

Preliminary Research Articles

Efficacy of 5-Day Continuous Lidocaine Infusion for the Treatment of Refractory Complex Regional Pain Syndrome

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ABSTRACT

Objective. Chronic regional pain syndrome (CRPS) is a severe pain condition that usually results from an injury or surgical procedure. The pain in CRPS often spreads from the site of injury, and with time becomes refractory to conventional therapy. The present study was undertaken to evaluate the effects of 5-day continuous intravenous lidocaine treatment in patients afflicted with CRPS.

Methods. Intravenous lidocaine was administered in an escalating dose schedule to 49 severely affected CRPS patients in a monitored setting over 5 days. Evaluation of pain parameters and other signs and symptoms of CRPS were obtained during the infusion and at 1, 3, and 6 months following therapy.

Results. The majority of patients demonstrated a significant decrease in pain parameters and other symptoms and signs of CRPS. The pain reduction lasted an average of 3 months. Lidocaine may be particularly effective for thermal and mechanical allodynia. Less clinically significant effects were documented on the motor aspects of the syndrome.

Discussion. Intravenous lidocaine administration titrated to 5 mg/L demonstrated: 1) a significant decrease in mechanical and thermal allodynia for three months, 2) lessened associated inflammatory components of CRPS, and 3) only minimal side effects and no severe complications.

Key Words. Refractory CRPS; Lidocaine; Thermal Allodynia; Mechanical Allodynia; Complex Regional Pain Syndrome

Introduction

Complex regional pain syndrome (CRPS) usually follows injury to a peripheral nerve, a surgical procedure, or minor trauma. The mechanism of action involves both central and peripheral components of the neuroaxis [1,2], as well as interactions between the immune and nervous system [3,4]. Factor analysis of a large group of CRPS patients has revealed that the signs and symptoms cluster into four distinct subgroups: 1) abnormal

pain processing; 2) skin color and temperature changes; 3) edema, vasomotor, and sudomotor abnormalities (hyperhidrosis most frequently); and 4) abnormalities of motor function and trophic changes [5,6]. The most recent consensus conference panel on CRPS held in Budapest in 2004 proposed that diagnostic criteria for CRPS include one symptom from each of the four factors and one sign in at least two with the provision that there is no other diagnosis that better explains the signs and symptoms [7]. It is clear that the process frequently spreads from the originally injured extremity [8], and in some patients may encompass a major part of the body. It is also evident in many patients that with time, there is increased intensity of pain and there is centralization of the process. This causes dysregulation of the central nervous

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system control of autonomic, somatosensory, and motor systems [2,9].

Until recently, there have been few therapeutic options for severe longstanding patients that have failed standard therapies [9–11]. The rationale for using systemic lidocaine for CRPS patients is based on both clinical studies and animal models of neuropathic pain. These have demonstrated that following peripheral nerve injury, tetrodotoxin-resistant sodium channels on primary nociceptive afferent fibers and small dorsal root ganglia pain transmission neurons are upregulated and undergo significant physiologic changes [12–14]. Intravenous lidocaine selectively blocks these specific channels and inhibits repetitive depolarization in a use-dependent manner [15]. In neuropathic pain models, intravenous lidocaine has been demonstrated to: 1) produce dose-dependent suppression of allodynia without blocking nerve conduction [16]; 2) reduce neuropathic pain behavior by increasing the threshold for mechanical allodynia; 3) reduce the discharge rate of injured nociceptive afferent fibers [17]; and 4) suppress tonic A-delta and C-fiber discharge initiated by acute injury [18].

In CRPS patients, a 6-week continuous subcutaneous infusion of 10% lidocaine provided significant pain relief [19]. Continuous lidocaine infusion has been found to be effective in burn patients without causing any major side effects [20]. A randomized placebo-controlled trial of intravenous lidocaine for neuropathic pain delivered at 5 mg/kg over 6 hours provided 4-hour pain relief after cessation of the infusion without causing adverse effects [21]. Experimentally induced secondary hyperalgesia in human subjects was decreased by systemic but not by regional administration of lidocaine, which suggests a central mechanism of action [22,23].

Systemic administration of local anesthetics in addition to lidocaine in neuropathic pain states have also been shown to provide potent clinical anesthesia and pain relief [24–27].

In patients with severe generalized CRPS, who have not responded to conventional therapies, more effective treatment is needed. Intravenous administration of lidocaine has been demonstrated to be effective in both animal models of neuropathic pain and in human studies [21,28], which supported its trial in CRPS patients. The purpose of this study is to retrospectively review the results of 5-day continuous intravenous lidocaine administration in a group of refractory CRPS patients that met the International Association for the Study of Pain (IASP) criteria for CRPS [7].

Methods

Patients

This was a retrospective study of 49 patients who were treated with an intravenous lidocaine protocol that consisted of a gradual upward titration to a blood level of 5 mg/L over a 5-day period unless limited by side effects. All were treated on a standard of care basis, had full information in regard to expected benefits and possible complications, had cardiac clearance, and were fully informed and gave their consent for treatment.

The same attending neurologist (R.J.S.) made the diagnosis, examined the patients on a daily basis, and recorded response to treatment and adverse events. Patient records were reviewed, and data regarding demographics, site of CRPS and consequent signs and symptoms, duration of illness, and response to treatment were obtained (Table 1).

The Institutional Review Board of Drexel University College of Medicine approval for review was granted for the period of January 2003 to December 2006.

Inclusion Criteria

Inclusion for intravenous lidocaine treatment was limited to severe, long-standing (>2 years) or fulminantly progressive disease (two patients <4 months and three patients <1 year). All patients met the Budapest 2004 IASP consensus criteria for CRPS [7]. Inclusion was limited to physically healthy patients who fulfilled the American Society of Anesthesiologists Physical Status Classification Class I or II.

