Intravenous Therapies for Complex Regional Pain Syndrome: A Systematic Review

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Complex regional pain syndrome (CRPS) remains a challenging clinical pain condition. Multidisciplinary approaches have been advocated for managing CRPS. Compared with spinal cord stimulation and intrathecal targeted therapy, IV treatments are less invasive and less costly. We aimed to systemically review the literature on IV therapies and determine the level of evidence to guide the management of CRPS. We searched PubMed, Embase, Scopus, and the Cochrane databases for articles published on IV therapies of CRPS up through February 2015. The search yielded 299 articles, of which 101 were deemed relevant by reading the titles and 63 by reading abstracts. All these 63 articles were retrieved for analysis and discussion. We evaluated the relevant studies and provided recommendations according to the level of evidence. We conclude that there is evidence to support the use of IV bisphosphonates, immunoglobulin, ketamine, or lidocaine as valuable interventions in selected patients with CRPS. However, high-quality studies are required to further evaluate the safety, efficacy, and cost-effectiveness of IV therapies for CRPS. (Anesth Analg 2016;122:843–56)

Complex regional pain syndrome (CRPS), formerly known as "reflex sympathetic dystrophy" (RSD) or "causalgia," is one of the most challenging clinical pain syndromes, with an uncertain pathophysiology and an unpredictable clinical course, despite decades of basic and clinical research.[1,2] Multiple pathophysiologic mechanisms[3] underlying the development and maintenance of CRPS may include vasoconstriction-mediated hypoxia, over-reactive inflammation, sympathetic dysfunction, *N*-methyl-D-aspartate (NMDA) receptor activation, and psychological derangement. Treatment of CRPS remains a clinical challenge to health providers.[4–7] An interdisciplinary approach,[1,6] including pharmacologic management (antiinflammatory therapy such as nonsteroidal antiinflammatory drugs [NSAIDs], analgesics, vasodilatory and anticonvulsant therapies), physical rehabilitation, and psychological support, remains the mainstay of therapy for CRPS. Interventional pain management techniques (IV regional block, sympathetic block, and neurostimulation) are options for reducing pain and improving function. Compared with spinal cord stimulation and intrathecal targeted therapy, IV treatments are less invasive and less costly. However, there are few clinical guidelines for using IV therapies in treating CRPS. Therefore, we conducted an updated systematic review of the literature focusing specifically on IV therapies for CRPS and reviewed the levels of evidence for various agents used in IV therapy. Such information can be useful in the clinical decision-making process.

METHODS

We systematically searched the literature from PubMed, Medline, Embase, Scopus, and the Cochrane library for all reports published in English on CRPS IV treatment from inception up through February of 2015. Search terms included the following: "complex regional pain syndrome," "CRPS," "reflex sympathetic dystrophy," "RSD," "causalgia," "treatment," and "intravenous." The following is an example of the query that was performed for the PubMed/Medline database: ("CRPS"[MeSH Terms] OR "complex regional pain syndrome"[All Fields] OR "RSD"[MeSH Terms]) OR ("reflex sympathetic dystrophy"[All Fields] OR "causalgia"[MeSH Terms]) AND "treatment"[All Fields] AND "intravenous"[All Fields] OR "Regional block" [All Fields]). Records from the query were further filtered to extract evidence-based publications in the format of systematic reviews, meta-analyses, clinical trials, case series, anecdotal reports, and clinical experience. A further manual search was undertaken to exclude irrelevant articles by screening the title and the abstract. The abstracts were subsequently reviewed, and full-text publications were retrieved whenever necessary. Levels of evidence and implications for recommendations of all studies were graded based on "grading strength of recommendations and quality of evidence in clinical guidelines" described by Guyatt et al.,[8] adapted by van Kleef et al.[9] and by our group[10] (Table 1). This method of classification considers the type of the study (systematic review with/without meta-analysis, randomized controlled trials [RCTs] or observational study), the quality of the study (methodological design such as sample size and power analysis), and the quantity of studies

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Table 1. Summary of Evidence Scores and Implications for Recommendation

Score	Description	Implication
1 A+	One or more RCTs of good methodologic quality demonstrate effectiveness. The benefits clearly outweigh risk and burdens	Positive recommendation
1 B+	One or more RCTs with methodologic weaknesses demonstrate effectiveness. The benefits clearly outweigh risk and burdens	
2 B+	One or more RCTs with methodologic weaknesses demonstrate effectiveness. The benefits closely balanced with risk and burdens	
2 B±	Different RCTs or observational studies yield contradictory results better or no better than the control treatment. The benefits closely balanced with risk and burdens or uncertainty in the estimates of benefits, risk, and burdens	Considered, preferably study related
2 C+	Effectiveness only demonstrated in observational studies. Given that there is no conclusive evidence of the effect, benefits closely balanced with risk and burdens	
0	There is no literature or there are case reports available, but these are insufficient to suggest effectiveness and/or safety. These treatments should only be applied in relation to studies	Only study related
2 C-	Observational studies indicate no or too short-lived effectiveness. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	Negative recommendation
2 B-	One or more RCTs with methodologic weaknesses, or large observational studies that do not indicate any superiority to the control treatment. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	
2 A-	RCT of a good quality, which does not exhibit any clinical effect. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	

RCTs = Randomized controlled trials.

