Sanjog Pangarkar, MD

Associate Professor of Medicine

David Geffen School of Medicine, UCLA

Director Inpatient and Interventional Pain Service

West Los Angeles VA Medical Center

Los Angeles, CA

Ketamine

Disclosure

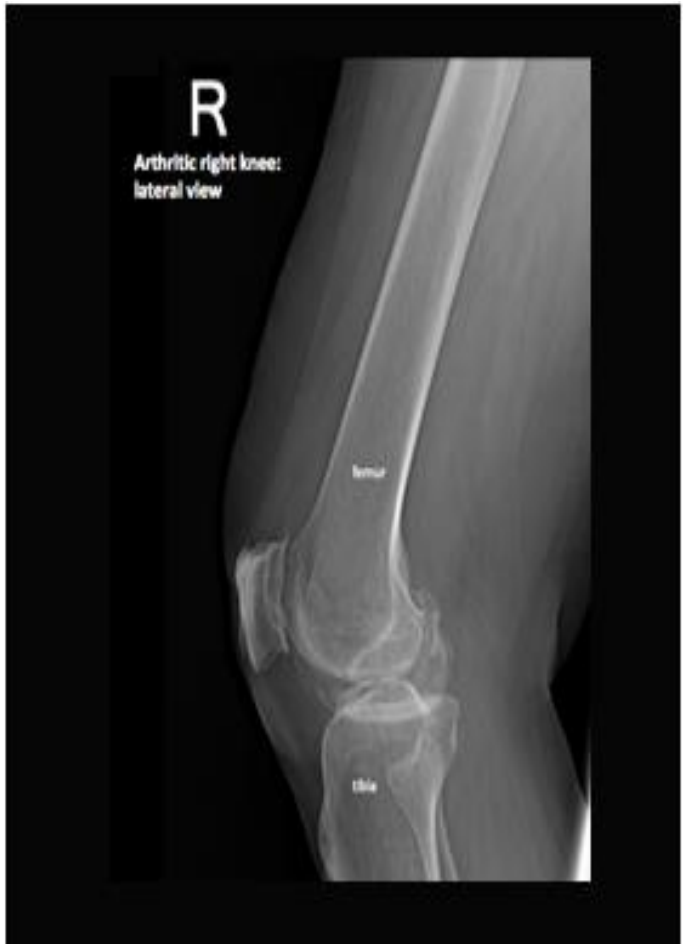
- None

Outline

- Case Report
- History
- Pharmacology
- Indications
- Contraindications
- Precautions
- Evidence
- Questions

