Retrospective Study

Retrospective Analysis of Liver Function Post Intravenous Ketamine for Treating Complex Regional Pain Syndrome

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Background: Complex Regional Pain Syndrome (CRPS) is a severely painful condition with very few effective treatments. One of the treatments used to treat CRPS is intravenous ketamine infusions. There has been one controversial anecdotal report on the effect of ketamine on liver dysfunction.

Objectives: This study aimed to determine the effect of ketamine on liver enzymes.

Study Design: A retrospective study.

Setting: Multilocation Pain Management Centers.

Methods: During the treatment period from January 2010 through December 2018, the medical records of 52 patients were reviewed and analyzed. All of them had undergone an intravenous ketamine infusion for managing CRPS. As per protocol, a liver function test was performed within 24 hours postinfusion. The Brown University Human Research Protection Program determined that the proposed research did not involve human subjects as defined by 45 CFR Part 46.102.

Results: A retrospective chart review was performed as part of ongoing quality assessment. All of the patients had received multiple days of a loading dose of ketamine infusion varying from 7 days to 10 days and received subsequent booster infusions varying from one day to 2 days. All the infusion days were limited to 4 hours each day. All the patients reported at least 50% pain relief lasting for more than 4 weeks to 6 weeks. Out of the 52 patients studied, 36 (69%) had returned to work or resumed attending school. Blood liver function tests were performed within 24 hours of the infusion. The liver function tests performed were serum albumin, total protein, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels. There was no evidence of liver dysfunction in any of the patients following their ketamine infusion.

Limitations: This was a retrospective analysis without a control group.

Conclusions: Intravenous ketamine infusions performed to achieve adequate pain control for CRPS does not alter liver function tests.

Key words: CRPS, Complex Regional Pain Syndrome, liver enzymes, ketamine, liver function test

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Complex Regional Pain Syndrome (CRPS) is a chronic pain syndrome characterized by pain disproportionate in magnitude or duration of pain. CRPS can be subdivided into CRPS I and II, based on the absence or presence of clinical signs of major peripheral nerve injury respectively (1). In the last decade, a better understanding of CRPS has emerged. In the development of CRPS, 3 pathophysiological pathways have been identified: aberrant inflammatory mechanisms, vasomotor dysfunction, and maladaptive neuroplasticity (2). The complexity of the condition and unclear pathology of CRPS have made it challenging to identify treatments for CRPS. The etiology of CRPS is grounded in CRPS having multiple causes, such as direct

nerve trauma, connective tissue disorder, autoimmune dysfunction, nerve entrapment, genetics, and changes in sympathetic-afferent coupling and endothelial dysfunction (3-9). A patient may present with CRPS from any one or multiple etiologies mentioned above. This then raises the conundrum of what should be the ideal treatment strategy for CRPS.

Whatever the etiology of CRPS may be (inflammation, genetic, autoimmune, trauma, or nerve entrapment), they all lead to functional and structural changes in the central nervous system (CNS) (10). These changes in the CNS result in central sensitization (11). Central sensitization is an amplification of neural signaling within the CNS that elicits pain hypersensitivity (12).

Central sensitization manifests as pain hypersensitivity, particularly dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, aftersensations, and enhanced temporal summation. Central sensitization introduces another dimension, one where the CNS can change, distort or amplify pain, increasing its degree, duration, and spatial extent in a manner that no longer directly reflects the specific qualities of peripheral noxious stimuli, but rather the particular functional states of circuits in the CNS (12).

One of the most important features of central sensitization is the activation and upregulation of glutamate receptors resulting in signal transmission enhancement in the nociceptors from the spinal cord to the cerebral cortex (13). Sensitized nociceptive neurons are very responsive to any peripheral input and may even fire spontaneously. Central sensitization explains chronic persistent pain, hyperalgesia, allodynia, and pain spreading to adjacent uninjured areas (12). Central sensitization of pain transmission neurons causes long-term potentiation which causes enhanced transmission of the neurons. Long-term potentiation releases glutamate and neuromodulators, such as the small vasoactive neuropeptide substance P, on to the pain transmission neurons. This is followed by release of the magnesium block of the N-methyl D-aspartate (NMDA) receptor that allows sodium and calcium to enter the cell. Intracellular calcium-induced cascades increase the excitability of the pain transmission neurons and the expression of new sodium channels and proteins, such as dynorphin (13). When fewer α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) fast-pain receptors are incorporated into the NMDA receptors, their synaptic efficacy is decreased or they are destroyed intracellularly when the NMDA receptor is blocked.

