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NEUROPATHIC PAIN SECTION

Review Article

Intravenous Ketamine Infusion for Complex Regional Pain Syndrome: Survey, Consensus, and a Reference Protocol

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Abstract

Objective. To find and reach a consensus on the usage of ketamine in the treatment of complex regional pain syndrome and to determine a reference protocol for future studies.

Design. Three hundred fifty-one medical professionals participated in our survey on practice procedures, with 104 respondents providing information on their usage of ketamine for treating the pain associated with complex regional pain syndrome. Respondents answered questions about inpatient treatment, outpatient treatment, children vs adults, safety, and basic demographic information. An expert group then met to reach a consensus for a reference protocol.

Results. There is a difference in how inpatients are treated compared with outpatients, making it necessary to have two different reference protocols. The duration of pain relief varied from one to 10 days to one to six months, with a correlation between the duration of pain relief and total infusion hours per round.

Conclusions. The consensus reference protocols are made up of nine recommended topics. Reference protocols need to be validated by extensive research before guidelines can be created.

Key Words. Complex Regional Pain Syndrome; Ketamine; Reference Protocol; Intravenous Infusion

Introduction

Ketamine (*RS*-2-[2-Chlorophenyl]-2-[methylamino] cyclohexanone) was first developed by Parke-Davis in 1962 and is a drug primarily used for general anesthesia in human and veterinary medicine [1]. It acts primarily as

an noncompetitive antagonist of the N-methyl-d-aspartate (NMDA) receptor [2], but it may also modulate monoamine, muscarinic, μ and κ opioid receptors, and voltage gated calcium channels [3]. Ketamine has a range of reported effects in humans including "dissociative" anesthesia, hallucinations, analgesia, elevated blood pressure (as opposed to most anesthetics), and bronchodilation. It is commonly employed in the initiation and maintenance of general anesthesia, but it is increasingly used in intensive care and pediatric procedures, emergency and battlefield medicine, and treatment of certain psychiatric conditions. It was used in psychiatric research in the 1970s [4] and now is an established second-line agent in depression [5].

The use of ketamine in pain management was first reported in 1989 [6]. Low-dose ketamine produces analgesia and modulates central sensitization, hyperalgesia, and opioid tolerance. Numerous reports of varying evidence quality suggest that ketamine may prove useful for intractable/refractory neuropathic pain conditions [7–13], particularly complex regional pain syndrome (CRPS) [14–18]. Ketamine is being used increasingly in intravenous (IV) infusion clinics to manage CRPS pain, but without guidance, standard protocols, or guidelines. We report the results of a survey of practice procedures and a follow-up on structured consensus process.

Background and Significance

CRPS, formerly known as reflex sympathetic dystrophy (RSD) and causalgia, is one of the most challenging clinical pain syndromes. Many common treatments for other hypothetically related types of pain are not effective for CRPS, perhaps due partially to the fact that the mechanism for CRPS is still not fully understood. One of the hallmarks of CPRS is central sensitization [19], namely amplification/augmentation of pain signals in the central nervous system (CNS), which is mediated to some degree by the NMDA receptor [20,21].

Since the 1990s, many case series have suggested that IV ketamine infusion is effective in reducing pain in CRPS/RSD [22–30]. These reports are limited by small samples and unclear diagnostic criteria for the disorder. Only a few randomized controlled trials (RCTs) have studied IV ketamine infusion in CRPS. The first RCT was reported by Sigtermans in 60 CRPS type I patients (i.e., with no discernable major nerve damage) who met the first International Association for the Study of Pain (IASP) criteria [31]. Patients were admitted for five days. IV ketamine was started at 1.2 μg/kg/min (or 5 mg/h for a 70-kg patient) on day 1 and was titrated to a maximal dose at 7.2 μg/kg/min (or 30 mg/h for a 70-kg patient). Ketamine ($N = 30$) provided significant pain relief compared with placebo ($N = 30$, $P < 0.001$) but the significance was lost at week 12 ($P = 0.07$). Ketamine did not cause functional improvement but did result in mild to moderate psychomimetic side effects. A secondary analysis on these data found that significant pain relief was achieved for up to six weeks, but it was incidentally noted that there was no direct effect on motor function [32]. A pharmacokinetic-pharmacodynamic (PK-PD) modeling study on these data showed that 100-hour infusion of S(+)-ketamine treatment is more effective in pain relief than placebo in CRPS-1 patients with analgesia, outlasting the treatment period by 50 days, but the plasma concentration decreases rapidly after the infusion is stopped [33].