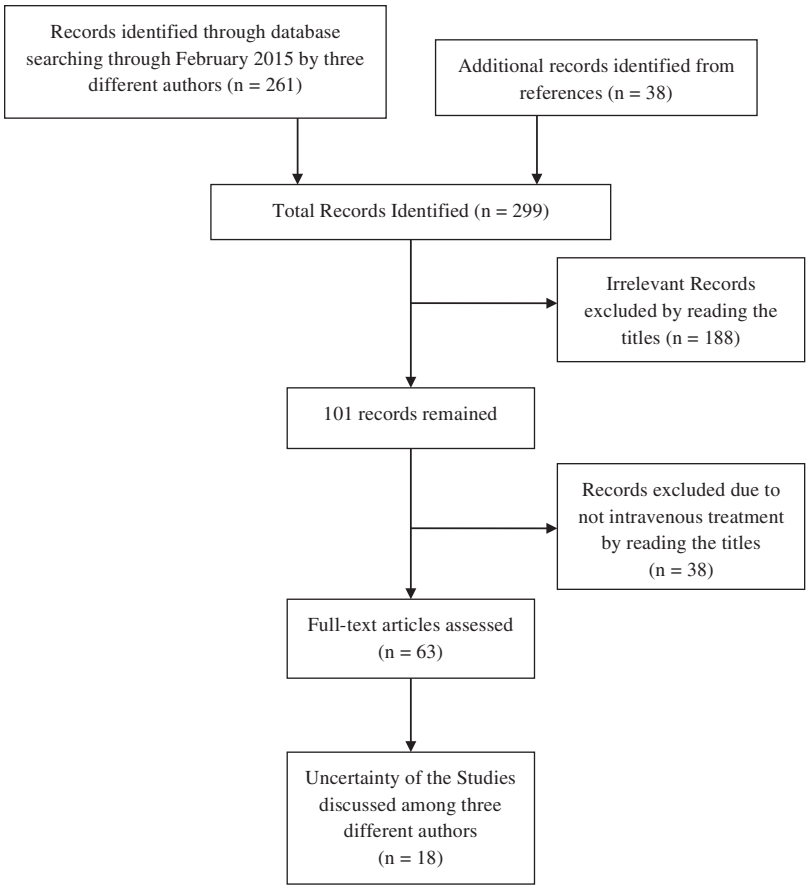

Figure 1. Study selection: a summary of the results of literature searches and the process of inclusion/exclusion of studies.

included in meta-analyses and systematic reviews. Levels of evidence of systematic reviews or meta-analyses were graded according to the same scale by the quality of studies incorporated into a particular meta-analysis or systematic review. Three of the authors independently performed the search and extracted data from articles. The extraction of publications thought to be of interest for pain physicians was also performed. Disagreements were resolved by discussion.

RESULTS

The search strategy yielded 299 articles, of which 101 articles were deemed relevant by reading the titles and 63 by

Table 2. Intravenous Therapies for CRPS

Agent	Level of evidence	Reference	Type of the study	*n* (size)	Results (pain and function improvement)	Dose of the medication	Side effects
Bisphosphonate							
Pamidronate	1B+	Robinson et al.[15]	RCT	27	Improvement of pain and physical function	Single dose 60 mg	Not reported
	2C+	Maillefert et al.[16]	Open prospective	11	More than 50% of the patients showed significant or excellent improvement in pain	30 mg in 500 mL NS infusion over 4 hours/d for 3 consecutive days	Transient fever, hypocalcemia
Alendronate	1B+	Adami et al.[17]	RCT	20	Beneficial effects last 2–4 wk	7.5 mg in 250 mL NS infusion daily for 3 d	Fever
Clodronate	1B+	Varenna et al.[18]	RCT	32	30 of 32 patients improved significantly	300 mg infusion daily for 10 consecutive days	Asymptomatic hypocalcaemia
Ibandronate	2C+	Breuer et al.[19]	Open-label pilot trial	10	Significant improvement lasting 4 wk	6 mg infusion over 2 hours on each of 3 consecutive d	Flu-like symptoms
Neridronate	1B+	Varenna et al.[20]	RCT	82	Significant improvement in pain and quality of life for 40 d	100 mg infusion given 4 times over 10 d	Mild to moderate musculoskeletal disorders, mild fever
Immunoglobulin							
	2B+	Goebel et al.[21]	RCT	13	The average pain intensity was 1.55 lower than the saline group	IVIG 0.5 g/kg versus normal saline infusion for at least 28 d	Moderate to severe headache, increased pain, nausea, tiredness
	2C+	Goebel et al.[22]	Prospective open-label cohort	11	18.2% of 11 patients reported 25%–70% pain relief and 27.3% patients reported >70% pain relief over a 36-mo follow-up period	9–18 g IVIG divided into 3 applications over 1 wk. If incomplete relief, 3 × 10 g over 1 wk 28 d after initial trial	Not specifically reported
NMDA receptor antagonist							
Ketamine	2B+	Schwartzman et al.[23]	RCT	19	Significant pain reduction for all parameters of at least 2 pain questionnaires at all post-treatment time points that lasted for 3 mo	0.35 mg/kg/h, not to exceed 25 mg/h over a 4-h period daily for 10 d	Nausea, headache, tiredness, or dysphoria
	2B+	Sigtermans et al.[24]	RCT	60	Significant pain relief but no functional improvement	1.2 μg/kg/min titrated to a maximum of 7.2 μg/kg/min for 5 d	Nausea, vomiting, psychotomimetic effects, and headache
	2C+	Goldberg et al.[25]	Open-labeled, prospective study	16	Significant reduction of pain from initiation of infusion to the 10th day, significant improvement in the ability to initiate movement by the 10th day	Started at 40 mg infusion lasting 4 hours, and the infusion was increased over a 10-day period to a maximum of 80 mg	Headaches and restlessness
	2C+	Sigtermans et al.[26]	Observational study	10	Significant reduction of pain at the end of infusion. Analgesia persisted 3 h after infusion	Doses are per 70 kg: 1.5 mg gradually increased to 10.5 mg over 120–125 min	Not reported
	2B+	Dahan et al.[27]	Placebo-Review Article controlled trial	60	Persistent analgesia outlasting the treatment period by 50 d	1.2 μg/kg/min titrated up based on analgesic effect, maximum 7.2 μg/kg/min for 5 d	All patients completed the protocol without major side effects
Magnesium							
	1B+	Collins et al.[28]	RCT	8	Significant improvement in pain scale, functional limitation, and quality of life	70 mg/kg in two 50-mL syringe infusion in 4 h a day for 5 d	Infusion site pain, flushing, fatigue, burning eyes, dizziness, etc., were all mild
	2B–	Fischer et al.[29]	RCT	56	Insufficient benefit over placebo	70 mg/kg infusion of 25 mL/h in 4 h a day for a period of 5 consecutive days	Flushing and dizziness

(*Continued*)

Table 2. (Continued)