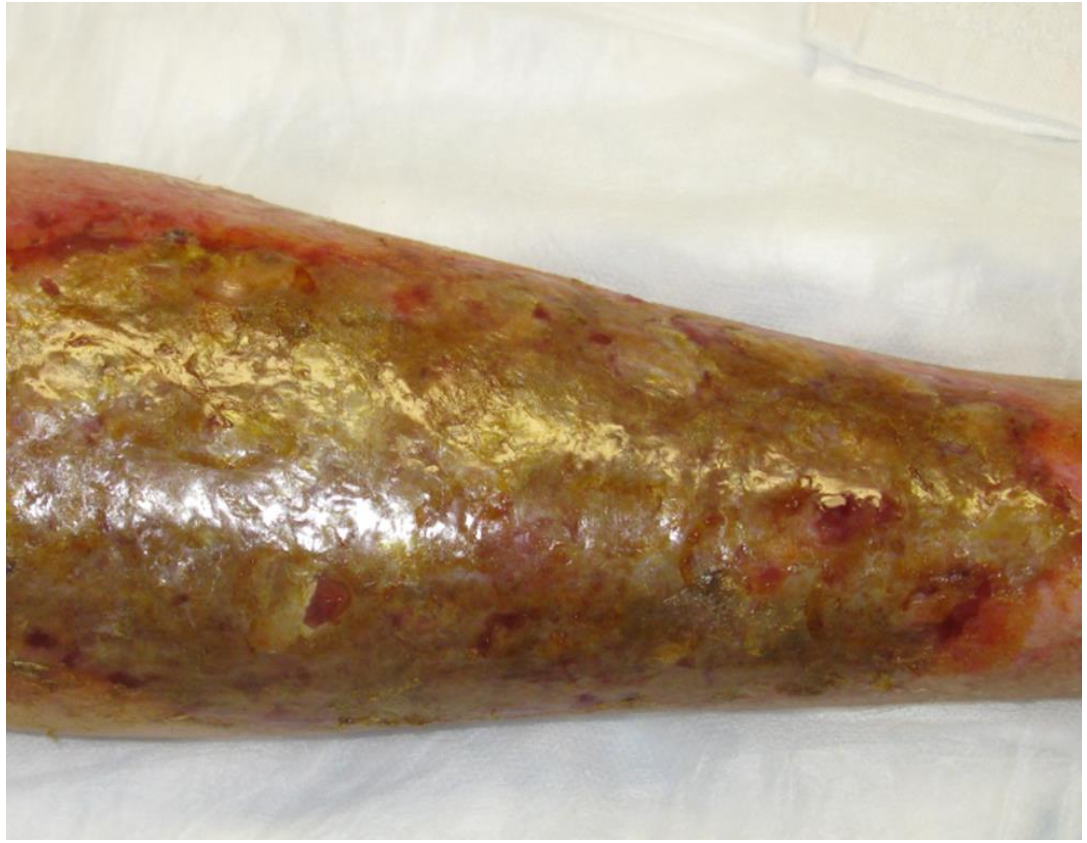
Case Report

- 50 year old RH Veteran with right-sided knee pain
- Daily symptoms, moderate in intensity 2/2 mod-severe knee arthritis
- Anti-inflammatories and therapy didn't help
- Steroid injections helped but for a limited time
- Knee stable, arthroscopy scheduled



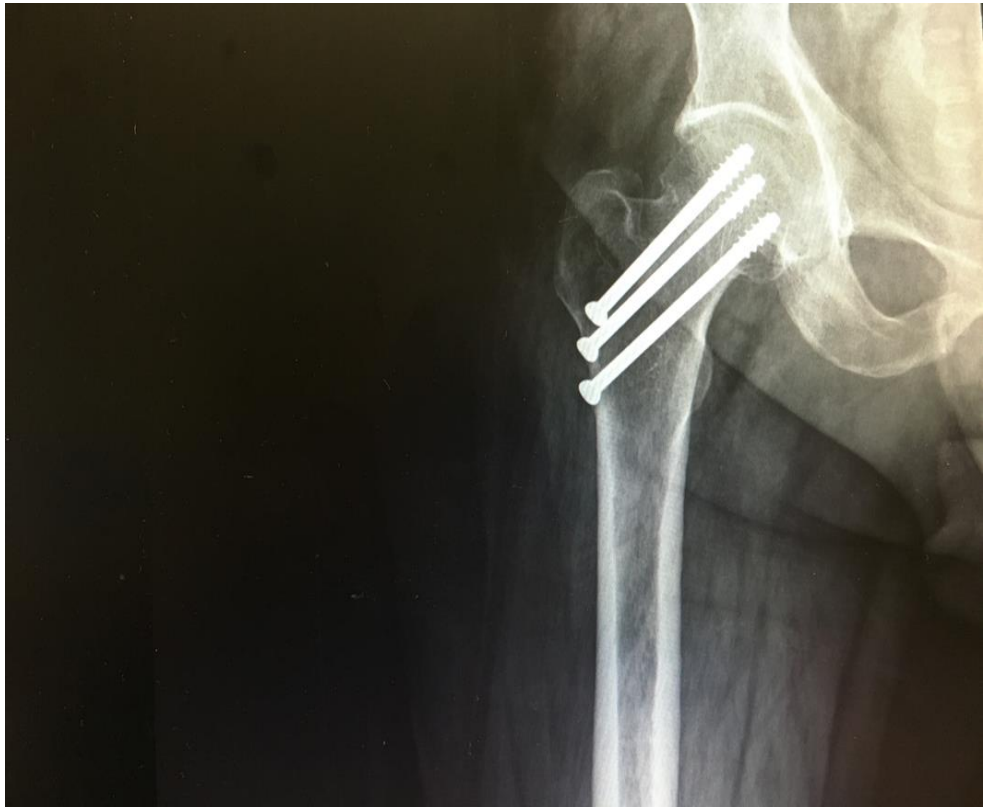
Case Report

- He developed allodynia, skin crusting, and discoloration extending from the right thigh to the toes after knee.
- He was diagnosed with CRPS 1, and over 17 years underwent the typical treatments for this disorder in a multi-disciplinary VA Chronic Pain Clinic.
- He eventually was placed on opioids, requiring > 400 mg of daily morphine equivalents (ME) for effective pain relief.