Schwartzman et al. [34] studied outpatient IV ketamine infusion for CRPS in a small double-blind, placebo-controlled trial. Subjects were infused intravenously with normal saline, with or without ketamine, for four hours daily for 10 days. The study was powered for 20 subjects per arm, but it was discontinued early at 10 subjects in the placebo group and nine in the ketamine group. The resulting pilot study showed that intravenous ketamine resulted in (marginally) statistically significant ($P < 0.05$) reductions in "many" pain parameters, but was underpowered. The authors concluded, "The results of this study warrant a larger randomized placebo controlled trial using higher doses of ketamine and a longer follow-up period" [34].

Systematic reviews [35–38] have evaluated IV ketamine in CRPS and concluded that, although ketamine shows some promise in the treatment of CRPS, there is not sufficient evidence to recommend routine use of ketamine, and furthermore, large, well-designed RCTs are needed. The current level of evidence is 2B (i.e., moderate evidence, positive but weak recommendation). In these subanesthetic parenteral paradigms, adverse effects observed included dizziness, sedation, nausea, hallucinations, transient liver toxicity, and neurotoxicity.

To summarize the currently available clinical data, IV ketamine infusion has been used at varying doses, comedication delivery, and exposure durations in patients with CRPS that is refractory to conventional therapy. There is no high-quality evidence for the use of ketamine in CRPS. Also, several different infusion protocols have been utilized, making comparison among the different studies impossible. In the absence of a "gold standard" protocol for ketamine infusion for CRPS, the most appropriate preliminary approach would be to conduct a survey of current practice to form an expert survey consensus, to then corroborate this survey approach with a consensus meeting of expert practitioners, which would finally be then validated by subsequent clinical practice and research [39].

Methods for the Survey

Electronic questionnaires were delivered using a common online survey tool (SurveyMonkey, San Mateo, CA, USA) (Supplementary Data). Fellowship Program Directors for ACGME pain medicine fellowship programs in the United States as well as authors of research publications that involved the utilization of intravenous ketamine in the treatment of CRPS in the United States and internationally were invited to participate. We also asked the recipients to forward the survey link to their expert

colleagues in an attempt to expand the scope of the survey.

Basic demographic information was collected, including primary specialty, location of practice, and years the providers have been treating CRPS (Supplementary Data). Questions related to use of IV ketamine infusion in CRPS included the diagnostic criteria used, number of CRPS patients treated, and number of IV ketamine infusion sessions prescribed annually. Specific questions on IV ketamine infusion protocol for adult and pediatric patients in both outpatient and inpatient settings included starting dose, titration criteria, maintenance infusion rate, maximum daily dose, infusion duration (hours per infusion and number of days per series), number of infusion series, subsequent infusion practices, use of adjuvant medications, outcome measures, treatment goals/end points, and adverse effect profiles. Based upon their observations, respondents were asked to select the incidence of adverse effects.

The analyses for this study were largely descriptive. Statistical analysis was performed using SPSS 24.0 (Chicago, IL, USA). The Wilcoxon sum rank test was used to analyze whether different infusion rates could affect the duration of pain relief. Univariate regression analysis was used to investigate the relationship between the total infusion hours per round and the duration of pain relief, with $P < 0.05$ considered statistically significant.

Results

Demographics

Three hundred fifty-one responses were received. The response rate could not be calculated as the targeted e-mail recipients were asked to forward the survey link to their colleagues. Only those who responded to the entire questionnaire were analyzed. Among those who responded to the "region of practice" question, 86 were from United States, 25 from Korea, five from Canada, four from Australia, four from Europe, and two from Israel. More than half the respondents were anesthesiologists (53.8%). The remaining specialties were physical medicine and rehabilitation (7%), orthopedics (5.8%), neurology (4.8%), and "other" (pain medicine, family medicine, psychiatry, etc.). Fifty-seven of 104 respondents reported practice in an outpatient setting (30 solo and 27 group practice). Thirty-four respondents had been practicing for one to five years, 22 for six to 10 years, 15 for 11–20 years, and 33 for more than 20 years. Thirty-two (53.3%) of 60 respondents used IASP version II (Budapest) diagnostic criteria for inclusion, six (10%) used the IASP criteria version I, and 22 (36.7%) used their own "clinical judgment" (i.e., no formal entry/diagnostic criteria). Sixteen of 63 respondents (25.4%) see fewer than 10 patients annually, 29 (46%) see 10–50, 13 (20%) see 51–100, and five (7.7%) see more than 100 CRPS annually. Twenty-nine of 63 respondents (46%) treat fewer than 10 patients yearly with ketamine infusions, another 29 (46%) treat 10–50 patients with ketamine, four (6.3%) treat 51–100 patients, and one (1.6%) treats more than 100 patients annually with ketamine. Fifty-three out of 66 respondents (80.3%) treat adult patients only, and 13 (19.7%) treat both adult and pediatric patients. Forty of 51 respondents (78.4%) perform outpatient ketamine infusion only; nine (17.6%) perform inpatient infusion only, and two (3.9%) do both. Thirty (28%) of the respondents are in outpatient solo practice, 27 (26%) are in outpatient group practice, 25 (24%) work in academic centers, 15% in hospital-based practice, and seven were categorized as "other."