Agent	Level of evidence	Reference	Type of the study	*n* (size)	Results (pain and function improvement)	Dose of the medication	Side effects
IV NSAIDs							
Parecoxib	2C+	Frade et al.[30]	Observational	30	5 mg parecoxib is effective in combination with clonidine/lidocaine regional block	Systemic (20 mg) versus local IVRB (5 mg) parecoxib in addition to IVRB (30 μg clonidine and 1 mg/kg lidocaine)	No adverse effect was noted
	2B–	Breuer et al.[31]	RCT	20	Short-term (2-d) treatment with parecoxib did not change pressure pain threshold nor edema or pain	IV 80 mg parecoxib per day or placebo (NaCl 0.9%)	No severe adverse events
Ketorolac	2B+	Eckmann et al.[32]	RCT	12	Significant short-term pain relief	Four IVRBs performed 1 wk apart in a random sequence with 50-mL lidocaine 0.5% and 0, 30, 60, and 120 mg ketorolac	No reported complications
	2C+	Vanos et al.[33]	Case series	7	Significant pain relief	IVRB ketorolac 60 mg in a total volume of 40 mL for upper extremities and 50 mL for lower extremities	Burning sensation during injection
	2C+	Suresh et al.[34]	Case series	2	Complete pain relief in 2 adolescent patients	IVRB ketorolac (0.5 mg/kg) and lidocaine (2 mg/kg)	No adverse effects reported
IV antiinflammatory medications							
IVRB glucocorticoids plus lidocaine	2B-	Taskaynatan et al.[35]	RCT	22	No significant difference from placebo	IVRB 100 mL of placebo (saline) versus 40 mg methylprednisolone and 10 mL of 2% lidocaine in saline once a week ×3	Transient, burning pain exacerbation and erythematous flat macular rash occurred in all patients. Nausea, dizziness, tinnitus, flushing, and pruritus in the affected limb were also reported
	2C+	Tountas and Noguchi[36]	Case series	17	Satisfactory pain improvement	IVRB 20–40 mL of 0.5% lidocaine and 80 mg methylprednisolone, repeated every 3–4 wk	Adverse effects were negligible
	2C+	Zyluk[37]	Case series	36	69% of patients had good pain relief at 1-y follow-up	IVRB 20 mL of 1% lidocaine, 80 mg methylprednisolone and 1000 IU heparin	Transient superficial thrombophlebitis in 2 cases and severe pain during injection in 2 other patients
	2C+	Varitimidis et al.[38]	Case series	168	92% of patients reported complete pain relief in a 5-y period	IVRB 25 mL of lidocaine 0.5% and 125 mg methylprednisolone diluted in 10 mL of normal saline (average total 4.8 sessions of treatment)	No major adverse effects reported
IV free radical scavengers							
Mannitol	2B-	Perez et al.[39]	RCT	41	No significant differences between mannitol and placebo treatment over 9-wk	IV 10% mannitol in 1 L 0.9% NaCl in 4 h for 5 consecutive days or equal volumes of 0.9% NaCl (placebo)	Mild side effects such as headache, dizziness, fatigue, and increased urination
IVRB with sympatholytics							
Lidocaine	2B+	Wallace et al.[40]	RCT	16	Lidocaine increased threshold to hot pain but not cool, warm, or cold pain	IV lidocaine (plasma concentration of 1, 2, and 3 mg/mL were targeted and maintained for 20 min) versus diphenhydramine (placebo)	Lightheadedness, sedation, and dry mouth

(*Continued*)

Table 2. (Continued)

Agent	Level of evidence	Reference	Type of the study	*n* (size)	Results (pain and function improvement)	Dose of the medication	Side effects
	2B+	Tremont-Lukats et al.[41]	RCT	32	5 mg/kg/h (but not 1 or 3 mg/kg/h) lidocaine was more effective than placebo in relieving pain intensity	6-h lidocaine infusion (1, 3, and 5 mg/kg/h)	23 of the 32 patients had CRPS. No serious adverse events reported
	2C+	Schwartzman et al.[42]	Case series	49	Significant pain reduction lasted an average of 3 mo	IV infusion of 2 g of lidocaine in 250 mL of 5% dextrose in water at a rate of 7.55 mL/h (60.4 mg/h) over the first 24 h, 11 mL/h over the next 24 h, 15 mL on day 3, 18 mL/h on day 4, and 21 mL/h (168.0 mg/h) on day 5	Mild side effects include nausea, fatigue, bradycardia, tachycardia, atrial arrhythmia, hypotension, disorientation, euphoria, hallucinations, and nightmares
Guanethidine/ reserpine	2A-	Jadad et al.[43]	Systemic review	7 RCT	No significant analgesic effect	Regimen varies on different IVRB agents	Postural hypotension
	2A-	Rocco et al.[44]	RCT	12	No improvement compared with placebo in short- and long-term follow-up	IVRB 20 mg guanethidine or 1.25 mg reserpine in 50 mL 0.5% lidocaine versus lidocaine only	Mild depression and diarrhea with reserpine
	2A-	Blanchard et al.[45]	RCT	21	Significant pain relief in all groups at 30 min but no significant difference among the 3 groups	IVRB 0.5–1 mg reserpine versus 20–30 mg guanethidine versus normal saline	Minimal changes in blood pressure in guanethidine group
	2A-	Ramamurthy and Hoffman[46]	RCT	60	Decrease in pain rating index score but no difference compared with the placebo group	IVRB at 4-d intervals with 20–40 mg guanethidine or placebo (saline) in 0.5% lidocaine 30–75 mL	No significant adverse effects reported
	2A-	Livingstone and Atkins[47]	RCT	57	No significant analgesic advantages over placebo	IVRB with 15 mg guanethidine in 30 mL 0.5% prilocaine versus 30 mL normal saline at weekly intervals with maximal 4 sessions	Altered hand temperature and color
Clonidine	2C+	Reuben and Sklar[48]	Case report	7	Great improvement in approximately 70% patients without side effects	IVRB with clonidine 1 μg/kg in 50 mL 0.5% lidocaine	No patient experienced hypotension, hypoxemia, bradycardia, or excessive sedation
Phenoxybenzamine	2C+	Malik et al.[49]	Case study	5	Significant and prolonged pain relief	IVRB with 15 mL of 0.5% lidocaine, 5 mg phenoxybenzamine, 0.05 mL of absolute alcohol, 0.05 mL of propylene glycol, and 0.0005 mL of hydrochloric acid	No hemodynamic changes after removal of the tourniquet
Droperidol	2B–	Kettler and Abram[50]	RCT	6	No significant analgesic effect than placebo but with adverse effects	IVRB with 2.5 mg droperidol and 500 U heparin in 30–50 mL of normal saline	Dysphoria, nausea, akathisia, and hypotension
Labetalol	2C+	Hord et al.[51]	Case report	1	Pain relief for >7 to 10 days and over 7 years with repeated blocks (158 times)	IVRB with 20–40 mg labetalol and 100–200 mg lidocaine	No significant side effects reported
Ketanserin	2B+	Hanna and Peat[52]	Double-blind crossover study	16	9 patients had signs of RSD. Significant sustained pain relief	IVRB 10–20 mg ketanserin versus placebo	Mild and transient drowsiness, faintness, and shakiness
Anti-TNF antibodies							
Infliximab	2C+	Huygen et al.[53]	Case report	2	Improvement in signs of local inflammation, such as pain, temperature, edema, and motor abnormalities	3 mg/kg 2 to 3 times during a 3- to 4-wk period	Not reported
	2B-	Dirckx et al.[54]	RCT	13	Significant decrease in health status	5 mg/kg infliximab versus placebo administered at week 0, 2, and 6	Increased blood pressure, headache, dizziness, diplopia, nausea, and flu-like symptoms