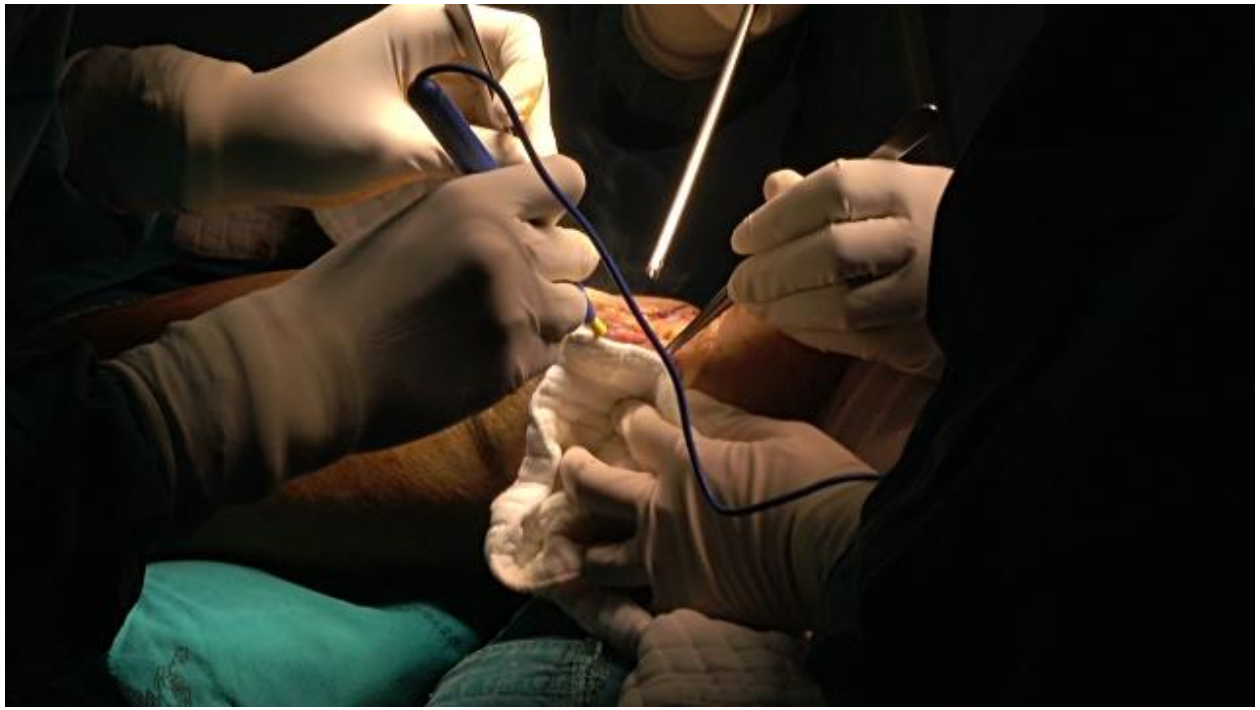
Case Report

- His pain and debility lead to several co-morbid conditions, including obesity and muscle atrophy. He sustained two major falls that caused hip and distal tibia fractures.
- Over time, he developed contractures, chronic cellulitis, and became wheelchair-bound.
- He eventually became severely depressed and attempted suicide. His opioids were subsequently tapered.



Case Report

- To assist in tapering and reduce neuropathic pain, ketamine infusions were performed at 80mg/hr for 4 hours.
- He received 10 infusions over one year, allowing him to reduce his ME opioid dose to 28 mg.
- After psychological evaluation and several multidisciplinary discussions, he underwent right AKA 11 days after the last ketamine infusion.