Table 1 Treatment frequency in the adult outpatient setting

Frequency	No. (%)
Daily	23 (58)
Weekly	5 (13)
Every other day	3 (8)
Other frequency	9 (23)

Table 2 The adult outpatient rate of IV ketamine infusion for patients with CRPS

mg/kg/d	No. (%)
0.05–0.7	7 (31.8)
0.75–4.0	12 (54.5)
5.0–10	3 (13.6)

CRPS = complex regional pain syndrome; IV = intravenous.

Infusion Protocols

Twenty-three of 40 (58%) respondents perform daily infusion, five (13%) do weekly infusion, three (4.8%) provide infusion every other day, with other frequencies ranging from one every three days to once per several months (Table 1).

The infusion doses range from 0.05 to 10 mg/kg/d, with 54.5% (12 of 22) of respondents using an infusion rate of 0.75–4 mg/kg/d. Four of 57 (7.0%) respondents use a rate of infusion of less than 0.1 mg/kg/h, 24 (42.1%) use 0.1–0.5 mg/kg/h, and 29 (50.9%) use more than 0.5 mg/kg/h (Table 2). If a set dose was used, the range per session (53.8%) was 100–500 mg. The maximum daily dose ranged from 200 mg to 2000 mg, with a mode of 200–600 mg (Table 3).

The duration of infusion ranged from one to eight hours, with four hours being the most commonly reported (Figure 1). The average total infusion hours per infusion

Table 3 The adult outpatient dose (dose range, minimum, and maximum dose) of IV ketamine infusion for patients with CRPS

Set Dose/Session, mg	No. (%)	Minimum Daily Dose, mg	No. (%)	Maximum Daily Dose, mg	No. (%)
Up to 99	5 (38.4)	Up to 99	7 (33.3)	Up to 199	3 (13.0)
100–499	7 (53.4)	100–199	4 (19.0)	200–299	5 (21.7)
500–2,000	1 (7.7)	200–299	5 (23.8)	300–399	2 (8.7)
		300–399	2 (9.5)	400–499	2 (8.7)
		400–499	2 (9.5)	500–599	5 (21.7)
		500–599	1 (4.8)	600–699	1 (4.3)
				700–799	0 (0.0)
				800–899	1 (4.3)
				900–999	0 (0.0)
				1,000–1,499	2 (8.7)
				1,500–2,000	2 (8.7)

Responses reported as number and (%).
CRPS = complex regional pain syndrome; IV = intravenous.

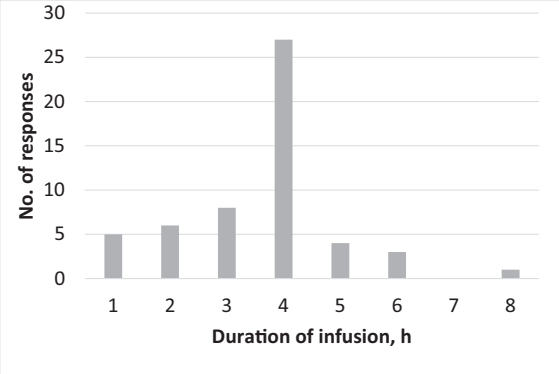

Figure 1 Duration of outpatients intravenous ketamine infusion session (hours; adult).

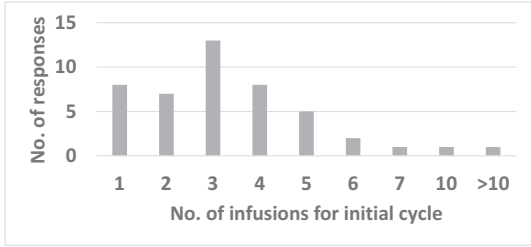

Figure 2 Number of outpatient infusions for initial cycle (adult).