CRPS = Complex regional pain syndrome; RCTs = randomized controlled trials; IVIG = intravenous immunoglobulin; IVRB = intravenous regional block; NSAID = nonsteroidal antiinflammatory drug; TNF = tumor necrosis factor.

reading abstracts. All these 63 articles were retrieved for analysis and discussion (Fig. 1).

It is noteworthy that most of the studies were conducted before the Budapest criteria were established.[11–13] The diagnosis of CRPS may thus have been less specific.[14] Every effort should be made to adhere to the Budapest diagnostic criteria of CRPS in future clinical studies (Table 2).

IV Bisphosphonate

IV Pamidronate

In an open prospective study[16] of 11 patients experiencing RSD refractory to calcitonin and physical therapy, more than half of the patients showed significant or excellent improvement in pain after 30 mg IV pamidronate in 500 mL of saline infused over 4 hours daily for 3 consecutive days. (The use of calcitonin in the management of CRPS is reviewed elsewhere[55] and was excluded in this review because it was administered either intranasally or IM.) Other case studies reported on the effectiveness and safety of IV pamidronate in recalcitrant RSD patients,[56,57] including a lactating mother[58] and an adolescent.[59] Pain was significantly improved, and adverse events included transient fever, venous inflammation, transient symptomless hypocalcemia, nausea, lymphopenia, and transient hypertension.[56] A single infusion of 60 mg pamidronate had no effect on phosphate excretion.[60] Urinary phosphate excretion parameters were identical in pamidronate cases and in controls.

A randomized, placebo-controlled study reported that overall improvements in pain score, patient's global assessment of disease severity score, and physical function score were noted with a single 60 mg IV pamidronate other than IV normal saline[15] in 27 patients with CRPS type 1. Although treatment response of pamidronate was variable among individuals, most patients improved.

IV Alendronate

In a randomized trial,[17] 20 patients with RSD were randomly treated with either 7.5 mg IV alendronate in 250 mL saline solution or placebo saline infusions daily for 3 days. Two weeks later, all patients received open alendronate 7.5 mg/d for 3 days. In the patients treated with blind alendronate, a diminution in spontaneous pain, tenderness, and swelling (circumference of the affected limb) and improvement in motion were significantly different from baseline ($P < 0.001$), from those observed within the first 2 weeks in the control group ($P < 0.01$), and from week 2 to week 4 ($P < 0.01$). In patients given blind placebo infusions, no relevant symptomatic changes were observed after the first 2 weeks of follow-up, but these patients responded to the open alendronate therapy given afterward. Alendronate, at a daily oral dose of 40 mg, provided better pain control and range of motion than placebo in a subsequent RCT in treating 39 posttraumatic CRPS patients.[61]

IV Clodronate

A short course of IV clodronate[62] was reported to be effective in treating RSD caused by an acute attack of gout. IV clodronate, 300 mg daily for 10 consecutive days, was compared with placebo[18] in a randomized trial in 32 patients with RSD. Forty days later, the placebo-treated patients received the clodronate treatment. At 40-day follow-up, the 15 patients randomly assigned to clodronate treatment showed significant decreases in visual analog scale (VAS) and clinical global assessment (CGA) ($P = 0.002$, $P = 0.001$, respectively). All 32 patients had a significant overall percentage decrease of VAS at 180-day follow-up, with 30 patients significantly improved or asymptomatic.

IV Ibandronate

An open-label trial ($n = 10$)[19] of 6 mg ibandronate infusions showed significant improvements in average and worst pain ratings during a 4-week follow-up period. Patients experienced characteristic transitory but tolerable flu-like symptoms with bisphosphonate treatments. Participants with hand CRPS improved significantly more than those with foot CRPS in average and worst pain.

IV Neridronate

A recent multicenter double-blind, placebo-controlled RCT (82 patients, all patients fulfilled the Budapest criteria) showed that IV infusion of 100 mg neridronate[20] given 4 times over 10 days (total dose 400 mg) to patients with a disease duration of <4 months resulted in significant decrease in VAS scores and improvement in other pain indices and quality of life for 40 days, whereas placebo only had some effect for 20 days. After 50 days, the placebo group received open-label neridronate and showed a significant decrease in VAS score. Smaller doses (200 and 300 mg) of IV neridronate did not provide significant remission, and symptoms partially relapsed within 1 to 3 months.

IV Immunoglobulin

IV immunoglobulin (IVIG) was anecdotally administered to a patient with primary hypogammaglobulinemia and unexplainable pain that was not caused by CRPS. Pain relief was unexpected and reproducible when IVIG treatment was repeated. In a prospective, multiple-dose, open-label cohort study,[22] IVIG was administered to patients between 18 and 65 years of age who experienced chronic (>3 months) noncancer pain, including CRPS, and who had insufficient pain relief with all appropriate established treatments, such as NSAIDs, opioids, anticonvulsants, antidepressants, and transcutaneous electrical nerve stimulation. An initial total dose of 9 to 18 g of IVIG divided into 3 applications was given over 1 week. If pain relief was suboptimal after 28 days, IVIG at a higher dose of 10 g was given 3 times over 1 week. In the CRPS group, 18.2% of 11 patients reported 25% to 70% pain relief and 27.3% patients reported >70% pain relief over a 36-month study period after IVIG therapy. IVIG should not be used in patients with selective IgA.