CRPS symptomatology had to be present in more than one body quadrant or was spreading rapidly. The average pain intensity had to be at least 5 on the Likert numerical rating pain scale (0 being no pain and 10 the worst pain imaginable). All patients had to have failed standard pharmacological or interventional treatments. Failure was defined as: 1) no response to treatment or; 2) no lasting relief of pain (<2 months); and 3) persistence, recurrence, or progression of the syndrome. Prior to treatment, all patients had a complete workup to rule out other possible causes of their syndrome. This included basic blood and chemical parameters that included collagen vascular disease biomarkers. All patients had EMG, quantitative sensory testing, autonomic sensory testing, magnetic resonance imaging (MRI), myelogram with computed tomography (CT) (if bony entrapment of roots was a possibility), and specific ultrasound

Table 1 Patient demographics

No.	Age	Sex	Triggering Injury/Site of Primary CRPS Manifestation	CRPS Duration (Years)	Type of Spread	Status of Spread Baseline
1	24	M	Fracture of navicular in R hand/R hand	6	Contiguous, mirror	R hand, B/L legs
2	13	F	L ankle sprain/L ankle	15	Contiguous, mirror	L ankle, L knee, R hand
3	37	F	L3/L4 back injury due to MVA/L leg	2.5	Contiguous, mirror	L foot, R leg, R foot, B/L arms
4	31	M	R shoulder surgery/R hand	3	Contiguous, mirror	R shoulder, R arm, L arm, L hand
5	46	M	Lumbar discectomy and L4/L5 fusion for herniated disk/L foot	2	Contiguous, mirror	L leg, R lower extremity
6	47	F	R knee and L heel injury due to fall/R knee	9	Contiguous, mirror	R arm, L arm, R leg, L leg
7	32	F	R brachial plexus traction injury/R shoulder	10	Contiguous, mirror	R arm, R hand, L hand, L ankle
8	29	M	Removal of pilonidal cyst/lower back	23	Contiguous, mirror	Midback, bilateral hips, bilateral legs
9	9	F	Viral illness, PVCs/L knee	9	Contiguous, mirror	L leg, L foot, R leg, R shoulder
10	24	F	Fracture of R foot with subsequent R foot surgeries/R foot	6	Contiguous, mirror	R leg below the knee, lower back, R hip, R groin
11	53	F	R leg fracture and surgery/R leg	0.33	Contiguous, mirror	Back
12	35	F	Flexion-extension injury of neck due to MVA/bilateral hands	4	Contiguous, mirror	B/L feet
13	46	F	L knee meniscal tear and L knee arthroscopy/L leg		Mirror	R quadriceps, R knee
14	43	F	R brachial plexus traction injury due to R shoulder trauma and arthroscopy/R arm	6	Contiguous	R deltoid, R forearm, R hand
15	49	F	L knee replacement and arthroscopy/L leg	6	Contiguous	L foot, L buttock, lower back, L hip
16	30	F	L brachial plexus traction injury due to MVA/L arm	8	Contiguous, mirror	R arm, bilateral lower extremities
17	46	F	MVA/B/L legs	1	Contiguous, mirror	Bilateral arms
18	23	F	R ankle sprain and reconstruction surgery/R leg	2	Contiguous, mirror	Left lower extremity, R arm, R hand
19	16	F	R heel surgery/R foot	7.5	Contiguous, mirror	R knee, R leg, bilateral brachial plexus distributions
20	61	F	R knee fracture and arthroscopy/R knee	0.33	Contiguous, mirror	Bilateral lower extremities, R upper extremity
21	46	F	Crush injury to L foot/L foot	1	Contiguous, mirror	L leg, R foot
22	15	M	Surgical reconstruction of R ankle/R foot	3	Contiguous, mirror	L foot, B/L arms, B/L hands
23	23	F	Brachial plexus traction injury due to trauma to R shoulder/R shoulder	10	Contiguous, mirror	L arm, bilateral lower extremities
24	45	F	L brachial plexus traction injury due to fall/L arm, hand and shoulder	2	Mirror	R upper extremity
25	44	M	R knee surgery complicated by DVT and hematoma/R upper leg	2	Contiguous, mirror	Bilateral upper extremities, bilateral lower extremities
26	39	F	R brachial plexus traction injury due to rotator cuff repair surgery/R shoulder	6	Contiguous, mirror	R chest, R arm, R forearm, left upper extremity, bilateral legs
27	28	M	L arm fracture due to fall/L hand	2	Contiguous	L shoulder, L arm, L forearm
28	31	F	R brachial plexus traction injury due to shoulder trauma/R shoulder	3	Contiguous	R arm, R hand, R leg
29	44	M	R foot surgery for plantar fasciitis/R foot	4	Contiguous	R leg
30	37	M	R brachial plexus traction injury/R arm	3	Contiguous, mirror	R hand, L arm
31	17	F	Multiple R ankle injuries/R ankle	4	Contiguous, mirror	L ankle, B/L hands
32	37	F	Nonhealing L ankle fracture and subsequent L ankle surgery/L lower leg	2	Contiguous, mirror	Bilateral brachial plexus distributions
33			R carpal tunnel syndrome surgery/R hand	4	Contiguous, mirror	L hand, bilateral elbows, bilateral knees
34	52	F	R brachial plexus traction injury/R arm	1.5	Contiguous, mirror	L arm, R leg
35	46	F	L brachial plexus traction injury/L shoulder	3	Contiguous, mirror	Bilateral upper extremities, bilateral lower extremities
36	45	F	R brachial plexus traction injury due to repetitive strain injury/R arm	15	Contiguous, mirror	Bilateral shoulders, R face, R chest, R back, L arm, L hand
37	11	F	Brachial plexus traction injury due to gymnastics injury/lower back	9	Contiguous, mirror	Bilateral arms, buttocks, hips, bilateral legs
38	60	F	Several R knee arthroscopies/R knee	1.5	Contiguous, mirror	R leg, L leg
39	32	F	Back injury due to MVA/B/L legs	3	Contiguous, mirror	B/L feet, B/L hands
40	49	F	Repair of L5/S1 disk collapse/R foot	3	Mirror	L leg, L foot
41	44	F	Brachial plexus traction injury due to heavy lifting/L arm	15	Contiguous, mirror	R arm, L chest, L breast, L leg, L hip (G)
42	59	F	Cervical laminectomy/L shoulder	2	Contiguous	L arm, L hand
43	57	M	L knee meniscal tear/L knee	1	Contiguous	L leg
44	34	F	L knee injury at gym/L knee	5	Contiguous, mirror	Bilateral arms, bilateral legs
45	39	F	Flexion-extension neck injury/R neck and R shoulder	3	Contiguous, mirror	Bilateral arms, bilateral legs, bilateral hands
46	32	F	Brachial plexus traction injury/neck and bilateral arms	15	Contiguous, mirror	L face, bilateral hands
47	43	F	R brachial plexus traction injury/R arm	6	Contiguous, mirror	R hand, L arm, bilateral legs
48	49	F	R tibia fracture /R lower leg	3	Contiguous, mirror	L lower extremity, L upper extremity, bilateral feet
49	46	F	Hysterectomy/R hand	3	Contiguous, mirror	Bilateral legs