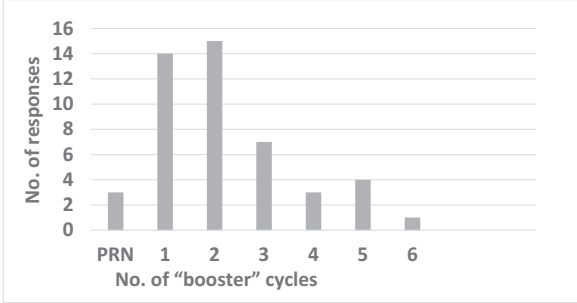

Figure 3 Sessions for outpatient intravenous ketamine "booster" infusion cycles (adult).

cycle (product of hours per session and number of sessions per round of treatment) was 16 ± 11 hours.

Most providers administer three infusions (mode) for the initial infusion cycle (Figure 2) and one or two "booster" (subsequent) infusion cycles (Figure 3). Intervals for subsequent infusion cycles ranged from one week to one year, or as needed with a mode of one month (32.5%, 12 of 38).

There were many fewer responses (N = 33) concerning adult inpatient protocols. The dose for inpatient (continuous) infusion ranges from 0.35 to 5 mg/kg/d (rate = 10–40 mg/h, duration = 3–5 d). The interval for subsequent booster infusion was three to four months.

There were even fewer responses [15] to the pediatric infusion protocol questions. Most infusions were completed as outpatient (12 of 15). Most practitioners reported using a daily infusion with a duration of one to five hours. Five responded to the infusion rate question, with one of five using less than 0.1 mg/kg/h, two of five using 0.1–0.5 mg/kg/h, and two of five using >0.5 mg/kg/h. Three to six sessions were given in the initial infusion cycle, and two of five practitioners used two "booster" sessions at as-needed intervals.

Use of Adjuvant Medications

The most used adjuvant medications among the respondents are IV midazolam (34 of 35 respondents,

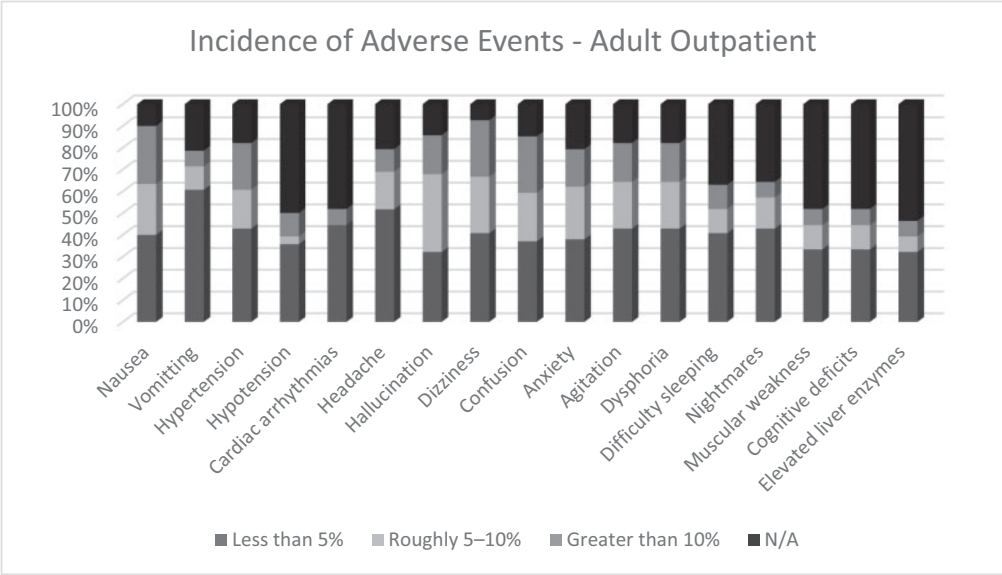

Figure 4 Reported adverse effects of intravenous ketamine infusion in complex regional pain syndrome patients.

range = 1–9 mg, mode = 2–4 mg) and ondansetron (25 of 35 respondents, range = 4–8 mg, mode = 4 mg). Other adjuvants used include metoclopramide (eight of 35 respondents), promethazine (two of 35), aprepitant, lorazepam, and dexamethasone. Four respondents used dexmedetomidine, and eight used clonidine. Other adjuvants infrequently mentioned include lidocaine, ketorolac, thiopental, magnesium, diazepam, alprazolam, di-henhydramine, hydroxyzine, olanzapine, and Propofol.

Reported Adverse Effects of IV Ketamine Infusion for CRPS (from Survey)

Respondents generally reported that the incidence of most adverse effects of ketamine infusion was less than 5% (e.g., nausea, vomiting, hypertension, hypotension, cardiac arrhythmias, headache, dizziness, confusion, anxiety, agitation, dysphoria, difficulty sleeping, nightmares, muscular weakness, memory problems, other cognitive deficits, elevated liver enzymes). Hallucination occurred in 5–10% of patients, but may have been dose dependent (Figure 4).