In another randomized, double-blind, placebo-controlled crossover trial,[21] 13 CRPS patients with a pain score >4 on a scale of 0 to 10, and who had had pain syndrome for 6 to 30 months that was refractory to standard treatment were administered either IVIG 0.5 g/kg or normal saline divided by a washout period of at least 28 days. Twelve patients completed the trial. The average pain intensity was 1.55 lower in the IVIG group than in the saline group. No serious adverse reactions were observed. In a recent literature review based on Medline database and International Trial Registry databases, Goebel[63] indicated that IVIG has emerged as a novel treatment modality for refractory pain cases of CRPS. A multicenter, double-blind, randomized parallel-group, placebo-controlled trial designed to evaluate

the efficacy, safety, and tolerability of IVIG treatment for CRPS is currently underway in the United Kingdom.[64]

IV NMDA Receptor Antagonist

IV Ketamine

Complete pain relief has been reported in severe refractory CRPS using an IV anesthetic dose of ketamine[65] but not with subanesthetic dose of S(+)-ketamine (gradually titrated, 50–500 mg/d over a 10-day period).[66] A retrospective review[67] analyzed 33 patients with CRPS who had undergone ketamine treatment at least once. There was complete pain relief in 25 (76%) and partial relief in 6 (18%) patients after the initial course of therapy. All 12 patients who received second courses of treatment experienced complete relief of their CRPS pain. The most frequent side effect observed was a feeling of inebriation and hallucinations. Less frequent side effects included complaints of lightheadedness, dizziness, and nausea. A 4-hour ketamine infusion, escalated from 40 to 80 mg over a 10-day period, resulted in a significant reduction of pain in an open-labeled, prospective study.[25] Analgesia persisting beyond the ketamine infusion period was reported in an observational study[26] and a placebo-controlled trial.[27] A comparison in brain structures between pain state CRPS and pain-free state CRPS (pain relief after IV ketamine) using functional MRI[68] showed significant changes throughout the cerebral cortex (frontal, parietal, temporal, cingulate, and hippocampus), in subcortical regions such as caudate nucleus, and in the cerebellum.

A randomized double-blind placebo-controlled trial[23] showed that IV ketamine (0.35 mg/kg/h, not to exceed 25 mg/h over a 4-hour period daily for 10 days, diagnosis met revised International Association for the Study of Pain [IASP] criteria) but not normal saline resulted in statistically significant ($P < 0.05$) reductions in many pain parameters. Subjects in both the ketamine and the placebo groups were administered clonidine and midazolam. A pharmacokinetic-pharmacodynamic modeling study[27] showed that 100-hour infusion of S(+)-ketamine treatment is more effective in pain relief than placebo in CRPS type 1 patients with analgesia outlasting the treatment period by 50 days. A 4.2-day IV infusion of low-dose ketamine resulted in significant pain relief, but not functional improvement, in a double-blind randomized placebo-controlled parallel-group trial.[24]

In an attempt to minimize the possible adverse effects of IV ketamine infusion, dexmedetomidine was used in combination with ketamine to provide additional analgesia in CRPS. Nama et al.[69] reported treatment of acute pain symptoms from CRPS type 1 with subanesthetic IV infusion of ketamine and adjunct dexmedetomidine in a 47-year-old female patient with severe pain, burning, and allodynia from CRPS type 1 refractory to conventional therapy. The patient received a subanesthetic IV infusion of ketamine at a rate of 100 μg/kg/h. Pain subsided at approximately 1 hour after the start of the infusion. A 1-time dose of 8 μg of dexmedetomidine in 2 mL was bloused at 6 hours after starting the ketamine infusion, which further improved her pain. The patient reported complete resolution of pain (0/10 pain rating) at 19 hours after the infusion was started. The synergistic effect of the ketamine and dexmedetomidine together provided excellent symptom relief while decreasing the total ketamine administered.

A 5-year retrospective analysis showed that subanesthetic ketamine infusions significantly decreased the VAS pain score in CRPS patients.[70] However, in a recent meta-analysis, no significant pain relief could be established for ketamine IV in treating CRPS (−0.65 [95% confidence interval, −1.47, 0.16], $P = 0.11$).[71] The authors indicated that additional RCTs are needed to explore the therapeutic potential of NMDA receptor antagonists in CRPS.

IV Magnesium

IV magnesium administration was evaluated in acute stage CRPS type 1 patients in an RCT.[28] Eight patients received 70 mg/kg magnesium sulfate infusions in 4 hours for 5 days, and 2 patients received an equal amount of normal saline solution. Interventions were accompanied by standardized physical therapy. Assessments of pain were performed at baseline and 1, 3, 6, and 12 weeks after intervention. Mild systemic side effects were experienced. Pain was significantly reduced at all follow-up compared with baseline (T1: $P = 0.01$, T3: $P = 0.04$, T6: $P = 0.02$, T12: $P = 0.02$). Impairment level ($P = 0.03$) and quality of life (EuroQol $P = 0.04$, SF-36 physical $P = 0.01$) were significantly improved at T12. No improvement was found for skin sensitivity and functional limitations. The same group consequently conducted a double-blinded placebo-controlled RCT to evaluate the effect of the magnesium regimen on 56 chronic CRPS type 1 patients.[29] They found no significant difference between magnesium and placebo on pain and impairment scores, although the magnesium group did show statistically significant improvement on the impairment and McGill scores compared with baseline. The authors concluded that magnesium provides insufficient benefit over placebo in long-standing CRPS type 1 patients.

IV Regional Block with Antiinflammatory Medications

IV Regional Block with Glucocorticoids and Local Anesthetics

In a retrospective review of 17 consecutive patients with posttraumatic RSD,[36] IV 20 to 40 mL 0.5% lidocaine and 80 mg methylprednisolone were administered using regional block after limb exsanguination. The block was maintained for 20 to 30 minutes under a tourniquet and followed by an average 2-month physical therapy. Most blocks were repeated at 3- to 4-week intervals, and the number of total blocks ranged from 1 to 4 (average 2.4). At the assessment point of 6 months, 11 of 16 patients reported satisfactory pain improvement and most of which occurred in the initial 2 months of the treatment. Furthermore, there was no relapse or worsening of pain in those patients with early improvement at the follow-up time of 28.3 months. These findings were echoed by another study[37] where 36 patients with posttraumatic RSD of the upper extremity were treated with regional IV blocks using a solution of 80 mg methylprednisolone, 20 mL 1% lidocaine, and 1000 IU heparin. At 1-year follow-up, 25 patients (69%) had good relief of spontaneous pain, no limitation in finger movement, and 8 (22%) had moderate responses. The authors concluded that regional IV block with methylprednisolone and lidocaine followed by standard physical therapy was an effective treatment for the early stages of posttraumatic RSD. In

a 5-year retrospective study, regional block with lidocaine and methylprednisolone provided complete pain relief in 92% of 168 patients with CRPS as a consequence of trauma or surgery to the upper extremity.[38]

