

Outpatient Ketamine Infusion for CRPS

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Work Related Injuries Workshop
May 1st & 2nd, 2017

Disclosures

I have nothing to disclose



‘[...] It is a safe rule to have no teaching without a patient for a text, and the best teaching is that taught by the patient himself.’

(Sir William Osler, Address to the New York Academy of Medicine, 1903)

Why Treat CRPS with Ketamine Infusions?

- Treatment options are limited for CRPS
- Provide a treatment alternative for CRPS and other neuropathic pain states
- Low Dose Outpatient Ketamine Infusion has been shown to decrease or alleviate pain from CRPS
- Offered in very few Pain Centers in the U.S.



CRPS:

*“the most terrible
of all the tortures
which a nerve
wound may inflict”*

-Silas Weir
Mitchell, MD

*Injuries of Nerves
and Their
Consequences
(1872)*

CRPS

- **Incidence: 50,000 new cases of CRPS 1 annually in US. ¹**
- **Incidence increases with age.**
- **Women are affected 3-4 times more than men**
- **Arm: 60% of cases, Leg: 40% of cases**
- **Triggering Events:**
 - **Fractures**
 - **Sprain**
 - **Elective surgery**

CRPS Risk Factors

- Does not appear to be associated with underlying depression or anxiety
- Immobilization
- Ace inhibitor use at time of trauma
- Migraine
- Asthma
- Genetic factors

CRPS Diagnostic Criteria

- CRPS is a syndrome characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion.
- The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings.
- The syndrome shows variable progression over time.

Revised complex regional pain syndrome criteria by the Budapest consensus group (accepted and codified by the Committee for Classification of Chronic Pain of the International Association for the Study of Pain).

Harden et al, Pain Medicine 2013; 14: 180–229.

CRPS Diagnostic Criteria

	SYMPTOMS (≥ 3)	SIGNS (≥ 2)
SENSORY	hyperalgesia +/- allodynia	hyperalgesia +/- allodynia
VASOMOTOR	temperature asymmetry +/- skin color changes +/- skin color asymmetry	temperature asymmetry +/- skin color changes +/- asymmetry
SUDOMOTOR/ EDEMA	edema +/- sweating changes +/- sweating asymmetry	edema +/- sweating changes +/- sweating asymmetry
MOTOR/ TROPHIC	decreased ROM +/- motor dysfunction (weakness, tremor, dystonia) +/- trophic changes	decreased ROM +/- motor dysfunction +/- trophic changes (hair, nail, skin)

CRPS Diagnostic Criteria

- Continuing pain, which is disproportionate to any inciting event
- There is no other diagnosis that better explains the signs and symptoms

CRPS

- **CRPS 1**

- “No nerve lesion can be identified” ^{1,2}
- Formerly known as Reflex Sympathetic Dystrophy

- **CRPS 2**

- Associated with a nerve lesion
- Formerly called Causalgia

¹ Oaklander et al. Pain 2006: 235-43

² Albrecht et al. Pain 2006: 244-66

Pathophysiology of CRPS

Manifestations of CRPS

An illustration of an iceberg floating in water. The tip of the iceberg, which is above the water line, is white and jagged. The much larger part of the iceberg, which is submerged below the water line, is a solid blue color. This visual metaphor represents the visible symptoms of CRPS (the tip) versus the underlying pathophysiology (the submerged part).

- Inflammation
- Role of Sympathetic Nervous System
- Neural Plasticity
- Neuroimmune Interactions

Treatment Options for CRPS

■ PHARMACOTHERAPY

- Membrane stabilizers
- Antidepressants
- Calcitonin
- Bisphosphonates
- Vasodilators
- NMDA receptor antagonists
- Topical ointment
- Opioids