Clinical Outcome Measures

Nineteen of 33 respondents (57.6%) used a verbal numeric rating scale (NRS), and 15 (45.5%) used a visual analog scale as their pain score. One respondent for each reported using the Multidimensional Personality Questionnaire (MPQ), pain pressure threshold, or Brief Pain Inventory. Fifty percent or greater improvement in pain score was utilized by most respondents (50%, 15 of 30) to define a successful infusion. Six of 35 respondents did not use any metrics for functional assessment. Four used the Pain Disability Index (PDI), four used short-form SF-36, and one each used the short Brief Pain Inventory (BPI) "self-report" and physical therapy/occupational therapy assessment. The COMPACT core data set for CRPS was not available at the time of the survey or consensus meeting [40].

Duration of pain relief was reported in days (range = 1–10 days, 9 [25%] of 36 responders), weeks (1– 12 weeks, 12 [33%] of 36 responders), or months (range = 1–6 months, 15 [42%] of 36 responders). Univariate regression analysis indicated that there was a moderate relationship between the duration of pain relief (days) and total infusion hours per round (Pearson correlation coefficient $r = 0.48$) (Figure 5). The ratio of geometric means was 1.23 (95% CI = 1.03–1.47, $P = 0.028$) (Table 4), indicating that for every five hours' increase in total infusion hours per infusion cycle, there was a 23% (95% CI = 3–47%) increase in the provider-perceived duration of pain relief (days) on average.

Methods for Consensus Meeting for Development of Reference Protocols

A day of didactic lectures about the "State of the Art and Science" of ketamine infusions for CRPS was followed by a half-day, closed workshop designed to generate a consensus-based reference protocol. Experts in the field (clinical and research leaders) were selected for the closed consensus workshop by the conference organizers (Supplementary Data).

The results of the survey were presented in detail and served as the starting point for the consensus deliberations. Sample protocols and safety issues were

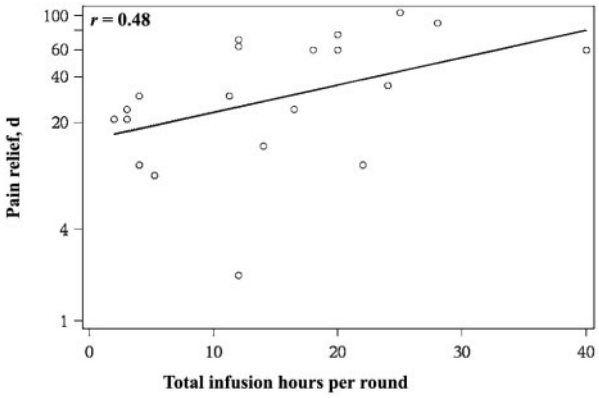

Figure 5 Scatterplot with the regression line between length of pain relief and total infusion hours per round.

Table 4 Univariate regression between length of pain relief and total infusion hours per round

Exposure	Unit	Ratio of Geometric Means (95% CI) of Length of Pain Relief, d	*P* Value
Total infusion hours per round	Unit = 5 h	1.23 (1.03–1.47)	0.028

CI = confidence interval.

discussed. Four breakout groups then convened for detailed discussion focused on four topics: (1) inpatient protocols, (2) outpatient protocols, (3) safety, and (4) recommended outcome measures. The full group of attendees then resumed deliberations on these and other specific topics relevant to ketamine infusion for CRPS.

The Reference Protocol

The consensus process (general or unanimous agreement) produced two separate reference protocols: one for inpatient ketamine infusion and one for outpatient treatment. These are intended to be a "reference" (starting point) for clinical and research protocols. These reference protocols must be validated by extensive research before guidelines can be formally generated. The consensus reference protocols consist of nine recommended topics: informed consent, minimal setting characteristics, techniques for monitoring the infusions, premedication, ketamine infusion parameters, adjuvant medications, tapering, recommendations for subsequent "booster" infusions, and outcome metrics.

Informed Consent

The informed consent for ketamine IV infusion should include, at minimum, print and oral presentation of rationale, potential benefits and risks of ketamine therapy, and common adverse events. It should also include a complete description of the protocol to be utilized. If a local IRB is available to assist in the development and approval of the informed consent document, this is strongly recommended.

Setting and Monitoring

We recommend avoidance of disquieting environments to decrease the incidence of ketamine-induced hallucination [41].