In a randomized, double-blinded, placebo-controlled trial[35] of 22 patients with CRPS type 1 in their upper limbs, IV methylprednisolone 40 mg and 2% lidocaine 10 mL were compared with 100 mL saline using a bier block technique in a large cubital vein over 20 minutes. Treatments were applied once a week and repeated for a total 3 sessions. Pain severity, which was assessed using a 0 to 10 numeric scale after each session of block, was improved significantly at 3 assessment time points in both groups. There was no significant difference in improvement of pain scores in either group. These improvements were not observed 1 week or 1.5 months after the block. The authors concluded that IV bier block with methylprednisolone and lidocaine was not superior to placebo. The last study was questioned with respect to the bier block because a large cubital vein was used for drug administration.[72] The use of this vein as an access for bier block was questioned on grounds that the injectate should be retained in the periphery to exert the anti-inflammatory effect peripherally. The authors replied by indicating that many CRPS patients demonstrate severe peripheral edema and pain, which prevents cannulating a vein at the distal part of the affected extremity.[72] In all these studies, IV regional block (IVRB) steroids were given together with lidocaine; it is therefore difficult to evaluate the effect of steroids alone.

IVRB with NSAIDs

In a randomized, double-blinded, prospective study,[32] IV regional block (after limb exsanguination) with 50 mL 0.5% lidocaine plus 0, 30, 60, and 120 mg ketorolac was performed at 1-week interval (total 4 blocks) in 12 adult patients with CRPS of the lower extremity. The block was maintained for 20 minutes. All ketorolac treatment groups showed a reduction in pain score at 1 day after the block. However, no significant long-lasting pain relief was found at 1 week after injection.

Another study showed that IVRB with ketorolac (60 mg in 40 mL for upper limbs and in 50 mL for lower limbs) produced significant pain relief in 7 patients with RSD[33] whether or not lidocaine was coadministered. The duration of pain relief tended to extend with each subsequent block in most patients. In another case report, 1 or 2 IVRB sessions with ketorolac (0.5 mg/kg) and lidocaine (2 mg/kg) resulted in a complete resolution of the pain in 2 adolescents after conventional pharmacologic therapy and nerve stimulation had failed.[34] Frade et al.[30] compared systemic (20 mg) versus local (5 mg) effects of IV-specific cyclooxygenase-2 inhibitor, parecoxib, in addition to their routine IV regional block regimen (30 μg clonidine/1 mg/kg lidocaine) in 30 patients with upper-limb CRPS type 1. The time of tourniquet application was 5 minutes, and the limb was not exsanguinated. A small volume (10 mL) was injected. Analgesia was evaluated by the 10-cm VAS. The authors found that, compared with systemic IV parecoxib plus clonidine/lidocaine and control groups (clonidine/lidocaine only), regional IV administration of parecoxib along with clonidine and lidocaine required less daily rescue analgesic (ketoprofen) in the second and third weeks after the block. They concluded that 5 mg parecoxib used in regional bier block is an effective drug in combination with clonidine/lidocaine regional block for CRPS type 1. However, a recent RCT showed that short-term (2-day) treatment of IV parecoxib did not influence pressure pain threshold or edema or pain in CRPS patients.[31]

IV Free Radical Scavengers

IV Mannitol

In a retrospective observational study, 1 L of 10% mannitol was administered preferably via a subclavian vein every 24 hours (100 g per 24 hours) in 65 patients after conservative treatments had failed.[73] Successful overall improvement was seen in 24% of patients after 1 week and 30% after 1 month. The authors concluded that mannitol did not significantly improve the treatment of CRPS, although warm CRPS and CRPS of the upper extremity appeared to respond better to mannitol treatment than cold and lower extremity CRPS. However, in an earlier retrospective report,[74] 75 patients with early CRPS type 1 (present for <4 months) received 10% mannitol 2 × 250 mL and 8 mg dexamethasone IV bolus per day for 1 week as inpatients. Significant improvement in pain scores was observed at the initial 1 week and the final 9 (range 8–12) month assessments. The drawback of this study is that there was no control group, and the addition of dexamethasone confounded the effect of mannitol treatment.

In a prospective, randomized, placebo-controlled, double-blinded trial,[39] 41 patients were randomly infused with either 1 L 10% mannitol (administered over 4 hours via an IV cannula in the unaffected extremity) or 0.9% NaCl (placebo) each day for 5 days. There was no significant improvement with mannitol treatment, except in a subgroup of the Jebsen-Taylor hand function test. No significant differences were found between mannitol and placebo treatment over a 9-week study period. No significant differences were found between both groups in the number of patients requesting rescue pain medication or the amount or strength of pain medication used. The authors concluded that IV 10% mannitol is not more effective than placebo in CRPS type 1 treatment.

IVRB with Sympatholytics

IVRB with Local Anesthetics

Pain from CRPS type 1 may be relieved by blocking sympathetic efferent-dependent vasoconstriction or by enhancing nitric oxide–dependent vasodilatation in an animal model of postischemic pain.[75] IVRB with lidocaine was reported effective in CRPS treatment in case reports,[76] and lidocaine may be particularly effective for thermal and mechanical allodynia.[42]

In a randomized, double-blind, placebo-controlled design in 16 patients with CRPS types 1 and 2 with a prominent allodynia, Wallace et al.[40] found that IV lidocaine and diphenhydramine infusion increased the hot pain thresholds in the painful area but had no significant effect on the cool, warm, or cold pain thresholds. Another

double-blinded, randomized, placebo-controlled parallel study showed that IV lidocaine 5 mg/kg/h was more effective than saline placebo in relieving spontaneous neuropathic pain in 32 patients (of whom 23 had CRPS).[41] Lower doses of lidocaine (1 or 3 mg/kg/h) were no better than placebo in relieving pain.[41]

