Treating Complex Regional Pain Syndrome (CRPS) with Ketamine

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Outline

- Overview of CRPS
- Brief review of Ketamine
- Examination of the literature to date describing the use of Ketamine to treat CRPS
- Conclusions
Also Known As CRPS

- Late 1800’s “Causalgia”
- 1946 “Reflex Sympathetic Dystrophy”
- 1994 the International Association for the Study of Pain defined Complex Regional Pain Syndromes (CRPS) 1 and 2
Defining CRPS

- Regional pain associated with sensory, autonomic, trophic and motor abnormalities after an initiating noxious event such as trauma
- CRPS 1 (formerly Reflex Sympathetic Dystrophy)
  - Symptoms follow injury to the area affected
- CRPS 2 (formerly Causalalgia)
  - Symptoms follow injury to a major peripheral nerve
Epidemiology of CRPS
Sharma Regional Anesthesia and Pain Medicine 2009

- The mean age range is 25-55 years
- More common in women (5:1)
- Slightly more common in lower extremity

causes

- postsurgical
- misc/MVC
- fracture
- sprain
- crush
- contusion
- dislocation
Common Signs and Symptoms

- Pain
  - Burning or aching
  - Little or no provocation (allodynia)
- Swelling
- Vasomotor
  - Skin temperature changes (warm then cold)
  - Discoloration of skin (dark, pale, or mottled)
- Sudomotor
  - Increased sweating
Common Signs and Symptoms

- Trophic changes
  - Abnormal nail growth
  - Increased or decreased hair growth
  - Thin, glossy skin
  - Stiff joints
  - Muscle wasting
  - Tremor
  - Dystonia
Diagnosis of CRPS

- No gold standard
- Clinically based diagnosis of exclusion assisted by
  - X-ray
  - Three-phase bone scan
  - Quantitative sensory testing
  - Autonomic testing
  - Thermography
  - Sympathetic blocks
* Important – Division Standards *

- The patient must have pain
- The patient has physical signs of at least vasomotor and/or sudomotor signs
  - Allodynia and/or trophic changes add strength to diagnosis
- At least 2 diagnostic testing procedures are positive
  - Further diagnostic testing may be appropriate
- For CRPS 2 must also have
  - Documentation of peripheral nerve injury with pain initially in the distribution of the injured nerve
Common Treatments of CRPS

- Interdisciplinary approach
  - Pain specialist
  - Psychological evaluation
- Active and passive physical therapy
- Desensitization
- Mirror Therapy
- Oral medications
- Injections (sympathetic, trigger)
- Surgery (neurostimulation)
Ketamine’s History

- Designed in 1962 as a veterinary anesthetic
- First became abused in the 1970’s as an adulterant in ecstasy, then used for its hallucinogenic properties or as a rape drug
- It can be taken in various routes
  - Oral
  - Intranasal
  - Intramuscular
  - Intravenous
  - Rectal
Ketamine’s Action

- Dissociative and dose dependent anesthetic
  - affects the cortex and limbic system
- Its effect is described as trancelike or cataleptic
  - dissociation from their environment
- Leaves airway reflexes intact
- Metabolizes to Norketamine (1/3 active)
- The (S)-enantiomer is generally thought to have a faster clearance and fewer side effects than the (R)
... But It’s Not a Perfect Drug

- Most concerning side effect
  - Emergence hallucinations which occur in up to 30% of adults but are more rare in children

- Rare side effects include
  - Tachycardia
  - Hypertension
  - Increased myocardial and cerebral oxygen consumption
  - Increased intracranial and intraocular pressure
Ketamine and CRPS

- The pathophysiology of CRPS is still uncertain
  - N-Methyl-D-Aspartate (NMDA) receptor in the dorsal horn is activated by pain stimulation and becomes excited which leads to abnormal pain manifestations
  - Ketamine which is a competitive NMDA receptor antagonist should be able to turn this excitation loop off
The First Case Reports

- In the 1990’s, Ketamine infusions began to show up in case reports as effective in the treatment of chronic neuropathic pain and RSD.
- In most of these cases, patient’s were refractory to many other treatments and experienced sometimes dramatic pain relief after receiving intravenous Ketamine infusions.
Workers’ Comp Guideline Process

- Multiple database search for Randomized Controlled Trials (RCTs) addressing Ketamine and CRPS or neuropathic pain
- Crosscheck references/reviews for others
- Review each article’s methods eliminating those with obvious bias or flaws
- Systematically judge evidence of each
- Draft a rough guideline for committee
### Article Summary

<table>
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<tr>
<th>Route</th>
<th>Author(s)</th>
<th>Journal/Year</th>
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<td>Intravenous</td>
<td>Sigtermans</td>
<td>Pain 2009</td>
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<td>Schwartzman</td>
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<td>Topical</td>
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<td>European Journal of Pain 2010</td>
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<td>Sublingual</td>
<td>Chong</td>
<td>Clinical Drug Investigation 2009</td>
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**Bold** indicates studies considered for guideline