CRPS = chronic regional pain syndrome; M = male; F = female; R = right; L = left; MVA = motor vehicle accident; PVCs = premature ventricular contractions; DVT = deep vein thrombosis; B = bilateral.

and MRI evaluation for possible neuroma of peripheral nerves (if clinically relevant) at the Hospital for Special Surgery of the Weil College of Medicine of Cornell University in New York City. All patients with swelling of an extremity had arterial and venous Doppler evaluation to rule out vascular disease.

Exclusion Criteria

Patients with known contraindications such as allergies to lidocaine, seizure disorder, a history of substance or drug abuse, psychiatric illness, or suspected somatoform pain disorder were excluded. The investigators felt that issues concerning monetary gain and or loss due to the patient's medical condition may adversely affect the study, therefore patients with active litigation, compensation, or disability issues related to their CRPS were excluded from this study. Cardiac clearance was obtained by the same cardiologists who evaluate all of our CRPS patients prior to initiation of inpatient treatment and included some or all of the following: 1) 24-hour Holter monitor; 2) routine 12-lead electrocardiogram (EKG); and 3) echocardiogram (ECHO) with ejection fraction determination. Pregnancy was an exclusion factor. During the study, the patients were allowed to continue prescribed medications but were not allowed to start new medications or change the dosage of formerly prescribed medications.

Treatment Protocol

All patients were monitored in a step-down unit. Blood pressure, EKG, and oxygenation were monitored in standard fashion.

Lidocaine infusion consisted of 2 g of lidocaine in 250 mL of 5% dextrose in water delivered by continuous infusion at a rate of 7.55 cc/h (60.4 mg/h) over the first 24 hours, 11 cc/h over the next 24 hours, 15 cc on day 3, 18 cc/h on day 4, and 21 cc/h (168.0 mg/h) on day 5. Blood lidocaine levels were obtained daily (Table 5), and the infusion rate increased only if the blood level was less than 5 mg/L. If the blood lidocaine level was greater than 5 mg/L, the rate of infusion was decreased to the rate used on the previous day. If side effects occurred, drop in blood pressure, cardiac arrhythmia, dysphoria, or dizziness, dosage was decreased or stopped. This 5-day treatment protocol was designed after successful treatment of eight previous patients. These patients responded successfully to a titrated maximal infusion rate of 21 cc/h (168.0 mg/h). Faster infusion rates and

longer than 5 days of treatment caused dizziness, dysphoria, and hypotension.

General Procedures

The same investigator (R.J.S.) examined all patients during their infusion. The patients were treated in a step-down unit in which their blood pressure, electrocardiogram, and oxygenation were continuously monitored. Spontaneous pain was rated on a numerical rating scale (NRS: 0–10; 0, no pain to 10, worst pain imaginable).

Dynamic mechano-allodynia was determined in the area of involvement by lightly stroking the skin proximally to distally at the midforearm, quadriceps, and gastrocnemius muscles. Patients were instructed to separate this pain from their spontaneous pain and to rate it on a numerical rating scale of 0–10 (NRS: 0–10). All patients noted a return to their baseline pain level within approximately 2 minutes after each stimulus.

Deep pressure pain was determined by palpation at similar points on the appropriate extremity as obtained for mechano- and thermal allodynia. Joint pain was evaluated by palpation at the first metacarpophalangeal joint of the hand and the first metatarsophalangeal joint of the foot. The patients were instructed to rate the intensity of the evoked pain using the NRS: 0–10 for each stimulus.

Sensitivity to a cool stimulus was assessed by response to the steel handle of a reflex hammer applied at the midforearm, quadriceps, and gastrocnemius muscles. Sensitivity to cold was evaluated at follow-up on a numerical rating scale of 0, no sensitivity, to 4, severe sensitivity (NRS: 0–4). Similarly, muscle weakness, spasm, dystonia, tremor, edema, and hyperhidrosis were evaluated using the same NRS scale of 0–4.

At the end of the protocol, patients were called and their records from follow-up visits were reviewed. They were asked to rate their response to treatment in regard to: 1) overall spontaneous pain intensities; 2) pain to light touch; 3) pain to brushing of the skin; 4) deep muscle pain; 5) joint pain; 6) sensitivity to cold; 7) muscle weakness; 8) muscle spasms; 9) dystonia; 10) tremor; 11) swelling; and 12) sweating. The intervals were 1, 3, and 6 months. All patients were called and queried specifically by one author (M.P.) and examined by the same investigator (R.J.S.).

Patients were asked to enter the average spontaneous pain intensities they suffered at 1, 3, and 6

months after their infusion protocol was completed. The answer was based on NRS as noted above where 0 was “no pain” and 10 the most severe pain “imaginable.”

Patients were queried in regards to mechano-allodynia in which skin brushing was perceived as pain and asked: 1) Do you feel pain now or over the last month when touched or lightly brushed?; and 2) Do you feel pain now or within the last month when pressure is applied to a joint? The patients were asked to rate the severity of pain to these parameters at 1, 3, and 6 months. Deep muscle pain and sensitivity to cold over the same time period were similarly evaluated.

The patients were also asked to rate the following parameters: 1) weakness; 2) abnormal hand or foot posture; 3) muscle spasms and tremors; 4) swelling and sweating for the 1-, 3-, and 6-month time periods.

All variables are presented as means \pm SDs. The statistical significance of differences between pretreatment and posttreatment variables at 1, 3, and 6 months were determined by paired *t*-tests. Pearson correlations were used for relating pain intensity to outcome variables. A $P < 0.05$ was considered significant for all analyses. SPSS version 15 was used for all analyses (SPSS Inc., Chicago, IL).