IVRB with Guanethidine and Reserpine

A series of IVRB with guanethidine produced good response in 11 of 20 patients with RSD with minimal side effects.[77] Bier blocks composed of lidocaine, methylprednisolone, and reserpine or guanethidine[78] improved range of motion in the affected joints (primarily the hand and wrist) from a preblock mean of 46% to 81% of normal following the blocks. Patients also reported an 80% mean improvement in their pain. IVRB with guanethidine provided complete pain relief with 2 injections in a 62-year-old woman experiencing RSD, and the patient remained pain-free for 18 months.[79] Complete disappearance of pain and return of the normal movement of the extremity were achieved in 17 patients with CRPS type 1 using a series of IVRB (Bier's block) sessions with 10 or 15 mg guanethidine and 1 mg lidocaine/kg body weight.[80] However, Kaplan et al.[81] found that, in 55 RSD patients who received regional IV guanethidine blocks (upper extremities received 20 mg [10 mg/mL] of guanethidine in 30–50 mL of 0.5% lidocaine; lower extremities received 40 mg guanethidine in 40–75 mL of lidocaine), pain resolution improved in only 23.6%, and there was no change in pain in 61.8% of the patients. There were 56 adverse effects in 19 (34.5%) patients (nausea, vomiting, orthostatic hypotension, dizziness, diarrhea, and weakness).

RCTs failed to support the effectiveness of IVRB guanethidine in CRPS management. In a double-blind crossover study,[44] 12 patients received 20 mg guanethidine in 50 mL 0.5% lidocaine, 1.25 mg reserpine in 50 mL 0.5% lidocaine, and 50 mL 0.5% lidocaine with a 1-week interval between medications. There were no significant changes in pain intensity for the first 3 days among IVRB guanethidine, reserpine, and control groups. Pain relief from 2 to 14 months was achieved in 2 patients receiving reserpine, 1 receiving guanethidine, and none receiving lidocaine. None of the patients experienced permanent relief. No difference was found between reserpine and guanethidine. A double-blind, randomized study[45] compared IVRB sympatholysis using guanethidine, reserpine, and normal saline in 21 patients with RSD. There was significant pain relief in all 3 groups at 30 minutes. There were no significant differences among the 3 groups in the degree of pain relief. A systemic review[43] identified 7 RCTs of IV regional sympathetic block in patients with RSD. Four used guanethidine; none showed significant analgesic effect in pain relief. Two reports, one using ketanserin and one bretylium, with 17 patients in total, showed some advantage of IV regional sympathetic block over control. The authors conducted a subsequent randomized, double-blind, crossover study[43] in 9 patients to assess the effectiveness of IV regional sympathetic block with guanethidine of high (30 mg for both upper and lower limbs) or low (10 mg for upper and 20 mg for lower limbs) dose and normal saline. The trial was stopped prematurely because of the severity of the adverse effects. No significant difference was found between guanethidine and placebo on any of the outcomes measured. In a double-blind, randomized, multicenter study, 60 RSD/causalgia patients received 4 IV regional blocks at 4-day intervals with either guanethidine or placebo in 0.5% lidocaine.[46] Four days after the initial block, the group treated with placebo experienced a greater decrease in pain scores than those treated with IVRB guanethidine, although this difference was not statistically significant. On long-term follow-up, there was no difference in pain scores between groups receiving 1, 2, or 4 guanethidine blocks. Overall, only 35% of patients experienced clinically significant relief on long-term follow-up. In a randomized trial in 57 patients[47] with CRPS type 1 of the hand after fracture of the distal radius, the IVRB guanethidine group (15 mg guanethidine in 30 mL of 0.5% prilocaine) experienced more pain in the affected hand ($P = 0.025$), and at 6 months had more vasomotor instability ($P < 0.0001$) compared with the control IVRB normal saline group. IVRB guanethidine offered no significant analgesic advantage over the normal saline placebo block in the treatment of early CRPS type 1.

IVRB with Clonidine or Dexmedetomidine (the α_2-Adrenergic Receptor Agonists)

Lidocaine/clonidine IVRB combined with parecoxib was discussed earlier.[30] A case study[48] reported complete pain relief with 4 to 6 IVRB with a solution containing clonidine 1 μg/kg in a total volume of 50 mL 0.5% lidocaine in 5 of 7 patients with the diagnosis of CRPS of the knee. IVRB clonidine was performed on each patient up to 6 times (maximum of once a week for 6 weeks). No hypotension (mean arterial pressure ≤20% baseline), hypoxemia (Spo_2 ≤90%), bradycardia (heart rate ≤60 beats/min), or excessive sedation was found. Another case reported successful treatment of RSD by bier block with 0.5 μg/kg clonidine,[82] but the pain relief was obtained using multiple concomitant drugs, including IVRB with 0.5% lidocaine, 0.2 mg/kg labetalol, and 2 mg/kg bretylium. IV dexmedetomidine was used in conjunction with IV ketamine with complete resolution of pain and associated symptoms in a case report as mentioned earlier.[69]

IVRB with Phenoxybenzamine

In a case study,[49] IVRB with phenoxybenzamine was performed in 5 patients after exsanguination using an Esmarch bandage and a double-cuff tourniquet. Thirty milliliter solution (15 mL of 0.5% lidocaine HCl, 5 mg phenoxybenzamine HCl, 0.05 mL of absolute alcohol, 0.05 mL of propylene glycol, 0.0005 mL of hydrochloric acid, and isotonic saline) was injected into the upper extremity. All patients had significant and prolonged symptom relief (ranging from 7 to 17 months) with a single treatment. Oral phenoxybenzamine was also found effective in treating CRPS in other case studies.[83,84]

IVRB with Droperidol

In a double-blind, placebo-controlled, crossover study, IVRB with droperidol (used as an α-adrenergic antagonist here) in 6 RSD patients failed to show any significant analgesic effect over placebo but with adverse effects, including akathisia and dysphoria in 3 patients.[50]

IVRB with Labetalol

IVRB with labetalol (a mixed α- and β-adrenergic antagonist) was reported in a 42-year-old man with CRPS after a right fifth metatarsal fracture. Bier block with bretylium and lidocaine did not improve his pain. An ischemic tourniquet block of the right foot made the pain worse. Bier block with normal saline and lidocaine provided him with only minimal pain relief for a few hours, whereas IVRB with combination of labetalol (20–40 mg) and lidocaine (100–200 mg) relieved his pain for >7 to 10 days.[51]