There has been increasing interest in the efficacy of using centrally acting drugs for treating central sensitization. NMDA receptor antagonists with efficacy in preclinical models can be tested in Phase 1b human proof of principal studies (11,14). Ketamine, an NMDA receptor antagonist, inhibits central temporal summation (15). It also inhibits mechanical hyperalgesia evoked by repetitive nociceptive electrical stimulation in humans as well as primary and secondary hyperalgesia after an experimental burn injury (16,17). It has been demonstrated to inhibit visceral conditioning inputs and topical or intradermal capsaicin (18-21). It does not inhibit A delta mediated nociceptive pain (22). The effect of ketamine and dextromethorphan on experimental pain can be shown on functional magnetic resonance imaging (23,24). These data clearly support the role of the NMDA receptor in acute activity–dependent central sensitization (25).

C-fiber nociceptive afferents release glutamate which activates NMDA receptors. At the same time, when the magnesium block is lifted from the NMDA receptor, the AMPA receptors are phosphorylated by phosphokinase A, altering the activation and deactivation kinetics (26). The qualities that make the NMDA receptor critical for its role in CRPS are its ligand-gated and voltage dependent activation; requirement of co-activation by 2 ligands; activity dependence that induces neural plasticity; complex activation and regulation; and its pleiotropic actions that lead to central sensitization of pain transmission neurons at all levels of the pain matrix (27). Interactions between the nervous system and the immune system that activate glial cells can induce central sensitization (28).

Glutamate receptors are present on pain transmission nerves in the peripheral and central nervous system (29). An NMDA receptor antagonist can block glutamate NMDA receptors, reducing central sensitization. Glutamate is present within sensory nerve endings and is released extracellularly by noxious stimulation. NMDA and other glutamate receptors are present on sensory nerve endings and on the cells adjacent to the nerve endings (e.g., keratinocytes, immune cells). Inflammation and tissue damage can cause elevated glutamate release from primary afferent nerve endings. Peripheral applications of glutamate receptor agonists lead to activation of sensory nerves (30).

A case report of 6 patients reported elevated liver enzymes occurred in 3 patients after repeated ketamine infusion (31). We undertook our analysis to better understand the hepatic toxicity of using intra-

venous ketamine for managing CRPS. In the study by Noppers, et al (31), the ketamine dose was extraordinarily high—1,220 mg and 3,297 mg (31). In addition, the infusions lasted for 100 hours and were repeated the following week. The accepted standard of care is to achieve 50% pain relief or functional improvement as identified by the patient while maintaining a balance between limiting side effects and increasing functionality. The authors of that article also had an unrealistic goal of achieving pain control as measured by the 11-point Numeric Rating Scale (NRS-11). The accepted form of ketamine used is a racemic mixture, whereas the authors used an S-isomer.

Methods

The medical records of 52 patients undergoing repetitive IV ketamine infusion for CRPS were reviewed. All the patients underwent IV ketamine infusion repetitively for CRPS from January 2010 through December 2018. The exclusion criteria were patients who received an IV ketamine infusion but did not have a CRPS diagnosis. All the patients in the study met the criteria for CRPS based on the International Association for the study of Pain (32). Every patient who underwent IV ketamine infusion reported NRS-11 scores of 6 or higher. The NRS-11 rates pain from 0 to 10, where 0 is no pain and 10 is the worst pain ever felt by the patient. As part of the standard protocol, patients had undergone an LFT within 24 hours after an IV ketamine infusion. The LFTs measured serum albumin, total protein, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels.