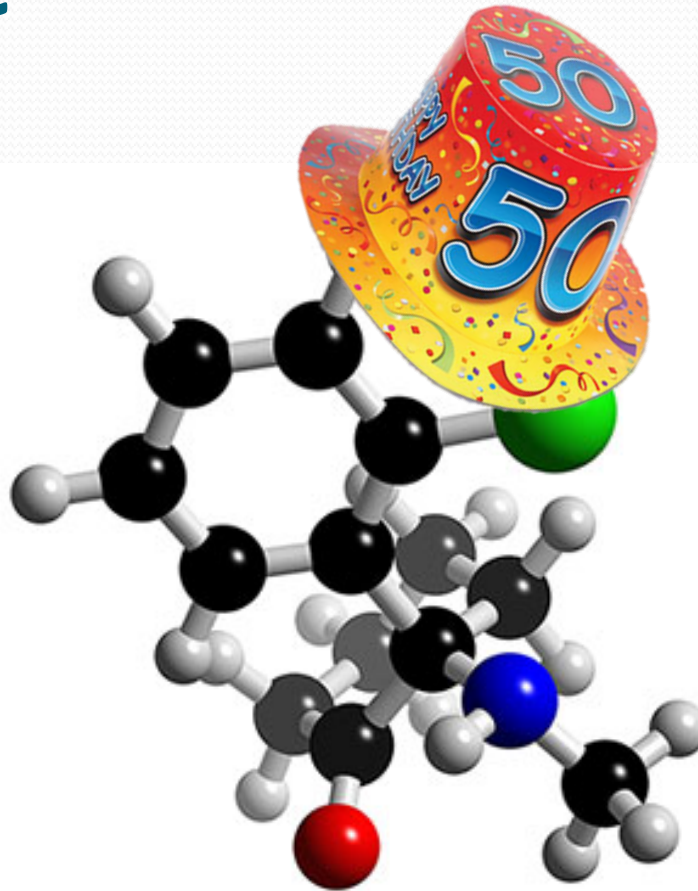
■ ANTI-INFLAMMATORY

- Corticosteroids
- NSAID

■ NON-PHARMACOLOGIC

- Mirror therapy
- Sympathetic Blocks
- Spinal Cord Stimulation
- Cognitive Behavioral Therapy
- Functional restoration
- Physical therapy
- Occupational therapy
- ECT