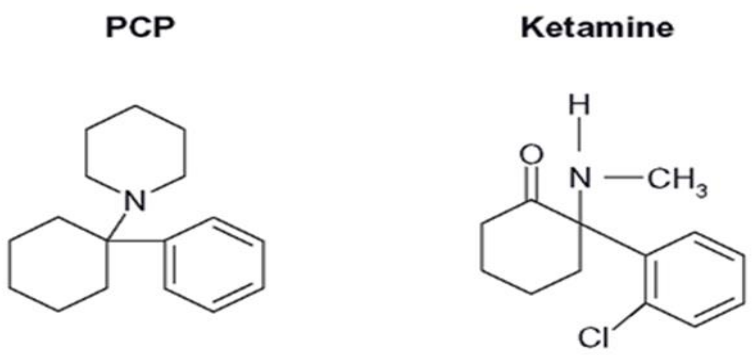


Case Report

- He is now completely off opioid therapy (Ibuprofen/Acetaminophen)
- He is a community ambulator and has completed driver safety courses through Occupational Therapy at VA
- He volunteers his time at the VA medical center and UCLA Medical School to teach students about CRPS and pain management

Ketamine

- Ketamine is FDA approved for the induction and maintenance of anesthesia
- It is a dissociative anesthetic that causes "... a peculiar anaesthetic state in which marked sensory loss and analgesia as well as amnesia is not accompanied by actual loss of consciousness." Bonta 2004
- It is used off-label for chronic pain and mental health disorders



History

- 1962 - First synthesized for anesthetic purposes (Parke-Davis)
- 1964 - Human trials started
- 1966 - Patent received
- 1970 - FDA approved for human use
- 1971 - Sub-dissociative doses trialed
- 1987 - Discovery of the NMDA receptor
- 1990 - Low dose ketamine for opioid-resistant cancer pain
- 1999 - Schedule III controlled substance

Pharmacology

- PCP derivative
- The major metabolite of ketamine is norketamine
- The therapeutic activity is due to ketamine and norketamine
- They are both NMDA inhibitors which is the basis of their pharmacological effects
- 2 Stereoisomers: S+, R- (S+ 4x more potent than the R)

Pharmacology

- Typically given IV, but can be given SQ, IM, oral, epidural, rectal, intrathecal, intraarticular, topical, intranasal, sublingual.
- Rapidly passes the blood brain barrier
- Peak plasma concentration reached in 1 minute
- IV half-life: 2-3 hours
- Oral administration: extensive 1st pass in liver (resulting in 16-24%)
  - Peak in 30 minutes
  - Substrate of CYP2B6 (major), CYP2C9 (major), CYP3A4 (major)