Adult patients that had a diagnosis of CRPS between the ages of 18 years and 65 years were administered a standard racemic mixture of ketamine. They had tried and failed all other conservative measures such as tricyclic antidepressants, anticonvulsants, antidepressants, selective serotonin norepinephrine inhibitors, nonsteroidal anti-inflammatory drugs, and opioids. Patients were administered doses varying between 1.6 mg/kg to 5.4 mg/kg over a period of 4 hours. Patients were also administered midazolam up to 4 mg spread over 4 hours and a single dose of ondansetron 4mg. The total volume of normal saline infused did not exceed 500 mL over the 4 hours.

The dose of ketamine infusion was based on pain relief. Patients were interviewed the day following the infusion. If they had achieved 50% pain relief from their pre-infusion levels, the last dose administered was maintained. If they reported any side effects, such as nausea or dysphoria, the dose was adjusted depending on the severity of the side effects. Patients underwent a loading dose of 7 days to 10 days, Monday to Thursday. The infusions were resumed the following Monday and continued until they achieved at least 50% pain relief either by day 7 or day 10. Essentially, the patients were administered IV ketamine 4 continuous days at a time. If the patients did not report significant (> 50%) relief after the first 4 days, the infusions were stopped. Patients who reported significant pain relief (> 50%) with the initial loading dose underwent booster infusions for 2 days 2 weeks after the initial loading dose. Subsequent booster infusions were administered for one day at intervals of 4 weeks to 6 weeks based on individual response.

As per protocol, patients underwent a LFTs within 24 hours after the last IV ketamine infusion day. The results were then tabulated.

Results

A retrospective chart review was performed as part of ongoing quality assessment. The woman to man ratio was 3:1. All patients in our study received multiple days of a loading dose of IV ketamine varying from 7 days to 10 days and received subsequent booster infusions varying from one day to 2 days. All infusion days were limited to 4 hours.

The number of IV ketamine infusions ranged from one to 19 sessions, with an average of 8 sessions and a mode of 5 sessions. The distribution of the number of ketamine transfusions is shown in Fig. 1.

LFTs were performed within 24 hours of infusion. The LFTs performed were serum albumin, total protein, total bilirubin, AST, ALT, and alkaline phosphatase levels. LFTs post IV ketamine infusion for all 52 patients were analyzed; a total of 395 LFTs were reviewed. The distribution of serum albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase levels, and ketamine dosage are shown in Fig. 2–Fig.8. A statistical analysis of these variablesusing Microsoft® Excel Version 16.89.1 (24091630)—minimum, maximum, and average—variables are summarized in Table 1.

There was no evidence of liver dysfunction in any of the patients following their ketamine infusion. None of the patients reported any significant side effects the day after the infusion;. no hallucinations were reported. Sixteen patients who were on opioids for their pain prior to starting infusions were eventually able to taper off opioids as their pain improved.

All patients reported at least 50% pain relief last-

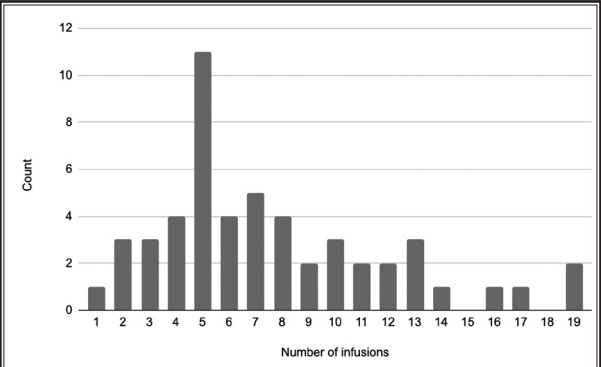

Fig. 1. *Distribution of IV ketamine infusion session counts of the 52 patients with CRPS.*