Inpatient therapy should take place in an intensive care unit (ICU)–type setting with full advanced cardiac life support (ACLS) capability.

Outpatient therapy should take place in a suite with continuous, direct cardio-respiratory monitoring and one-on-one or continuous remote audio-visual monitoring by trained medical personnel, at a minimum. Full ACLS capability must be maintained.

Pre-infusion monitoring/labs should include a pertained history, an airway assessment, vital sign measurement, electrocardiography, and serum studies to include liver and thyroid panels, with results available prior to a decision to proceed.

During infusion(s), a Foley catheter or portable urinal should be used to monitor urine output for calculation of intake/output variance. Intermittent pneumatic compression devices (IPCD) should be applied to prevent deep venous thrombosis.

Postinfusion monitoring should continue for six hours after inpatient therapy and 60 minutes after outpatient therapy. Inpatients require a sitter/minder for three days and daily serum liver panels for three days. Outpatients require a (nonprofessional) sitter/minder through the first night (Table 5).

Premedication

Inpatient: Routine premedication recommendations include clonidine (or alternatively dexmedetomidine), aspirin, and midazolam (or another, benzodiazepine, may help prevent ketamine-induced hallucinations [42]. Optional inpatient premedications include magnesium and anti-emetics, started the night before therapy.

Outpatient: Premedications are similar to inpatient premedication.

Table 5 Recommended ketamine screening and peri-administration adverse effect prevention and monitoring

Sequence	Recommendation
Pre-administration screenings	• Substance abuse disorder risk screening • Airway and respiratory history • Psychiatric evaluation and/or clearance for those at risk of schizophrenia, bipolar, PTSD • Cardiac history • Medication history (ideally opioids should be discontinued) • Washout of other NMDA active agents (e.g., memantine, amantadine, methadone, levorphanol, dextromethorphan) • Drug interaction evaluation (CYP active drugs) • Baseline LFTs, pregnancy test, urine analysis, and urine toxicology screen
Peri-administration	• ECG (continuous) • Oxygen saturation (continuous) • Vitals (Q15 X 4, Q30 X 2, and then hourly) • Supplemental O2 and suction available • Standard crash cart including flumazenil and naloxone • IV site assessment (infection, patency)
Post-administration	• Postinfusion observation (minimum of 1 h) to include ability to perform certain ADLs • Released to family member or friend for observation for evening of infusion • Fall risk • Agitation, nightmares (take benzodiazepine)

ADLs = activities of daily living; CYP = ; ECG = ; LFTs = ; NMDA = N-methyl-d-aspartate; PTSD = post-traumatic stress disorder.

Table 6 The RASS, recommend to achieve RASS score of –1 to –3

+4	Combative	Violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive, but movements not aggressive or vigorous
0	Alert & calm	
–1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening & contact $\geq$10 sec)
–2	Light sedation	Briefly awakens to voice (eye opening & contact $<$10 sec)
–3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
–4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
–5	Unarousable	No response to voice or physical stimulation

RASS = Richmond Agitation-Sedation Scale.

Ketamine Therapy

Inpatient Infusion

Initial rate: 10 mg/h (approximately 0.15 mg/kg/h based on ideal body weight), increased every two hours in 5–10-mg increments.

Maximum rate: 40 mg/h maximum.

Titrate to "drowsy to moderate sedation" (e.g., Richmond Agitation-Sedation Scale [RASS] score of –1 to –3) (Table 6) [43] or pain reduction by 50% using numeric pain rating scale (verbal), whichever is achieved first.

Duration: 24 hours for three to five days.

Outpatient Infusion

Initial rate on day 1: 0.4–0.7 mg/kg/h; then titrated to RASS score of –1 to –3 or pain reduction by 50% using numeric pain rating scale (verbal), whichever is achieved

first. If the patient becomes oversedated or dissociation is too great or not tolerated, then reduce infusion by 25%.

Maximum rate: 50 mg/h.

Total dose: 200 mg on day 1.

In subsequent sessions, dosing is 30% more than the prior day's maximum dose. The routine target dose is 150 mg/h, or 600 mg over four hours (some participants suggested that carefully selected patients may receive up to 1200 mg over four hours).

Duration: Four hours for each of five to 10 sessions.

Co-administered Adjuvant Medications

Inpatient adjuvant medications include routine clonidine (or dexmedetomidine) titrated to cardiorespiratory parameters, optional ondansetron or other anti-emetic, optional magnesium (4 g per liter over each 24 hours), optional ephedrine for hypotension, optional nonsteroidal anti-inflammatory drug of choice. Multiple other medications were endorsed by less than 14% of participants (e.g., barbiturates, Propofol, diphenhydramine).