Results

Forty-nine patients were treated (38 female and 11 male; mean age 42.6 ± 12.5 years, range: 18–61.5 years) (Table 1). All patients suffered severe or rapidly spreading CRPS. This was defined as symptoms and signs of CRPS that spread contiguously from the area of injury, to the opposite extremity or ipsilaterally to other extremity within 3 months to a year. Seven had rapid contiguous spread affecting the entire extremity, three suffered mirror spread to the opposite extremity, and 39 had spread to all extremities with involvement of thorax, head, and back to some degree. All patients were unresponsive to multiple conventional treatments and had failed standard pharmacological and physical therapy (Tables 2 and 3).

This study revealed that 76% of patients reported at least a 25% reduction of pain, while 31% had a greater than 50% reduction. Only 24% reported little beneficial effects on pain.

Average overall baseline pain intensity of the cohort ($N = 49$) was NRS 8.9 ± 1.37 . After treatment, a significant reduction of pain intensity was observed at 1, 3, and 6 months (NRS 5.5 ± 2.38

$P < 0.001$, 7.12 ± 2.29 $P < 0.001$ and NRS 8.45 ± 1.91 , $P < 0.05$), respectively (Figure 1).

The effect of lidocaine infusion on specific pain, motor, and autonomic symptoms is shown in Table 4.

At baseline, pain to light touch for the cohort was a NRS of 8.02 ± 3.00 . A significant reduction of pain was noted at 1 and 3 months (NRS 4.76 ± 3.14 and 6.10 ± 3.27 ; $P < 0.001$) respectively. At 6 months, statistically significant decrease of pain to light touch from baseline (NRS 7.61 ± 3.07 $P < 0.05$) was maintained.

Deep muscle pain at baseline was NRS 9.02 ± 1.39 . A statistically significant decrease of this pain was noted at all time periods: at 1 month, NRS 5.57 ± 2.69 , and 3 months (NRS 7.02 ± 2.33 , $P < 0.001$), and at 6 months (NRS 8.55 ± 1.54 ; $P < 0.05$).

Joint pain at baseline for the 49 patients was NRS 8.12 ± 2.41 . A statistically significant reduction of this pain was noted at all time points: at 1 month, NRS of 5.24 ± 2.96 ; $P < 0.001$, at 3 months 6.33 ± 2.86 ; $P < 0.001$, and at 6 months, a less robust decrease to NRS 7.92 ± 2.49 ; $P < 0.05$.

At baseline, sensitivity to cold was moderate to severe for most patients ($N = 49$) at 3.34 ± 1.37 . The scale (NRS: 0–4) utilized was 0 “no sensitivity” to 4 “severe sensitivity.” At 1 and 3 months, statistically significant decreases of cold sensitivity were observed NRS 2.04 ± 1.43 and 2.53 ± 1.41 ; $P < 0.001$. At 6 months, cold sensitivity had almost returned to baseline for the entire group (NRS 3.26 ± 1.41 ; $P = 0.209$).

Muscle weakness of the affected extremity was severe 3.39 ± 1.13 for the entire cohort ($N = 49$). The scale utilized being 0 “no weakness” and 4 being “severely weak.” A statistically significant increase in strength was noted at 1 month (NRS 2.73 ± 1.19 ; $P < 0.001$) and at 3 months (NRS 2.96 ± 1.22 ; $P < 0.001$), respectively. At 6 months, strength had decreased and returned to baseline for the cohort (NRS 3.35 ± 1.15 with a $P = 0.322$).

Muscle spasms were severe for the great majority of patient ($N = 44/49$) and were rated as 3.53 ± 1.04 . The scale utilized was 0 “no spasms” to 4 “very severe spasms.” A statistically significant reduction in muscle spasms was noted at 1 and 3 months for the entire cohort (NRS 2.55 ± 1.4 and 2.94 ± 1.25 , $P < 0.001$). At 6 months, spasms had returned to baseline for the entire group (NRS 3.47 ± 1.06 ; $P = 0.182$).

Utilizing a standard definition of dystonia as an abnormally maintained posture, all of the patients

Table 2 Previous pharmacological treatments

No.	Pharmacotherapy								
	Physiotherapy	NSAID	Antidepressants	Anticonvulsants	Spasmolytics	Na Channel Antagonists	Opioids	Ketamine	Analgesic Patches
1	+	+	+	+	+				
2	+	+	+	+	+			+	
3	+	+	+	+	+		+	+	
4	+	+	+	+				+	
5	+	+	+	+				+	+
6	+	+	+	+	+			+	
7	+	+	+	+	+			+	
8	+	+	+	+		+		+	
9	+	+	+	+	+			+	
10	+	+	+	+	+			+	+
11	+	+		+	+			+	
12	+	+	+	+		+		+	
13	+	+	+	+	+			+	
14	+	+		+	+			+	+
15	+	+	+	+	+			+	
16	+	+	+	+	+			+	
17	+	+	+	+	+			+	
18	+	+	+	+	+			+	
19	+	+	+	+	+			+	+
20	+	+	+	+					
21	+	+	+	+	+			+	
22	+	+	+	+	+			+	
23	+	+		+	+			+	+
24	+	+	+	+	+			+	
25	+	+	+	+		+		+	
26	+	+	+	+	+			+	+
27	+	+	+	+	+			+	
28	+	+	+	+	+				+
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35	+	+	+	+	+			+	
36	+	+	+	+	+			+	+
37	+	+	+	+		+		+	
38	+	+	+	+	+			+	
39	+	+	+	+	+			+	
40	+	+	+	+	+			+	
41	+	+	+	+	+	+		+	+
42		+	+	+				+	
43	+	+	+	+				+	
44	+	+	+	+				+	
45	+	+		+	+	+		+	+
46	+	+	+	+	+			+	
47	+	+	+	+		+		+	
48	+	+	+	+	+			+	
49	+	+	+	+	+			+	

NSAID = Nonsteroidal anti-inflammatory drug.

(N = 49) suffered this complication of CRPS in the affected extremity [29]. In the upper extremity, the arm, hand, and fingers were held in flexion. In the lower extremity, the foot was plantar flexed and inverted. The dystonias persisted in sleep and were all accompanied by some parameter of dystrophy and swelling.