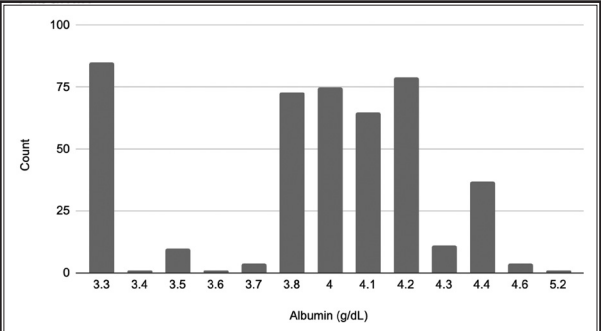

Fig. 2. *Distribution of albumin levels measures within 24 hours of IV ketamine infusion.*

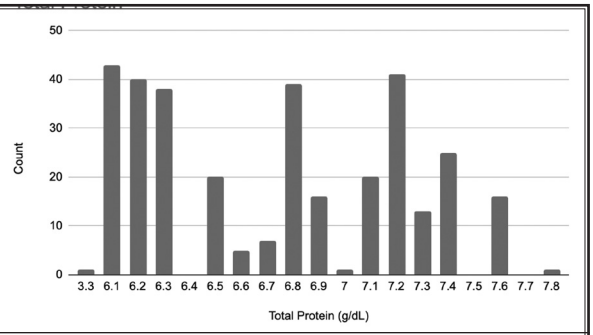

Fig. 3. *Distribution of total protein levels measured within 24 hours of IV ketamine infusion.*

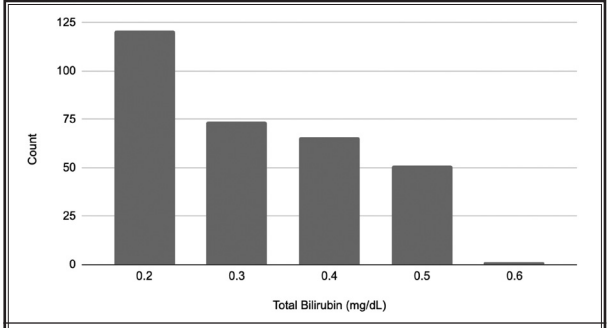

Fig. 4. *Distribution of total bilirubin levels measured with 24 hours of IV ketamine infusion.*

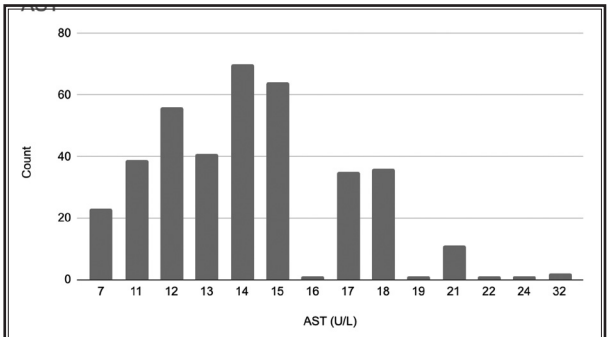

Fig. 5. *Distribution of AST (SGOT) measured within 24 hours of IV ketamine infusion.*

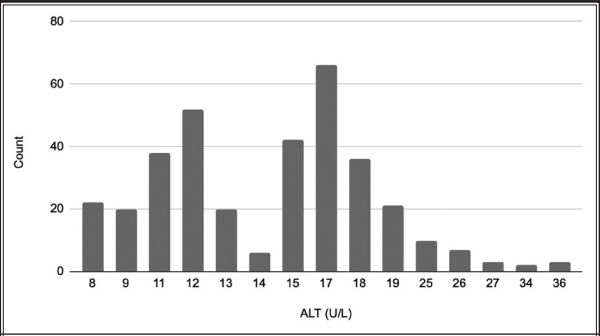

Fig. 6. *Distribution of ALT (SGPT) measured within 24 hours of IV ketamine infusion.*

ing for more than 4 to 6 weeks. Out of the 52 patients studied, 36 (69%) had returned to work or resumed attending school. One of them was a nurse who finished nursing school and took a full-time job. Another patient continued his college studies and research. One patient was an accountant and continued to work. One patient went back to work and has had several promotions at work. Twelve patients (23%) were retired. Four patients were on a disability pension.