Outpatient adjuvant medications differ from the inpatient reference protocol only in that clonidine and dexmedetomidine are considered optional.

Tapering

Optional at 10 mg per hour for inpatients. There was no tapering recommended for outpatients.

Subsequent ("Booster") Therapy

Inpatient booster sessions are considered optional, with a starting dose of 25% of the maximum dose during the previous inpatient therapy.

For outpatients, 25% of the maximum previous dose takes place for one or two days every one or two weeks.

Outcomes Assessment

The participants of the consensus process agree that pain is the pivotal measure in assessing the infusion pace and impact. A variety of measures were mentioned, but the verbal numeric pain score is probably the most efficient in the context of the infusion session. The "COMPACT" core data set for CRPS is now available [40], elements of which may be used in the infusion suite, and the full COMPACT is strongly recommended in the research context.

Safety

Ketamine is a relatively safe medication when used in subanesthetic doses, as is the case in the treatment of CRPS [37]. Judicious anticipation and prevention of common adverse effects (AEs) of ketamine greatly enhance tolerability and improve treatment outcomes. The side effects vary widely, depending primarily on the context of ketamine use (e.g., induction of anesthesia, subanesthetic analgesia, procedural analgesia, or recreational abuse).

Table 7 Reported adverse effects associated with ketamine at varying doses

System	Representative adverse effects
Central nervous system	Sedation
	Vivid dreams
	Psychotomimesis
	Dissociative reactions
	Euphoria
	Headache
	Dizziness
	Fatigue
	Mood alterations
	Paresthesias
	Dysarthria
	Tinnitus
Cardiovascular	Tachycardia
	Hypertension
Pulmonary	Hyperventilation
Gastrointestinal	Hypersalivation
	Dry mouth
	Altered taste
	Nausea
	Hepatotoxicity
Genitourinary	Cystitis
Musculoskeletal	Rigidity
Integumentary	Pruritus

Central nervous system (CNS)–related AEs of ketamine are the most widely recognized and potentially the most bothersome to patients. Sedation, vivid dreams, hallucinations, mood changes, paresthesias, and euphoria have all been reported owing to ketamine's abuse potential (Table 7).

Dissociative reactions after ketamine administration are significantly more common in adults than children and can present as visual and auditory distortions/hallucinations, a sense of floating, or feeling "detached from oneself or reality." These problematic psychotomimetic effects of ketamine are frequently experienced upon emerging from the pharmacodynamic influence of the drug (i.e., emergence phenomenon). As a result, delirium may impede recovery and, in severe cases, can result in movement or behavior dangerous to the patient or health care professionals. Typically, the delirium or hallucinations that do result are mild and minimally distressing. Patients may report seeing colored abstract

objects or that colors of the surrounding environment seem significantly more vivid. It is rare that patients hallucinate specific recognizable objects, people, or events.

Co-administration with a benzodiazepine often ameliorates emergence phenomenon symptoms, with midazolam being the preferred agent owing to its relatively rapid onset of effect and short half-life [42]. Midazolam is used both at the start of the infusion and often toward the end, given its pharmacokinetic and pharmacodynamic properties. If the patient is kept minimally sedated through the discontinuation of the infusion and for 30 to 60 minutes after, the emergence phenomenon is typically prevented.

Patients can vary widely in their tolerance to ketamine and the co-administered benzodiazepine. In some patients with a significant degree of tolerance, wakefulness may persist throughout all or most of the infusion. If the patient is either distressed during the infusion or experiences anxiety, hallucinations, or disturbing dreams after the infusion, it is recommended that sedation be maintained as long as needed, even if this does require larger doses of benzodiazepine. For patients with high tolerance to benzodiazepines, adjunctive agents such as hydroxyzine, diphenhydramine, haloperidol, and olanzapine can be helpful adjuncts in achieving or maintaining sedation. Additionally, pretreatment with oral diazepam may decrease the need for midazolam during the infusion [31,32]. Oral diazepam can also be considered to take at bedtime after discharge from outpatient infusion to prevent bad or vivid dreams and hallucinations.

Drugs with NMDA antagonist activity have been associated with neuro-apoptosis in the cerebral cortex and the development of neuronal vacuolation in the posterior cingulate cortex. While this finding has not been specifically identified in studies of ketamine in humans, many clinicians will co-administer clonidine with ketamine to reduce NMDA-mediated acetylcholine release in the posterior cingulate cortex.