Generally primary outcome of numerical pain scale and secondary outcomes of quantitative sensory testing or function
Method
- 60 subjects randomly allocated to receive a 4 day low dose infusion of S(+)‐Ketamine or a placebo of normal saline

Results
- On a numerical rating scale there was a significant difference that trended towards baseline over 11 weeks of follow up

Shortcomings
- They were unable to show functional improvements
- There was a high rate of deblinding
Method

- 19 subjects randomized to receive an infusion of Ketamine or normal saline for 4 hours a day x 10 days
- Subjects reported pain and quality of life via multiple questionnaires, wore activity watches, and underwent quantitative sensory testing

Results/Shortcomings

- Study aborted halfway citing that the placebo effect was so small that statistical differences were reached “on many of the study parameters” which were mainly shown in the questionnaire responses
- Ketamine dose should be doubled for better and longer-lasting pain relief
Methods
- 92 subjects randomized to use placebo (vehicle only), 2% Amitriptyline, 1% Ketamine, or a combination of 2% Amitriptyline and 1% Ketamine 3 x a day for 3 weeks & track numerical pain score.

Results
- There were no significant differences between treatments.

Shortcomings
- Dose possibly too low
- Short study
Methods
- 12 patients that had both topical racemic 10% Ketamine cream and a placebo at least a week apart

Results
- Ketamine inhibited allodynia to light brushing and hyperalgesia to skin prick

Shortcomings
- 10% topical Ketamine not routinely available
- Pain scales were not altered by topical Ketamine
Methods

- 20 patients randomly allocated to get
  - 30mg oral Morphine + 40mg of Memantine
  - 30mg oral Morphine + placebo
- Followed the functional MRI during movement tasks and movement & rest pain scores

Results/Shortcomings

- Functional MRIs did not differ between groups
- Morphine and Memantine group had better movement and resting pain compared to only resting pain for the Morphine and placebo group
Intranasal Ketamine
Huge Pain 2010

Methods
- 16 patients randomized to have intranasal (S)-Ketamine in a dose of either 0.2mg/kg or 0.4mg/kg
- Followed numerical pain scores and plasma concentrations

Results
- Pain scores significantly decreased (up to 40%) in both groups and the decreases correlated with the plasma concentrations (best at 60 minutes and lasting up to 3 hours)

Shortcomings
- The 0.4mg/kg group had more psychototropic side effects (sedation, vertigo, difficulty concentrating)
Pilot Sublingual Ketamine

Chong Clinical Drug Investigation 2009

Objective
- Develop a Ketamine lozenge for neuropathic pain

Methods
- 10 patients enrolled and got (with 1-2 days between)
  - 25mg sublingual Ketamine lozenge
  - 25mg of oral Ketamine
  - 10mg of intravenous Ketamine

Results
- The sublingual and oral routes had 24% bioavailability and metabolized substantially to Norketamine compared to intravenous

Shortcomings
- 4 out of 10 withdrew
- Efficacy studies needed
# Route Evidence Summary

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<tr>
<td>Intravenous</td>
<td>Low dose daily injections of Ketamine can provide a few weeks of pain relief</td>
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<tr>
<td>Topical</td>
<td>Does not alter patient’s perception of pain</td>
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<tr>
<td>Oral</td>
<td>Alone or in combination may improve pain – more studies needed to determine dosing and efficacy</td>
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<tr>
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<td>Sublingual</td>
<td>Pilot – look for efficacy studies in the future</td>
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Conclusions

- The best evidence for the use of Ketamine in CRPS based on the literature to date is that low dose daily injections of Ketamine can provide a few weeks of pain relief compared to placebo.
- No studies to date have shown any functional improvements in patients with CRPS treated with Ketamine.
- The risks and costs of Ketamine outweigh the proven benefits limiting its potential to be recommended for general use.
Questions?

- Does this literature review or the resultant guideline recommendations change your treatment of CRPS?
References

- Finch, Knudsen and Drummond “Reduction of Allodynia in Patients with Complex Regional Pain Syndrome: A Double-blind Placebo-controlled Trial of Topical Ketamine” Pain 2009 146:18-25
- Gustin et al. “NMDA-receptor Antagonist and Morphine Decrease CRPS-pain and Cerebral Pain Representation” Pain 2010 151:69-76
Lynch et al. “Topical 2% Amitriptyline and 1% Ketamine in Neuropathic Pain Syndromes: A Randomized, Double-blind, Placebo-controlled Trial” Anesthesiology 2005 103:140-146


Sigtermans et al. “Ketamine Produces Effective and Long-term Pain Relief in Patients with Complex Regional Pain Syndrome Type I” Pain 2009 145:304-311