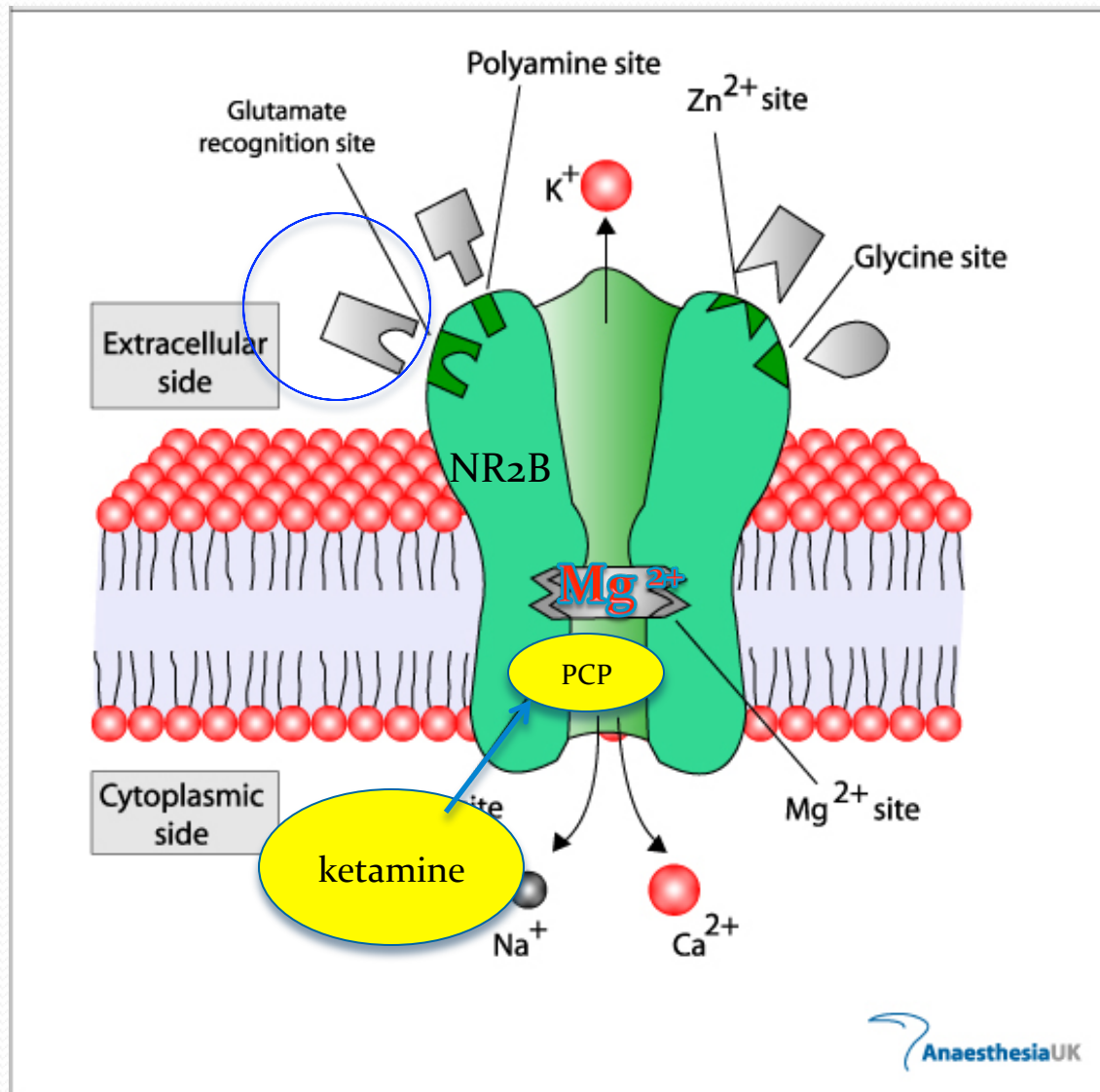
Ketamine



- Structurally related to PCP
- Dissociative anesthetic
- Rapidly crosses the blood brain barrier
- Metabolized in the liver to Norketamine