Dystonia of the affected extremity or extremities was rated 3.41 ± 0.91 on a scale of 0 "no dystonia" to 4 "very severe dystonia," with no or

minimal movement of the affected extremities. A statistically significant decrease in dystonia was noted at 1 and 3 months for all patients (NRS 2.41 ± 1.15 and 2.88 ± 1.05 ; $P < 0.001$, respectively). At 6 months, dystonia had returned to baseline (NRS 3.37 ± 0.97 with $P = 0.322$).

The tremors noted in these patients (N = 49) were minimal and are similar to that described by van Hilten [3]. They occurred in the affected extremity or one of the affected extremities on

Table 3 Previous nonpharmacological treatments

No	Acupuncture/ TENS	Trigger Point Infiltration	Selective Nerve Blocks	Plexus Blocks	Intrathecal Block	Intraleural Block	Stellate Ganglion Blocks	Epidurals	Lumbar Sympathetic Nerve Block	Spinal Cord Stimulation	Intrathecal Systems
1			+				+	+	+	+	
2	-/+		+					+		+	
3				+				+		+	+
4							+	+		+	
5	+/-		+				+	+		+	
6							+	+			
7	-/+						+	+			
8							+	+			
9				+			+	+			
10	None		+				+	+			
11							+				
12	None										
13	None										
14	-/+						+	+		+	
15							+	+			
16	-/+		+		+		+	+		+	+
17							+	+			
18	+/-						+	+		+	
19											
20	None						+				
21			+							+	
22			+							+	
23					+		+	+		+	
24					+		+	+		+	
25	None										
26				+			+	+		+	
27											
28					+						
29			+		+					+	+
30							+	+			
31									+		
32		+	+		+						
33	None										
34	None										
35					+						
36					+						
37	None	+									
38			+						+		
39		+							+		
40				+					+		
41		+								+	
42	None						+				
43									+		
44							+		+		
45	-/+						+				
46			+								
47	-/+	+			+						
48	None										
49									+		

Blank boxes represent no treatment for that therapeutic modality. The + denotes that the patient was treated with the modality. TENS = transcutaneous electrical nerve stimulation.

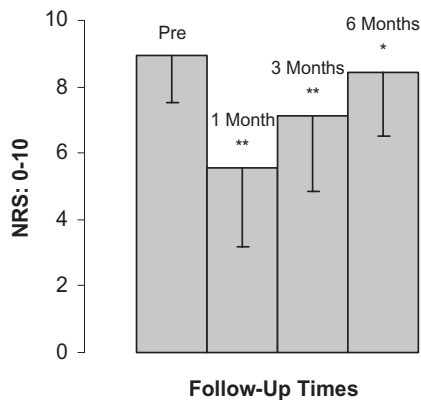


Figure 1 Overall pain intensity. This figure illustrates the reported overall pain as mean \pm SD before and at 1, 3, and 6 months following 5 days of intravenous lidocaine infusion, rated on an NRS scale of 0–10. Statistical significance was evaluated with a paired *t*-test (* $P < 0.05$; ** $P < 0.005$). NRS = numerical rating scale.

attempted movement. A significant reduction in tremor was noted from a baseline value of 1.38 ± 1.65 to that reported at 1 and 3 months for all patients (NRS 0.75 ± 1.18 ; $P < 0.001$ and 0.92 ± 1.4 $P = 0.003$). At 6 months, tremor had returned to baseline for the entire cohort (NRS 1.27 ± 1.59 with $P = 0.168$).

At baseline, swelling of the affected extremity or extremities affected all 49 patients. It was rated on a scale of 0 “no swelling” to 4 “severe swelling.” At baseline, swelling for the entire group ($N = 49$) was 3.57 ± 0.82 . A statistically significant reduction of swelling was noted at 1 month (NRS 1.88 ± 1.35 ; $P < 0.001$) and at 3 months ($2.45 \pm$

1.28 ; $P < 0.001$). At 6 months, swelling had returned to baseline (NRS 3.43 ± 0.91 , $P = 0.07$).

Sweating was noted in 36/49 patients (74%). The scale utilized was 0 “no sweating” to 4 “severe sweating.” Following treatment, there was a statistically significant decrease in patients with hyperhidrosis at 1 and 3 months (43%, $P < 0.001$, and 52%, $P < 0.004$), respectively. At 6 months, the percentage of patients in the group with hyperhidrosis had returned almost to baseline (69%, $P = 0.5$).

At 1 month, 36 patients had a minimum of 10% improvement in their pain parameters, and 13 patients had less than 10% relief in overall pain. For the patients that did improve, the average length of relief was 3.21 ± 1.73 months ($P < 0.001$).

Daily blood lidocaine levels are shown in Table 5. There was no correlation for length of relief with mean lidocaine level or highest measured lidocaine level. The length of relief was moderately and significantly correlated with baseline pain intensity ($r = 0.34$; $P = 0.02$). Interestingly, a previous study using acute lidocaine infusion also found that relief was related to initial pain intensity [28].

Complications

The side effects were mild, and no severe complications were noted. Sixteen of 49 (32.6%) patients had side effects. The mild side effects included nausea ($N = 1$), fatigue ($N = 1$), bradycardia ($N = 2$), tachycardia ($N = 1$), atrial arrhythmia