Discussion

Ketamine is one of the safest anesthetic agents. It is on the World Health Organization's List of Essential Medicines needed in a basic health system. The safety

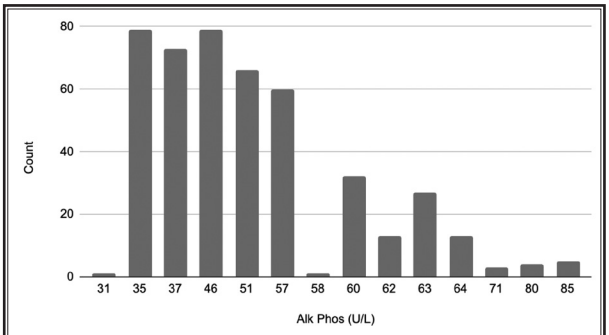

Fig. 7. *Distribution of Alk Phos measured within 24 hours of IV ketamine infusion.*

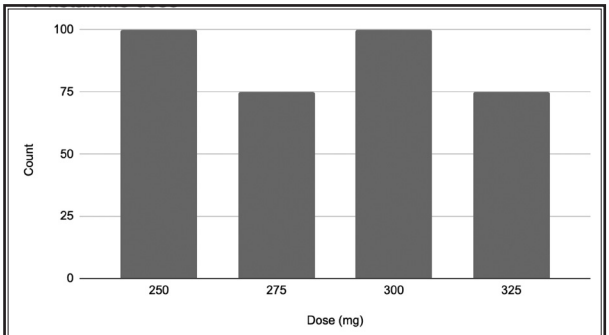

Fig. 8. *Distribution of dose of IV ketamine infusion used for study participants with CRPS.*

Table 1. *Summary of liver function tests within 24 hours after IV ketamine transfusion and dosage of IV ketamine infusions.*

	Albumin (g/dL)	Total Protein (g/dL)	T Bilirubin (mg/dl)	AST (SGOT, U/L)	ALT (SGPT, U/L)	Alk Phos (U/L)	Dose (mg)
Mean	3.9	6.9	0.32	14.5	15.2	47.9	294.1
Min	3.3	3.3	0.2	7	8	31	250
Max	5.2	7.8	0.6	32	36	85	325

of ketamine is based on its being a sympathetic nervous system stimulant. Most other anesthetics and drugs of the opioid class have a depressive effect on blood pressure and heart rate, as well as a diminishing effect on protective airway reflexes and breathing. Despite causing increases in blood pressure and heart rate, ketamine is considered safe due to its preservation of airway reflexes and respiration. The safety of administering intravenous ketamine makes it a drug of choice in emergencies, intensive care units, and trauma. It was first used for treating American soldiers during the Vietnam War after its approval by the US Food and Drug Administration in 1970.

Ketamine belongs to the phencyclidine group of drugs. Of all the NMDA receptor antagonists from the phencyclidine group; ketamine has the strongest affinity to the NMDA receptor. It is an arylcyclohexylamine anesthetic that acts as a noncompetitive inhibitor of NMDA receptors. Ketamine is considered a safe anesthetic primarily for its stimulant properties. It stimulates respiration and increases blood pressure and heart rate. Ketamine undergoes extensive hepatic metabolism largely via the cytochrome P450 system.

The principle behind using IV ketamine for treating CRPS is to reduce central sensitization by antagonism of the NMDA receptors. Additional mechanisms for its analgesic properties are inhibiting nitric oxide synthesis blocking voltage-gated calcium and sodium channels, altering cholinergic neurotransmission, and reuptaking serotonin and norepinephrine. At the dose required to reduce central sensitization, psychotropic side effects are not common and are well managed with benzodiazepines. More common side effects are lethargy and nausea.

In a study by Noppers et al., 6 patients were scheduled to receive 2 continuously intravenous 100 hours S (+) ketamine for a total dose of 1,220 mg and 3,297 mg with an average of 10 mg/hour to 30 mg/hour (31). The infusion rate was increased until the patient reached a pain rating of zero on the NRS where 0 is no pain and 10 is the most pain the patient has felt. The authors reported that 3 (50%) of the 6 patients developed elevated liver enzymes. The study had several flaws to it.