- Eliminated in the Bile and Kidneys

Ketamine Effects

NMDA Receptor



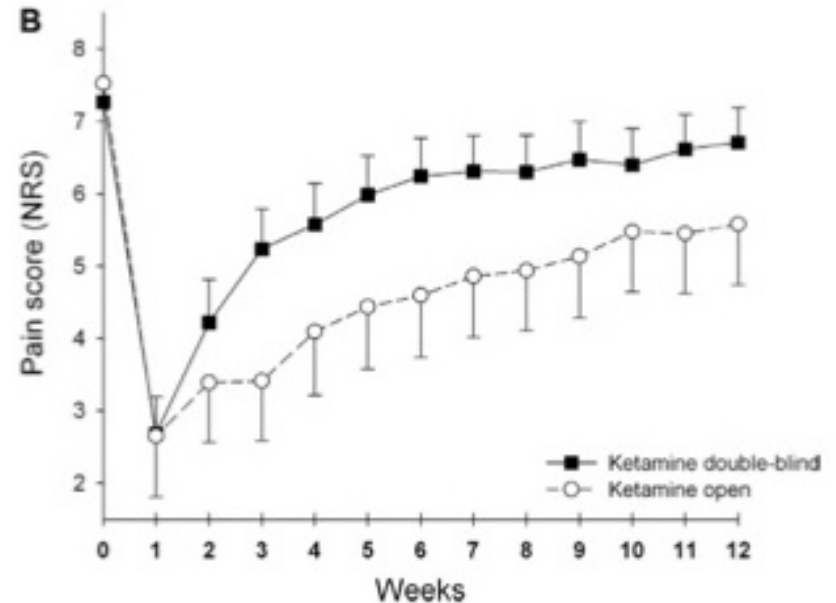
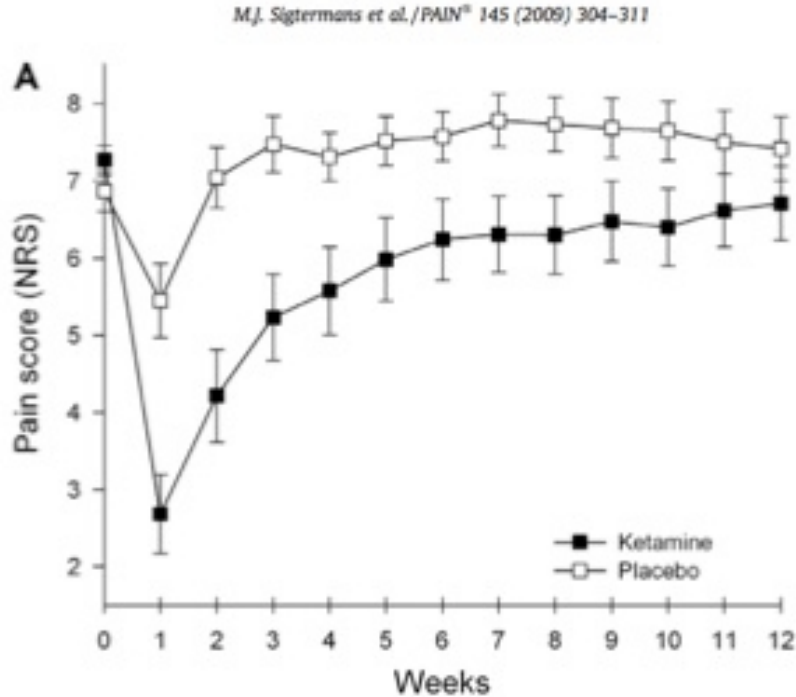
Studies