Table 4 Results

Variable	Before Mean \pm SD	Month 1 Mean \pm SD	Month 3 Mean \pm SD	Month 6 Mean \pm SD
(NRS: 0–10)				
Total pain	8.92 ± 1.37	$5.55 \pm 2.38^{**}$	$7.12 \pm 2.29^{**}$	$8.45 \pm 1.91^*$
Light touch	8.02 ± 3.00	$4.76 \pm 3.14^{**}$	$6.10 \pm 3.27^{**}$	$7.61 \pm 3.07^*$
Deep muscle	9.02 ± 1.39	$5.57 \pm 2.69^{**}$	$7.02 \pm 2.33^{**}$	$8.55 \pm 1.54^{**}$
Joint pain	8.12 ± 2.41	$5.24 \pm 2.96^{**}$	$6.33 \pm 2.86^{**}$	$7.92 \pm 2.49^*$
(NRS: 0–4)				
Cold	3.34 ± 1.37	$2.04 \pm 1.43^{**}$	$2.53 \pm 1.41^{**}$	3.26 ± 1.41
Weakness	3.39 ± 1.13	$2.73 \pm 1.19^{**}$	$2.96 \pm 1.22^{**}$	3.35 ± 1.15
Spasms	3.53 ± 1.04	$2.55 \pm 1.40^{**}$	$2.94 \pm 1.25^{**}$	3.47 ± 1.06
Dystonia	3.41 ± 0.96	$2.41 \pm 1.15^{**}$	$2.88 \pm 1.05^{**}$	3.37 ± 0.97
Tremors	1.38 ± 1.65	$0.75 \pm 1.18^{**}$	$0.92 \pm 1.40^{**}$	1.27 ± 1.59
Swelling	3.57 ± 0.82	$1.88 \pm 1.35^{**}$	$2.45 \pm 1.28^{**}$	3.43 ± 0.91
(% present)				
Sweating	73.8	42.9**	52.4**	69.0

* $P < 0.05$; ** $P < 0.005$.

Clinical parameters, tabulated as mean \pm SD, before and at 1, 3, and 6 months following 5 days of intravenous lidocaine infusion. The first four parameters (total pain–joint pain) were rated on an NRS scale of 0–10; the remaining parameters were rated on a 0–4 scale, except increased sweating, which was rated as present or absent and tabulated as percent present. Statistical significance was evaluated with a paired *t*-test. NRS = numerical rating scale.

Table 5 Lidocaine levels (mg/L)

	Patient	Lido Level Day 1	Lido Level Day 2	Lido Level Day 3	Lido Level Day 4	Lido Level Day 5
1	JB		3.1	4.4	2.2	0.79
2	SC		2.4	3.0	3.8	3.4
3	DC	<1.0	1.5	2.1	2.4	3.8
5	RC		1.5	1.9	4.4	5.8
6	DC	<1.0	1.2	2.0	3.0	3.7
8	GD		<1.0	1.5	2.1	2.0
9	JF	<1.0	1.5	2.6	2.4	2.8
10	KF	1.1	2.0	3.4	5.1	6.9
11	MG	1.0	1.5	1.5	2.1	1.8
12	DH		1.4	1.9	2.4	2.7
13	VH	<1.0	1.3	2.4	2.4	3.6
14	TH	<1.0	1.3	1.1	4.6, 2.0	<1.0
15	DH	<1.0	1.7	3.8	2.7	3.9
16	NH	<1.5	1.9	2.3	2.4	3.2
18	DH	1.2	1.9	2.4	4.9	4.6
19	KH	<1.0	1.3	2.1	4.8	4.5
20	MI		1.2	2.0	2.8	4.3
21	KJ		<1.0	1.4	1.8	2.6
22	KJ	<1.0	1.8	3.3	3.3	1.2
23	RL	0.8	1.9	2.4	3.2	4.3
24	MM	<1.0	1.9	2.8	2.6	3.5
25	BO		0.6	1.1	1.6	1.9
26	JR			2.3	2.7	3.2
27	SR		2.9	3.5	6.1	4.7
28	DR		1.2	2.3	2.1	3.3
29	DR		1.1	2.2	2.1	4.0
30	KS	<1.0	1.5	2.6	2.5	3.5
31	SS		1.8	2.7	3.9	4.1
32	AS	<1.0	2.3	2.9	3.7	3.7
33	LS		1.4	2.1	3.7	4.3
34	FS		1.1	2.0	3.5	4.0
35	AV	1.1	1.8	4.0	3.3	4.1
36	JW	<1.0	2.6	3.2		
37	TY		1.2	2.0	2.4	3.4
38	DZ		2.7	4.5	5.1	0.9
39	SM		1.0	2.3	2.4	3.2

(N = 1), and hypotension (N = 2). As soon as cardiac complications were noted, the treatment was stopped. Psychiatric side effects included disorientation (N = 1), euphoria (N = 3), hallucinations and nightmares (N = 1). These complications occurred at a dose of 15–18 cc/h (120–144 mg/h). One patient suffered a seizure, one vertigo, and one suffered blurred vision. All side effects disappeared within 12 hours of cessation of treatment, and no long-term effects were noted in any patient.

Discussion

This retrospective review documents a statistically significant effect of an escalating level of intravenous lidocaine on reducing pain in a group of refractory CRPS patients. At 1 month, pain relief from baseline was robust, dropping 3.37 points on a numeric rating scale of 0 to 10. At 3 months, relief was statistically significant and clinically meaningful. At 6 months, only slight improvement

remained for most patients, although there were a few outliers with clinically significant relief (12%). For the entire cohort, pain scores were significantly improved for approximately 3.2 months. During this same 3-month period, there was statistically significant improvement in all pain parameters, which included dynamic and static mechano-allodynia, deep muscle pain, joint pain, and thermal allodynia (cold stimulus). Components of the movement disorder (weakness, spasms, dystonia, and tremor) demonstrated a statistically significant but a much less robust response. Neurogenic edema and hyperhidrosis had a statistical and clinically relevant response for 3 months. In general, by 6 months, CRPS factors had returned to baseline. All CRPS factors were statistically improved for 3 months and were clinically relevant with the intravenous lidocaine protocol [5]. The most profound effect was on thermal and mechanical allodynia. Moderate improvement was seen in the movement disorder [30].

CRPS I may be a subset of neuropathic pain [31,32]. Recent experimental and clinical studies point to central sensitization of pain transmission neurons by both N-methyl-D-aspartate (NMDA) and immune neuronal interactions as a major mechanism in chronic neuropathic pain [9,33–36].