Typical Side Effects

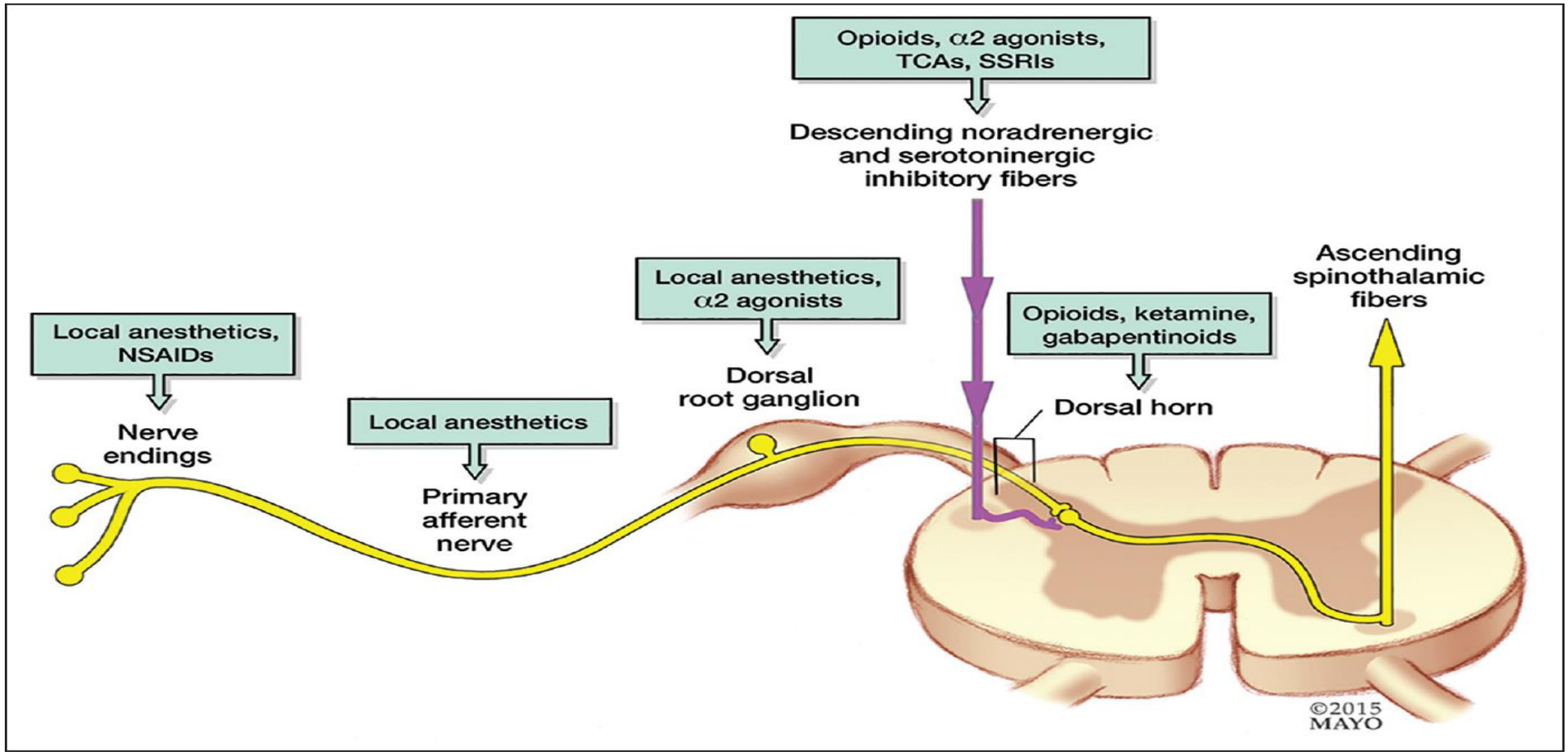
>10%	1-10%	<1%
Emergence rxns	Bradycardia	Anaphylaxis
Hypertension	Diplopia	Cardiac arrhythmia
Increased cardiac output	Hypotension	Depressed cough reflex
Increased ICP	Increased IOP	Fasciculations
Tachycardia	Injection-site pain	Hypersalivation
Tonic-clonic movements	Nystagmus	Increased IOP
Visual hallucinations		Increased metabolic rate
Vivid dreams		Hypertonia
		Laryngospasm
		Respiratory depression or apnea

Emergence

- Altered short term memory
- Decreased ability to concentrate
- Decreased vigilance
- Altered cognitive performance
- Hallucinations
- Nightmares
- Nausea
- Vomiting

Mechanism of Action

- Non-competitive NMDA antagonist
  - Binds to PCP site when receptor is in open state
- Inhibits NMDA receptor-mediated responses in the spinal cord and thalamus
- Inhibits wind up phenomenon
  - Frequency-dependent increase in excitability of spinal cord neurons evoked by electrical stimulation of c-fibers
- Binds to subtypes 2A-2D
- Raises arterial pressure, increased heart rate and cardiac output with relative preservation of airway reflexes and respiration
  - Valuable as an anesthetic agent


Opioids, α2 agonists, TCAs, SSRIs
Descending noradrenergic and serotoninergic inhibitory fibers
Local anesthetics, α2 agonists
Dorsal root ganglion
Opioids, ketamine, gabapentinoids
Dorsal horn
Ascending spinothalamic fibers
Local anesthetics, NSAIDs
Nerve endings
Local anesthetics
Primary afferent nerve
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Other Mechanisms of Action

- Neuronal hyperpolarization cationic currents (HICN1)
- Nicotinic Acetyl-choline ion channels
- Delta and Mu Opioid potentiation
- Nitric Oxide-cGMP
- Non-NMDA Glutamate receptors (AMPA)
- Metabotropic glutamate receptors (mGluR)
- Reduced cholinergic neuromodulation
- Increased dopamine and noradrenaline release
- Neurosteroids
- L-type Ca2+ channels