The S-isomer of ketamine is not available for intravenous (IV) human use in the United States. The authors of that article also failed to properly screen patients by obtaining pre-infusion liver function tests (LFTs). It is possible that the patients with elevated LFTs post ketamine infusions had elevated LFTs prior to the infusion. These patients had elevated LFTs weeks after the infusion, again implying that these patients either had elevated LFTs prior to the infusion or had more susceptible liver functions. Any publication reporting adverse event conclusions must exclude all other potential causes that lead to adverse events. Noppers, et al (31) did not include pre-infusion testing and used

very high total dosing with an S-isomer of ketamine. This created a "perfect storm," resulting in elevated LFTs in 3 out of the 6 patients. It is important to note that despite the study flaws and extraordinarily high total dosing, the other 3 patients in that study did not have elevated LFTs. This is important as it establishes that even incredibly high doses of ketamine do not necessarily cause elevated LFTs.

Most countries use the racemic mixture of ketamine. The S-form of ketamine is not marketed in the United States; however, Spravato—esketamine—is marketed in the US. The clinically used form of ketamine is a 50:50 racemic mixture of the S- and R- form. The S- and R- isomers have significantly different properties. The S- isomer is a more potent analgesic. The R- isomer is responsible for its psychomimetic property (33). In the study by Noppers, et al (31), only the S (+) isomer of ketamine was used, a form of ketamine not used clinically.

In the treatment of CRPS, as with most chronic pain conditions, the generally accepted goal of pain relief is 50% and/or improved function. These goals are achieved by a multimodal approach using medications, physiotherapy, biofeedback, and other modalities. Attempting to achieve 100% pain relief solely based on medications is risky and not recommended. It puts patients at risk of overdosing and potential side effects.

Continuous infusion of most anesthetic agents decrease liver blood flow secondary to a decrease in cardiac output. Ketamine is an exception, in that it increases cardiac output and does not affect liver blood flow (34,35). It is unrealistic to compare the effect of ketamine on liver function used for anesthesia with its use for treating CRPS. When ketamine is administered for anesthesia, a large bolus of the drug is given. It is rarely administered as the sole anesthetic agent. General anesthesia using ketamine always involves multiple drugs. Surgery, per se, has also been known to alter liver blood flow and alter LFTs. During surgery, patients are administered multiple drugs, many of which can cause an elevation of liver enzymes. There are wide fluctuations in blood pressure from the effects of anesthetic medications and surgical blood loss.

In the study by Noppers, et al (31), 2 out of the 3 patients that developed hepatotoxicity had symptoms of autoimmune dysfunction. They developed pruritis, rash, urticaria pyrexia, and increased leukocyte count. These symptoms developed with the second ketamine infusion. It was unclear if these patients had a pre-existing autoimmune dysfunction (common in a subset of patients with CRPS). In one of the patients, the eosinophil count increased to 8% and the neutrophilic leukocytes to 77%. One patient developed an increase in her LFTs and also developed pruritis. Her antinuclear antibodies were positive. In the study, 3 (50%) of the patients did not demonstrate any increase in LFTs (31).

A PubMed key word search of ketamine, chronic pain, and LFTs resulted in only one paper (18). That study's drawback was that it had a small sample.

One of the limitations of our study was that it was a retrospective analysis. We acknowledge that the dose of ketamine used to treat CRPS has not been standardized and there is variation among physicians' choices and patients' responses. The dose range administered to the patients in our study (250 mg–325 mg) is considered the standard dose by most pain specialists for managing CRPS.

Conclusion

In a study of 52 patients undergoing repetitive ketamine infusion for managing CRPS, there was no evidence of liver dysfunction within 24 hours of ketamine infusion. Patients were administered varying doses of ketamine between 1.6 mg/kg to 5.4 mg/kg over a period of 4 hours. Other than short-term side effects of nausea and headache, none of the patients reported any long-term side effects. None of the patients had long-term cognitive side effects. The only reason for discontinuing ketamine infusion was for lack of pain relief. None of the patients had their infusion stopped for evidence of liver dysfunction.

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