Cognitive function is a clear concern of long-term utilization of ketamine [44,45]. Short-term infusion of subanesthetic ketamine (IV infusion at 0.5 mg/kg over 40 minutes on a Monday-Wednesday-Friday schedule during a 12-day period, six infusions) in patients with treatment-resistant depression significantly improved visual memory, simple working memory, and complex working memory during a four-week observational period [46]. In CRPS patients, studies reported that at six-week follow-up, there was improved brief attention and processing speed, whereas other cognitive functions remained stable after short-term use of ketamine (all patients reached a Ramsay Score 4–5 depth of anesthesia and had ketamine levels of 250–300 ug/dl for at least 4.5 days) [47]. Long-term frequent ketamine use (defined as treatment that lasted six months or more, and "frequent use" was defined as two times or more per month over the course of 3.82 ± 1.3 mean years [$\pm$ SD]) resulted in significant impairment on digit span, digit symbol, the Controlled Oral Word Association Test, and the Trail Making Test, as compared with less long-term users (duration of ketamine treatment 1.86 ± 2.2 years) [48]. However, the dose of ketamine was not mentioned in this study. Further studies are warranted to delineate the true association of repeated subanesthetic ketamine infusion (as we recommended in this article) with long-term cognitive function.

More recently, ketamine has been associated with the development of a myriad of genitourinary symptoms. Drug-associated ulcerative cystitis syndrome presents with dysuria, variable forms of incontinence, urgency, and painful hematuria. Cystitis [49,50] tends to affect young patients using ketamine recreationally. Single infusions of subanesthetic doses of ketamine resulted in less than 10% of patients having increased urinary frequency or painful urination [51]. We have observed one case of debilitating dysuria, spastic polyuria, and urinary urge incontinence after a seven-day IV infusion of subanesthetic ketamine (2–30 mcg/kg/min) for intractable trigeminal neuralgia [52].

The pathophysiology of this phenomenon is poorly understood but likely involves direct cellular toxicity. It is noteworthy that the preponderance of reports for ketamine-associated ulcerative cystitis involve illicit use of the drug for recreational purposes and not use under closely monitored direct medical care.

Infusion tolerance criteria included lethargy/dysphoria, altered mental status, intense dissociation, titration to analgesic effects, an achievement of serum concentration at or >600 ng/mL, or patient psychological profiles/vitals.

Discussion

The process of survey→consensus meeting→validation has been used successfully to generate diagnostic criteria [53] and validate outcomes [54]. This manuscript reports on the first two steps of this process for developing guidelines by a large survey followed by a consensus-building process (general or unanimous agreement by the participants). The participants constructed two protocols after determining that inpatient and outpatient protocols required distinct parameters. The resulting reference protocols, one for inpatient ketamine treatment and one for outpatient ketamine treatment, do not represent guidelines for ketamine infusion for CRPS; rather, they are a reference/orientation by which practitioners can access the consensus of highly experienced practitioners. Importantly, this consensus result can provide a starting point for statistical validation of formal guidelines and a more uniform approach to research protocols that will validate the safety and efficacy of ketamine through controlled clinical trials. A shorter duration of trial, for example, three-day infusion, can be considered to evaluate outcomes before the

patient is committed to the extensive (five to 10 days consecutive) outpatient infusion.

While ketamine infusion therapy for CRPS has been an occasional approach for decades, recent interest in nonopioid treatments has spurred new attention to various types of infusion therapies. In the United States, there has been a national increase in the use of such therapies and a dramatic increase in the number of centers performing these procedures. Unfortunately, research has not kept pace with this trend, and there is currently a paucity of evidence to conduct the creation of formal guidelines (e.g., by meta-analytics). The decision to survey experienced practitioners and then conduct a consensus-building exercise was designed as a first step in guidelines generation, not only for clinical intervention, but to guide and standardize research in the area. Thus, we present these reference protocols. It is our hope that future studies will use this reference protocol and validate its feasibility and make it possible to compare outcome measurements among different infusion centers using the same protocol and to compare protocols by using the same outcomes.

There was general agreement that the setting for an infusion needs to be "ICU level" with full ACLS capability for proper monitoring and control. There was general agreement that premedication should include clonidine and midazolam, with the addition of an antiemetic drug before or during infusion. Multiple other drugs were suggested less frequently by the survey and consensus groups. There was good agreement as to a 50% pain reduction end point for titration, but many opined that failing that, a secondary titration end point could be moderate sedation and/or dissociation. The unanimous consensus for outcome commonality is to use the COMPACT core data set [40].

Consensus group participants do not endorse the use of anesthetic doses of ketamine. While ketamine is relatively safe when used in subanesthetic doses, management of anticipated common adverse events to improve outcomes is necessary.

Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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