There are several possible mechanisms that may underlie the significant and lasting effects of prolonged intravenous lidocaine in these severely affected CRPS patients. Nerve injury induces changes in the density and location of tetrodotoxin-resistant (TTX-R) sodium channels on sensory neurons, decreases their activation threshold and rate of deactivation, which increases their sodium current. These physiological changes may lead to peripheral nociceptive terminal membrane sensitization [37]. TTX-R sodium channels in rat dorsal root ganglion (DRG) neurons are inhibited by intravenous lidocaine, which may block peripheral sensitization [38]. Peripheral nerve injury may maintain a central hyperexcitable state by continual spontaneous discharge due to an abnormal concentration of sodium channels in the injured nerve trunk or its terminal twigs [39]. Earlier experimental studies in the chronic constriction injury model demonstrated that the release of substance P (SP) evoked by noxious stimuli was coupled to preprotachykinin-1 gene expression in small nociceptive DRG ganglia cells, which peaked with the development of hyperalgesia [40,41]. Experimental studies suggest that sustained release and increased utilization of SP and related tachykinin peptides may be associated with increased spontaneous electrical discharges in large and small diameter sciatic axons generated by ectopic firing near or within the DRG [42]. A recent study in the spinal nerve L5 and L6 transection model also supports the involvement of substance P and calcitonin gene-related peptide (CGRP) in the development and maintenance of neuropathic pain [43]. Treatment with lidocaine and SP and CGRP antagonists delayed the onset of neuropathic pain by 1–4 days compared with saline control rats [43]. Nerve injury has a physiologic correlate, which is instability of the axon membrane with consequent potential oscillation, which may contribute to the initiation of ectopic firing of nociceptive afferents [44,45]. Following tissue injury in which small nociceptive afferents are damaged, an inflammatory cascade ensues that is associated with persistent low-frequency spontaneous discharge of A-delta and C-fiber afferents [46]. Systemic lidocaine suppresses this tonic A-delta and C-fiber afferent barrage [18]. Blockade of this abnormal spon-

taneous afferent drive from damaged nociceptive afferents by systemic lidocaine may decrease NMDA-mediated central sensitization. However, the nociceptive afferent drive may also induce descending facilitating pain transmission from the rostroventromedial medulla, which may be suppressed by lidocaine [47,48]. This study and experimental work suggest that lidocaine is particularly effective for tactile allodynia [48].

Limitations of this study are its retrospective nature with all of the pitfalls of this method. These include: 1) recall bias; 2) nonrandomization, nonblinding; 4) and uncontrolled design. In addition to the limitations noted above, the CRPS patient population studied is not representative of most pain centers, as they are drawn from the entire United States and were longstanding and severe. Strengths of the study are: 1) a single physician examined and treated all patients; 2) all patients were seen daily during their treatment and most were followed at regular intervals in the clinic. All of the patients were surveyed by telephone (MP); and 3) all patients met strict IASP 2005 criteria for CRPS [7]. This retrospective study provides evidence that intravenous lidocaine administered in an escalating dose to 5 mg/L under carefully monitored conditions is safe and may decrease many signs and symptoms of severe CRPS. A definitive, large, randomized placebo-controlled multicentered clinical trial is needed to confirm these results.

References

- 1 Schwartzman RJ, McLellan TL. Reflex sympathetic dystrophy. *Arch Neurol* 1987;44(5):555–61.
- 2 Jänig W, Baron R. Complex regional pain syndrome: Mystery explained? *Lancet Neurol* 2003; 2(11):687–97.
- 3 Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. *Nat Rev Neurosci* 2005;6(7):521–32.
- 4 Watkins LR, Maier SF. Immune regulation of central nervous system functions: From sickness responses to pathological pain. *J Intern Med* 2005;257(2):139–55.
- 5 Harden RN, Bruehl S, Galer BS, et al. Complex regional pain syndrome: Are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain* 1999;83(2):211–19.
- 6 Bruehl S, Harden RN, Galer BS, et al. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. *International Association for the Study of Pain. Pain* 1999;81(1–2):147–54.