Ketamine Infusion for CRPS

Sigtermans et al:

- Double blind randomized placebo controlled study
- 60 patients with CRPS 1 with pain $\geq 7/10$
 - 30 received 4.2 day IV infusion of low dose ketamine
 - 30 received placebo (normal saline)
- Median disease duration was 7 years (0.1-39 years)
- Final dose: 20-24 mg/h/70 kg
- Infusion given over 4.2 days (100 hours)

Primary Outcomes



Primary outcome: Pain scores significantly lower in 12 weeks

Ketamine Infusion for CRPS

Schwartzman et al:

- Randomized double-blind placebo controlled study.
 - 10 placebo, 10 ketamine*
- CRPS for at least 6 months
- No significant difference in age, initial pain level or duration of disease
- Failed at least 3 therapies

*Study was powered for 20 subjects per arm, but reached statistic significance with a smaller number of study subjects.

Ketamine Infusion for CRPS

- 50 mg/h over 4 hours
- 10 day infusion
- Placebo and ketamine also received
 - Midazolam IV
 - Clonidine PO
 - NS 100 ml

Changes in Pain Score

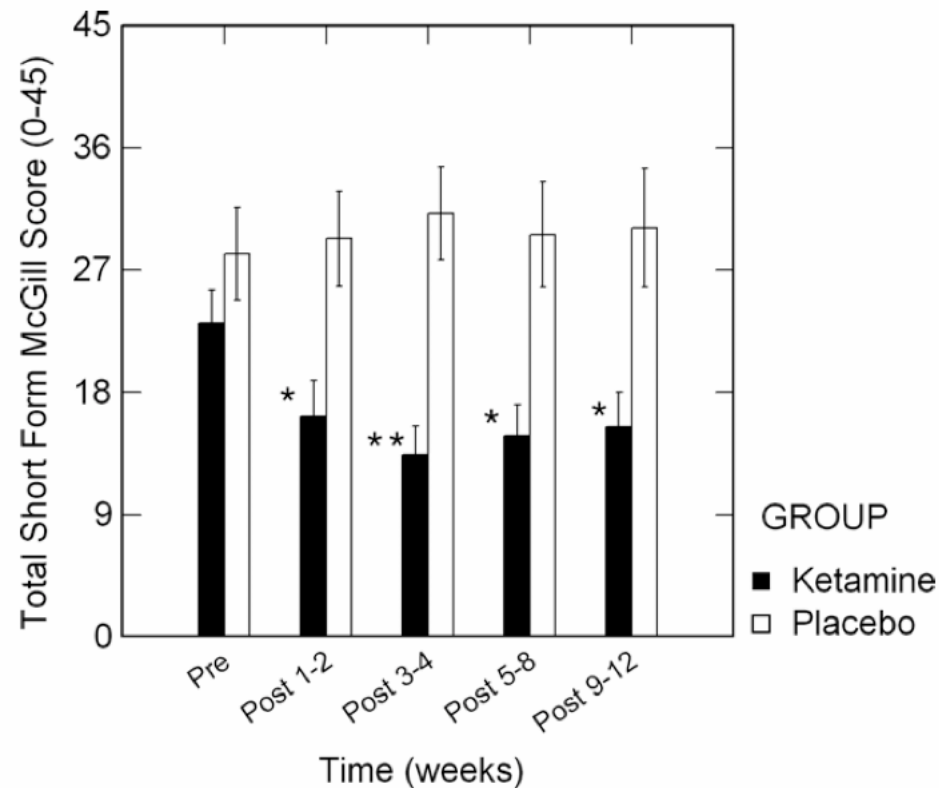
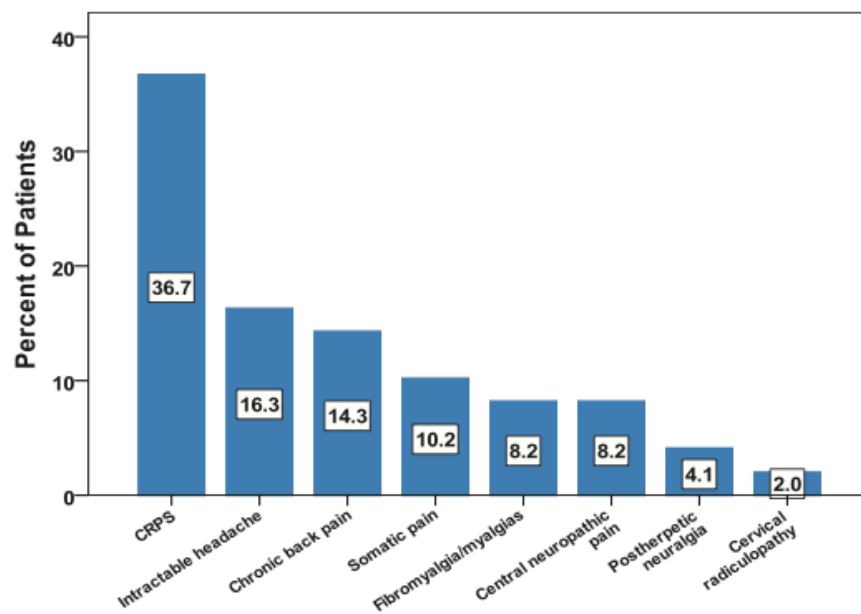


