12 weeks
- Dosing ranges
  - Bolus: up to 0.35mg/kg
  - Infusion 0.5 to 2 mg/kg/hr (up to 7mg/kg/hr)
  - Dose-response relationship; higher dosages provide more benefit

(Schwenk, 2018)

AANA's Practice Considerations: Ketamine Infusion Therapy

- Patient specific tailoring with multidisciplinary team
- Recognition of use:
  - Adjunctive psychiatric treatment
  - Reduction of PTSD symptoms
  - Treatment of Chronic Pain
- AANA created checklist for CRNAs
- Encourage CRNAs to contribute to the development of new publication and research on ketamine infusion therapy for chronic pain and psychiatric disorders

(AANA, 2016)

Key Take Home Points

1. Ketamine can be an efficacious adjunctive therapy during general anesthesia
2. Patient populations who may benefit the most include: PTSD, CRPS, Depression, Bipolar, and Opioid Dependence
3. If the patient presenting for surgery currently utilizes ketamine infusion therapy, consider using it as their primary anesthetic

References

Albott, C., Lim, K., Forbes, M., Erbes, C., Tye, S., Grabowski, J., . . . Shiroma, P. (2018). Efficacy, Safety, and Duration of Repeated Keamine Insusions for Comorbid Posttratmautic and Stesss Disorder and Treatment-Resistant Depression. *Journal of Clinical Psychiatry, 79* (3)

American Association of Nurse Anesthetists. (2016, September). *Ketamine Infusion Therapy.* Retrieved from AANA Website: https://www.aana.com/docs/default-source/practice-aana-com-web-documents-(all)/ketamine-infusion-therapy-for-psychiatric-disorders-and-chronic-pain-management.pdf?sfvrsn=950049b1_2

Feder, A., Parides, M., Murrough, J., Perez, A., Morgan, J., Saxena, S., . . . Charney, D. (2014). Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, 681-688.

Fond, G., Loundou, A., Corentin, R., Macgregor, A., Lancon, C., Brittner, . . . Boyer, L. (2014). Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology 231,* (18), 1-14.

Harless, M., Depp, C., Collins, S., & Hewer, I. (2015). Role of Esmolol in Perioperative Analgesia and Anesthesia: A Literature Review. *American Association of Nurse Anesthetists Journal, 83* (3), 167-177.

References

Mion, G. (2017). History of anaesthesia: The ketamine story- past, present and future. *European Journal of Anaesthesiology*, 571-575.

Schwenk, E., Viscusi, E., Buvanendran, A., Hurley, R., Wasan, A., Narouze, S., Bhatia, A., Davis, F., Hooten, W., Cohen, S. (2018). Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologist. *Regional Anesthesia and Pain Medicine, 43* (5), 1-11.

Watts, R., Thiruvenkatarajan, V., Calvert, M., Newcombe, G., & Van Wiijk, R. (2017). The effect of perioperative esmolol on early postoperative pain: A systematic review and meta-analysis. *Anaesthesiology Clinical Pharmacology, 33* (1), 28-39.

Zhao, J., Wang, Y., & Wang, D. (2018). The Effect of Ketamine Infusion in the Treatment of Complex Regional Pain Syndrome: a Systematic Review and Meta-analysis. *Current Pain and Headache Reports*, *22* (2) 1-8.

Zheng, W., Zhou, Y.-L., Liu, W.-J., Wang, C.-Y., Zhan, Y.-N., Li, H.-Q., . . . Ning, Y. P. (2018). Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and dipolar depression. *Journal of Psychiatric Research*, 61-68.