- 7 Harden NR, Bruehl S. Diagnostic criteria: The statistical derivation of the four criterion factors. In: Wilson PR, Stanton-Hicks MD, Harden RN, eds. *CRPS: Current Diagnosis and Therapy*. Seattle, WA: IASP Press; 2005:44–58.
- 8 Maleki J, LeBel AA, Bennett GJ, Schwartzman RJ. Patterns of spread in complex regional pain syndrome, type I (reflex sympathetic dystrophy). *Pain* 2000;88(3):259–66.
- 9 Schwartzman RJ, Alexander GM, Grothusen J. Pathophysiology of complex regional pain syndrome. *Expert Rev Neurother* 2006;6(5):669–81.
- 10 Kiefer RT, Rohr P, Ploppa A, et al. Open-label study of the efficacy of Subanesthetic isomeric S(+)-Ketamine in refractory CRPS patients. *Pain Med* 2008a;9(1):44–54.
- 11 Kiefer RT, Rohr P, Ploppa A, et al. Efficacy of Ketamine in anesthetic dosage for the treatment of refractory complex regional pain Syndrome: An Open-Label Phase II Study. *Pain Med* 2008a. Epub Feb 5, 2008. doi: 10.1111/j.1526-4637.2007.00402.x.
- 12 Rabert DK, Koch BD, Ilnicka M, et al. A tetrodotoxin-resistant voltage-gated sodium channel from human dorsal root ganglia, hPN3/SCN10A. *Pain* 1998;78(2):107–14.
- 13 Tanaka M, Cummins TR, Ishikawa K, et al. Na⁺ channel expression increases in dorsal root ganglion neurons in the carrageenan inflammatory pain model. *Neuroreport* 1998;9(6):967–72.
- 14 Lai J, Hunter JC, Porreca F. The role of voltage-gated sodium channels in neuropathic pain. *Curr Opin Neurobiol* 2003;13(3):291–7.
- 15 Leffler A, Reiprich A, Mohapatra DP, Nau C. Use-dependent block by lidocaine but not amitriptyline is more pronounced in tetrodotoxin (TTX)-resistant Nav1.8 than in TTX-sensitive Na⁺ channels. *J Pharmacol Exp Ther* 2007;320(1):354–64. Epub Sep 27, 2006.
- 16 Chaplan SR, Bach FW, Shafer SL, Yaksh TL. Prolonged alleviation of tactile allodynia by intravenous lidocaine in neuropathic rats. *Anesthesiology* 1995;83(4):775–85.
- 17 Abdi S, Lee DH, Chung JM. The anti-allodynic effects of amitriptyline, gabapentin, and lidocaine in a rat model of neuropathic pain. *Anesth Analg* 1998;87(6):1360–6.
- 18 Tanelian DL, MacIver MB. Analgesic concentrations of lidocaine suppress tonic A-delta and C fiber discharges produced by acute injury. *Anesthesiology* 1991;74(5):934–6.
- 19 Linchitz RM, Raheb JC. Subcutaneous infusion of lidocaine provides effective pain relief for CRPS patients. *Clin J Pain* 1999;15(1):67–72.
- 20 Jönsson A, Cassuto J, Hanson B. Inhibition of burn pain by intravenous lignocaine infusion. *Lancet* 1991;338(8760):151–2.
- 21 Tremont-Lukats IW, Hutson PR, Backonja MM. A randomized, double-masked, placebo-controlled pilot trial of extended IV lidocaine infusion for relief of ongoing neuropathic pain. *Clin J Pain* 2006; 22(3):266–71.
- 22 Koppert W, Zeck S, Sittl R, et al. Low-dose lidocaine suppresses experimentally induced hyperalgesia in humans. *Anesthesiology* 1998;89(6):1345–53.
- 23 Koppert W, Ostermeier N, Sittl R, Weidner C, Schmelz M. Low-dose lidocaine reduces secondary hyperalgesia by a central mode of action. *Pain* 2000;85(1–2):217–24.
- 24 Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain* 1992; 48(2):261–8.
- 25 Yaksh TL. Regulation of spinal nociceptive processing: Where we went when we wandered onto the path marked by the gate. *Pain* 1999;82(suppl 6):S149–52.
- 26 Ferrante FM, Paggioli J, Cherukuri S, Arthur GR. The analgesic response to intravenous lidocaine in the treatment of neuropathic pain. *Analgesia* 1996;82(1):91–7.
- 27 Kalso E, Tramèr MR, McQuay HJ, Moore RA. Systemic local-anaesthetic-type drugs in chronic pain: A systematic review. *Eur J Pain* 1998;2(1):3–14.
- 28 Carroll I, Gaeta R, Mackey S. Multivariate analysis of chronic pain patients undergoing lidocaine infusions: Increasing pain severity and advancing age predict likelihood of clinically meaningful analgesia. *Clin J Pain* 2007;23(8):702–6.
- 29 Schwartzman RJ. Involuntary movements. Chapter 6. *Neurologic Examination Oxford: Blackwell Publishing; 2006:143.*
- 30 vanHiltten JJ, Blumberg H, Schwartzman RJ, Factor IV. Factor IV: Movement disorders and dystrophy—Pathophysiology and measurement. In: Wilson P, Stanton-Hicks M, Harden RN, eds. *CRPS: Current Diagnosis and Therapy. Progression Pain Research and Management*. Washington, DC: IASP Press; 2005:119–37.
- 31 Oaklander AL, Rissmiller JG, Gelman LB, et al. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). *Pain* 2006;120(3):235–43.
- 32 Jänig W, Baron R. Is CRPS I a neuropathic pain syndrome? *Pain* 2006;120(3):227–9.
- 33 Woolf CJ, Salter MW. Neuronal plasticity: Increasing the gain in pain. *Science* 2000;288 (5472):1765–9.
- 34 Sheng M, Kim MJ. Postsynaptic signaling and plasticity mechanisms. *Science* 2002;298(5594):776–80.
- 35 Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: A review. *Anesth Analg* 2003;97(4):1108–16.

- 36 Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. PGE2 modulates the tetrodotoxin-resistant sodium current in neonatal rat dorsal root ganglion neurones via the cyclic AMP-protein kinase A cascade. *Nat Rev Neurosci* 2005;6(7):521–32.
- 37 England S, Bevan S, Docherty RJ. PGE2 modulates the tetrodotoxin-resistant sodium current in neonatal rat dorsal root ganglion neurones via the cyclic AMP-protein kinase A cascade. *J Physiol* 1996; 495(Part 2):429–40.
- 38 Bräu ME, Dreimann M, Olschewski A, Vogel W, Hempelmann G. Effect of drugs used for neuropathic pain management on tetrodotoxin-resistant Na(+) currents in rat sensory neurons. *Anesthesiology* 2001;94(1):137–44.
- 39 Cepeda MS, Lau J, Carr DB. Defining the therapeutic role of local anesthetic sympathetic blockade in complex regional pain syndrome: A narrative and systematic review. *Clin J Pain* 2002;18(4):216–33.
- 40 Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 1988;33(1):87–107.
- 41 Noguchi K, Morita Y, Kiyama H, Ono K, Tohyama M. A noxious stimulus induces the preprotachykinin-A gene expression in the rat dorsal root ganglion: A quantitative study using in situ hybridization histochemistry. *Brain Res* 1988; 464(1):31–5.
- 42 Kajander KC, Wakisaka S, Bennett GJ. Spontaneous discharge originates in the dorsal root ganglion at the onset of a painful peripheral neuropathy in the rat. *Neurosci Lett* 1992;138(2):225–8.
- 43 Lee SE, Kim JH. Involvement of substance P and calcitonin gene-related peptide in development and maintenance of neuropathic pain from spinal nerve injury model of rat. *Neurosci Res* 2007;58(3):245–9.
- 44 Lyu YS, Park SK, Chung K, Chung JM. Low dose of tetrodotoxin reduces neuropathic pain behaviors in an animal model. *Brain Res* 2000;871(1):98–103.
- 45 Cummins TR, Dib-Hajj SD, Black JA, Waxman SG. Sodium channels and the molecular pathophysiology of pain. In: Sandhulerr J, Bromm B, Gebhart GF, eds. *Nervous System Plasticity and Chronic Pain*. Amsterdam: Elsevier Press; 2000:13–19.
- 46 Xiao WH, Bennett GJ. Persistent low-frequency spontaneous discharge in A-fiber and C-fiber primary afferent neurons during an inflammatory pain condition. *Anesthesiology* 2007;107(5):813–21.
- 47 Ossipov MH, Lai J, Malan TP Jr, Porreca F. Spinal and supraspinal mechanisms of neuropathic pain. *Ann N Y Acad Sci* 2000;909:12–24.
- 48 Chen Q, King T, Vanderah TW, et al. Differential blockade of nerve injury-induced thermal and tactile hypersensitivity by systemically administered brain-penetrating and peripherally restricted local anesthetics. *J Pain* 2004;5(5):281–9.