Fig. 1. Changes in the total McGill questionnaire score (means \pm SE) at five time periods

Ketamine Infusion for CRPS

Patil et al: Outpatient Ketamine Infusions in Refractory Pain



CRPS (N = 18)	
Infusion dose (mg/kg)	
Mean	1.0
SD	0.5
Infusion duration (minute)	
Median	43.8
Range	30–60
Days between infusion	
Median	30.8
Range	18–680
VAS before infusion	
Mean	8.5
SD	1.1
VAS after infusion	
Median	0.8
Range	0–6

*P<.001

Ketamine: Risks and Side Effects

- **Psychotropic**
 - Hallucinations
 - Anxiety
- **Transient memory deficits**
- **Neurocognitive**
- **Other CNS**
 - Dizziness
 - Blurred vision
 - Vertigo
 - Nystagmus
 - Nightmares
 - Vivid dreams

Ketamine: Risks and Side Effects

Cardiovascular

- Increase cardiac output
- Increase myocardial oxygen consumption
- Hypertension
- Tachycardia
- Systemic and pulmonary hypertension

Hepatic

- Elevated liver enzymes

Ketamine: Risks and Side Effects

Miscellaneous

- Nausea
- Headache

Bladder

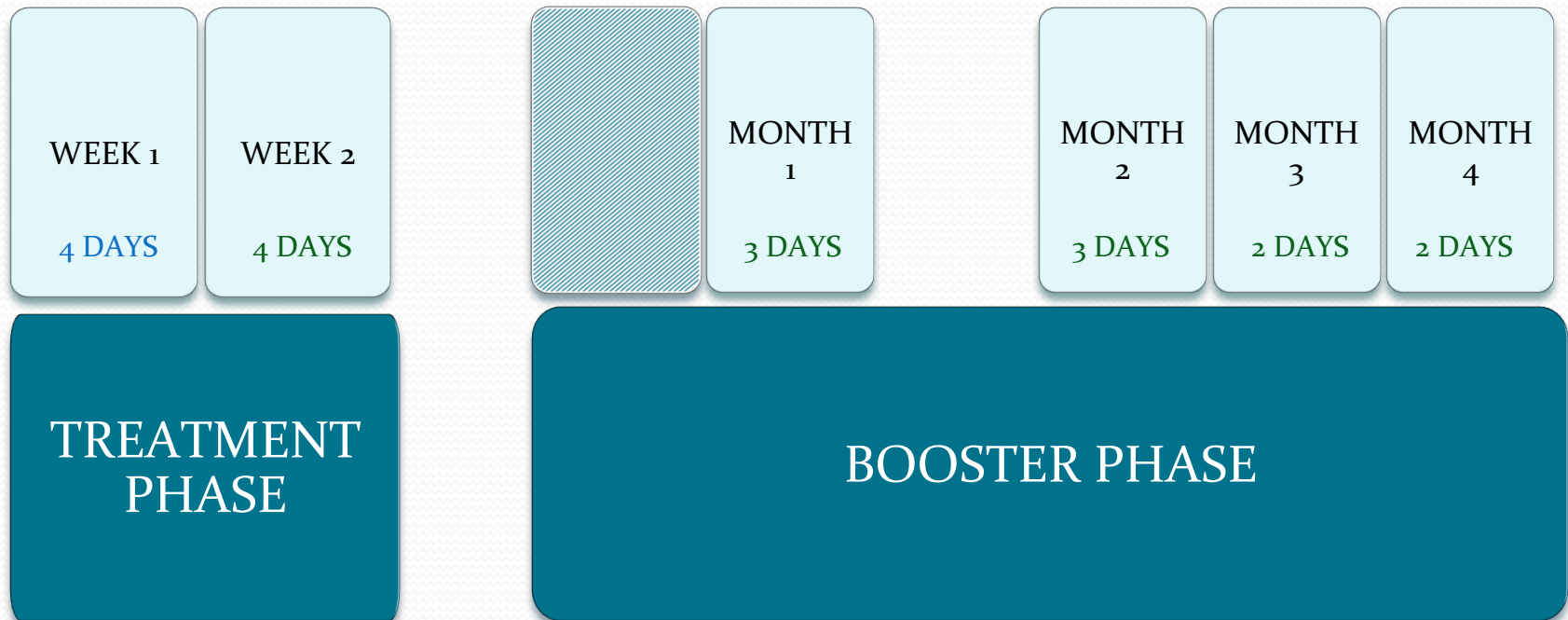
- Seen in abusers of Ketamine
- Ulcerative Cystitis

Outpatient Ketamine Infusion Clinic

Pre-infusion Preparation

- **Diagnosis based on current IASP guidelines (Budapest Criteria)**
- **Trialed other treatments for CRPS**
- **Treatment goals identified**
- **Psychological evaluation**
- **Cardiac evaluation**
- **Lab work**
- **All patients must be weaned off of opioids (completed 2 weeks prior to start of infusion)**

Infusion Protocol



Ketamine Dosing

TREATMENT PHASE	KETAMINE DOSE (MG/4 HOURS)
DAY 1	80
DAY 2	100
DAY 3	150
DAY 4-8	200

BOOSTER PHASE	KETAMINE DOSE (MG/4 HOURS)
MONTH 1-4	200*

*or last dose tolerated

Infusion Management

- **IV access: peripheral IV, PIC line, or infusion port**
- **Treatment environment: darkened, quiet, recliners**
- **Monitoring: ECG, Pulse Oximetry, NIBP, RR, Level of consciousness**
- **Monitored by RN certified in ACLS and DHMC Conscious Sedation Protocol**
- **Patients may listen to music**

Infusion Management


- PO Ativan and Clonidine before arriving at infusion suite (home medication)
- Ondansetron IV prior to infusion
- Midazolam: IV bolus prior to starting infusion, or component of Ketamine infusion
 - IV bolus prior to infusion
 - 1 mg/hour infusion
- Oxygen if needed

Clinical Measures

- **Goals**
- **Each day, prior to infusion:**
 - Exam
 - Side effects
 - Pain score
- **Pre and post infusion psychological evaluation**

Ketamine Infusion for CRPS

- Multiple outpatient visits using the longest feasible duration of infusion
- Using a dose of ketamine between 0.1 and 0.5 mg/kg/h
- Using adjunctive medication
 - Decrease side effects
 - Improve pain relief
- Monitored setting
 - Standard ASA monitors
 - Physician supervision
- Outpatient ketamine infusions: safe and effective

A painting of a path through a forest. The path is a light, dusty trail that leads from the bottom center towards the top center of the frame. The trees on either side are dark and dense, with their leaves creating a canopy that filters the sunlight. Bright, glowing patches of light are visible where the sun hits the path and the leaves, creating a dappled effect. The overall mood is serene and contemplative.

"Perhaps few persons [...] can realize the influence of which long-continued and unendurable pain can have upon both body and mind".

-Silas Weir Mitchell "Nerve Injuries" 1864

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