Evidence for Use- CRPS

- Finch et al, Topical, N=20, Ketamine vs Placebo
  - No diff 30min s/p application
  - K- significantly dec allodynia, punctate hyperalgesia in symptomatic limb
- Schwartzman et al, IV, N=19, Ketamine vs Placebo
  - K-27% decrease in pain; NS- 2% decrease in pain
- Sigtermans et al, IV, N=60, Ketamine vs Placebo (NS)
  - 100 hours infusion over 5 days
  - Dec pain in K group up to 11 weeks after infusion (no detectable plasma concentration)
  - No change in functional change

Evidence for Use- Orofacial Pain

- Eide and Stubhaug, PO, N=1, Ketamine vs placebo
  - Ketamine dec pain including marked dec in pain intensity with swallowing
- Baad-Hansen et al, IV, N=20 (10 with odontalgia, 10 placebo)
  - No effect on spontaneous AO pain
- Rabben et al, IM, N=30, Ketamine vs Demerol
  - 9/30 no relief from either
  - 8/30 prolonged anesthesia from both (K>D)
  - 9/30 transient relief with K as compared to Demerol
- Rabben and Oyer, PO, N=26, Continuation of above study with oral Ketamine
  - 5/8 with prolonged relief had relief
  - 0/9 with transient relief had relief with oral had PO relief
  - Non-responders to IM had no relief with PO

Evidence for use- Phantom Limb Pain

- Nikoljsen et al, IV, N=11, Ketamine vs Placebo
  - Dec residual limb and phantom limb pain
  - Increase pressure threshold
- Eichenberger et al, IV ,N=20, Ketamine vs Calcitonin vs K+Calcitonin vs Placebo
  - Ketamine decreased phantom limb pain

Evidence for Use- Ischemic Limb Pain

- Persson et al, IV, N=8, Ketamine vs Morphine
  - K- 8/8 with complete pain relief
  - M- 5/8 with complete pain relief
- Mitchell and Fallon, IV< N=35, Opioids+Ketamine vs Opioids vs Placebo
  - K- 65% improvement in pain 24 hrs post infusion and 69% 5 days post infusion, also improved general activity and enjoyment of life

Evidence for Use- Fibromyalgia

- Sorensen et al, IV, N=18, Ketamine vs Morphine vs Lidocaine vs NS
  - Improved pain intensity, decreased tenderness at tenderpoints, increased endurance
- Graven-Nielsen et al, IV, N=29, Ketamine vs Placebo
  - 15/29 responded to Ketamine and were then Double blinded for Ketamine vs NS
  - In responders- dec pain at rest, referred pain, muscular hyperalgesia
- Noppers et al, IV, N=10, Ketamine vs Versed (placebo)
  - At 15 minutes (inc plasma conc), 8 (K) vs 3 (V) had >50% pain relief

A Case Series Investigating Opioid Medication Utilization in patients with Complex Regional Pain Syndrome before and after Ketamine Infusion Therapy

U.S. Department of Veterans Affairs
VA Greater Los Angeles Healthcare System

UCLA/Greater Los Angeles VA Healthcare System
Gabriel Rudd-Barnard, MD, MS, Sanjog Pangarkar, MD, Agnes Wallbom, MD, MS

ABSTRACT

Complex Regional Pain Syndrome (CRPS) is a debilitating painful condition characterized by a constellation of signs and symptoms outlined in the Budapest criteria. Current thought, identifies CRPS as a systemic disease of the central and peripheral neuraxis resulting from dysfunctional interactions between the bodies nervous and immunological systems. Opioid use is prevalent in the treatment of CRPS, although suggested only as a last resort. Ketamine infusion therapy has also been used in patients with severe symptoms. We retroactively characterized CRPS patient's opioid use and ketamine infusions to see if opioid use changed. We found that ketamine infusions significantly reduced pain and that some patient's were able to drastically reduce opioid burden, but the actual etiology of this reduction is unclear as some patients did not change their opioid use and one did not use opioids before or after ketamine infusion. Future study should randomize patients and prospectively analyze opioid usage prior to and after ketamine infusion.

Patient	Morphine Meq prior to 1st infusion	Last Morphine Meq used	VAS before infusion	VAS after last infusion
1	600	0	8.5	5
2	82.5	62.5	5.5	2
3	180	0	6	0
4	0	0	5	3
5	15	15	8	3
6	30	30	7	5.25

METHODS & RESULTS

We conducted a retrospective case report analysis of six patients with CRPS at an urban tertiary VA Medical Center who have undergone ketamine infusion treatment. Our goal was to assess patient opioid usage before and after ketamine treatment. In our patients with CRPS who underwent ketamine infusions the average morphine Meq used prior to infusion was 151 compared with 18 Meq after. This was accompanied by a change in the visual analog score (VAS) from an average of 6.5 to 3.

INTRODUCTION

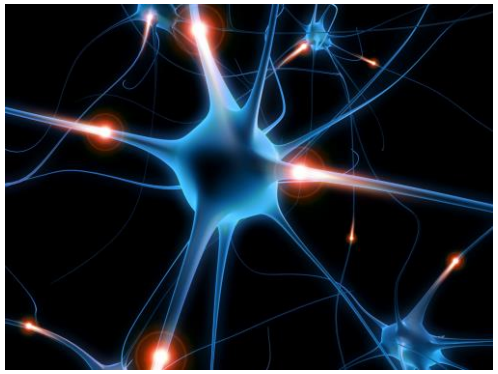
Complex Regional Pain Syndrome (CRPS) is a debilitating painful condition characterized by severe allodynia, autonomic dysfunction, motor, and trophic changes. It is currently believed, that CRPS is a systemic disease of the central and peripheral neuraxis resulting from dysfunctional interactions between the bodies nervous and immunological systems. Experts have agreed, a multimodal approach to treatment is optimal, including: skilled therapy (physical, occupational, and recreational therapy), psychological intervention, medications such as antidepressants, cation channel blockers, bisphosphonates, opioids, infusion therapy of NMDA antagonists or IVIG, interventional nerve/sympathetic blockade, and neurostimulation. For patients with treatment resistant CRPS, ketamine infusion therapy has provided significant relief from pain symptoms. Opioid therapy, although not recommended as first line treatment in neuropathic pain, is still commonly used. Opioid medications can have deleterious side-effects including overdose and death. Reducing opioid use should be a goal in any chronic pain syndrome. The reduction in opioid requirement before and after ketamine infusion therapy has not yet been characterized.

CONCLUSIONS

Patients with CRPS receive significant pain reduction with ketamine infusion therapy. Half of the patients also substantially reduced the amount of opioids used. This is significant as it indicates that ketamine infusions not only reduce pain, but may reduce the risks associated with high dose opioid use in chronic pain patients. Due to the retrospective nature of the analysis, the true motivation for opioid reduction is difficult to ascertain and future prospective controlled trials may shed light on actualities.

Indications at GLA

- Complex regional pain syndrome (CRPS)
- Deafferentation pain
- Ischemic limb pain
- Phantom limb pain
- Fibromyalgia
- Central headache
- Cancer pain
- Other neuropathic conditions



Exclusions at GLA

- Pregnancy or lactation
- Uncontrolled hypertension
- History of psychosis or current uncontrolled psychiatric illness
- History of heart transplant
- Uncontrolled elevated intraocular pressure
- Altered mental status
- Known hypersensitivity to ketamine
- Porphyria
- Ulcerative cystitis +/-
- Thyroid disorders +/-

Monitoring performed in CPC

- Nurse dedicated to infusion
- Monitored setting
- NPO before infusion
- Continuous EKG
- Blood pressure q 15 minutes
- Continuous pulse oximetry
- One hour hold prior to discharge

GLA Protocol

- Evaluation in clinic
- Discussion with multidisciplinary team

- Ketamine (generally 40mg/hour x 4 hours)
- Midazolam 1-2 mg IVP q 2 hours PRN
- Clonidine 0.1mg PO prior to infusion
- Ondansetron 4mg IVP PRN nausea
- Labetolol PRN

"Your three-o'clock hallucination is here."

Points for further study…

- Ketamine may be useful for some neuropathic pain syndromes
- More studies are required for possible protocol and further elucidation of relevant mechanism of action
- Decreasing the side-effect profile
- Feasibility of repeated infusions as they are likely to be more helpful
- Lack of efficacy in topical administration
- Role of oral ketamine and the possible risk of diversion/abuse
- Addressing concomitant depression in pain