IVRB with Ketanserin

Ketanserin, a selective serotonin receptor antagonist with weak adrenergic receptor blocking properties, was assessed against placebo in a double-blind crossover study of 16 patients with chronic peripheral burning pain. Nine of these patients had signs of RSD. In those patients with RSD, ketanserin, but not placebo, provided significant sustained pain relief as assessed by linear analog scales. No significant relief was seen with placebo or ketanserin in non-RSD pain patients. Side effects were reported at a higher frequency after ketanserin than after placebo, but all were mild and transient.[52]

IV Anti-TNF-α Antibodies

Infliximab 3 mg/kg 2 or 3 times during a 3- or 4-week period showed pain improvement in 2 cases of CRPS type 1.[53] An RCT using infliximab failed to demonstrate significant change in total pain score impairment level sumscore [ISS]) but yielded a significant decrease in health status (EuroQol VAS) compared with placebo group. The RCT was therefore terminated before the required number of the patients had been reached.[54]

DISCUSSION

Different classes of medications have been tried intravenously in treating CRPS. In this review, we discussed the use of IV bisphosphonates, immunoglobulins, NMDA receptor antagonists, antiinflammatory drugs (glucocorticoids and NSAIDs), free radical scavengers (mannitol), sympatholytics, and anti-tumor necrosis factor (TNF)-α antibodies in CRPS. Recommendations are made based on current available level of evidence (Table 1).

IV Bisphosphonate

Bone demineralization has been found to accompany CRPS. Bisphosphonates have been used in treating CRPS[85] by inhibiting bone resorption. A systemic review[86] showed that bisphosphonates have the potential to reduce pain associated with bone loss in patients with CRPS type 1. A recent Cochrane review concluded that bisphosphonates may be effective for CRPS when compared with placebo, although the quality of evidence is low.[87] On the basis of the level of evidence reviewed, we recommend that IV bisphosphonates can be used to reduce pain associated with bone loss in patients with CRPS (evidence level: 1B+/2C+).

IV Immunoglobulin

The possible mechanisms underlying IVIG-mediated pain relief are still unclear but may include[22] the following: (1) elimination of proinflammatory cytokines (such as interleukin-2, TNF, and interleukin-6); (2) stimulation of macrophages to increase the catabolism of immunoglobulins and potentially noxious autoantibodies present in the serum may thus be eliminated; (3) antiinflammatory action via binding C3b and C4b and reducing the number of activated complement fragments; and (4) downregulation of the production of autoantibodies in B cells or inhibition of cytotoxic T cells. On the basis of the level of evidence reviewed, we recommend that IVIG can be considered for CRPS patients with refractory pain (2B+/2C+).

IV NMDA Receptor Antagonists

Activation of NMDA receptor signaling has been proposed in induction and maintenance of CRPS. Ketamine and magnesium might be effective in treating refractory CRPS patients by blocking central sensitization of pain transmission neurons through inhibiting NMDA receptors. On the basis of the level of evidence reviewed, we recommend that IV ketamine infusion can be used in selected patients with refractory CRPS (2B+/2C+). Different RCTs yielded contradictory results of IV magnesium in CRPS (2B±).

Patients receiving ketamine often experienced mild to moderate psychotomimetic side effects during drug infusion (76% vs 18%, $P < 0.001$).[26] In a case series of 6 patients who received 2 continuous IV 100-hour ketamine infusions separated by 16 days, liver enzymes (alanine transaminase, alkaline phosphatase, aspartate transaminase, and γ-glutamyl transferase) were reported to be transiently elevated to 3 times the normal upper limits in 3 patients during ketamine infusion.[88] The enzyme levels slowly returned to normal range within 2 months once the infusion was promptly discontinued. This observation may suggest that there is an increased risk of ketamine-induced liver injury if the infusion is prolonged and/or repeated within a short period.

IVRB with Antiinflammatory Medications

The rationale of using antiinflammatory medications in CRPS is that these drugs act against the local neural inflammatory process, which may be involved in the pathophysiology of CRPS. Glucocorticoids and NSAIDs act by inhibiting synthesis of prostaglandins, which may be responsible for tissue inflammation and vasoconstriction. IVRB with methylprednisolone and lidocaine was reported more effective in reducing CRPS pain score/intensity in case series but not superior to placebo in an RCT. IVRB with lidocaine and ketorolac showed short-term pain relief in an RCT. A case series also reported effectiveness of IVRB ketorolac with or without lidocaine. IVRB parecoxib was found to be effective in combination with clonidine or lidocaine in case reports but not in RCT. On the basis of the level of evidence reviewed, we recommend that IVRB with ketorolac (preferable with lidocaine) may be considered for short-term pain reduction in CRPS patients (2B+/2C+), whereas the effectiveness of IVRB with methylprednisolone or parecoxib is not supported by RCTs (2B−/2C+).

IV Free Radical Scavengers

Free radical scavengers, such as mannitol, have been used to attenuate the excess, oxygen-radical–mediated, exaggerated inflammatory responses to tissue injury in CRPS. RCT and retrospective studies failed to demonstrate the effectiveness of IV mannitol in CRPS patients (2B–).

IVRB with Sympatholytics

Sympathetic activation is found in chronic CRPS.[89] There is evidence of heightened expression of α_1-adrenoreceptors in the dermal nerves and epidermal cells of CRPS patients.[90,91] Sympathetic activation leads to vasoconstriction, cold skin, and tissue hypoxemia.[92–94] One RCT reported that IVRB with lidocaine at 5 mg/kg/h but not lower doses (1 or 3 mg/kg/h) was more effective than saline placebo. Another RCT and case reports showed that IV lidocaine was effective to reduce pain—particularly thermal pain—in CRPS patients (2B+/2C+).

Sympathetic blockers, such as guanethidine and reserpine, α_1-adrenergic receptor antagonist, and vasodilators, have been historically prescribed in treating CRPS patients based on these concepts. Reserpine depletes storage of norepinephrine, and guanethidine inhibits presynaptic release of norepinephrine in the sympathetic nerve terminal. Both regional IV guanethidine[95] and reserpine have been reported in the treatment of RSD. Results from case reports are inconsistent, and RCTs failed to support the effectiveness of IVRB guanethidine, reserpine, or droperidol in CRPS management (2A–/2B–).

The rationale for the use of phenoxybenzamine lies in its noncompetitive, irreversible blockade of α-adrenergic receptors, which might decrease or eliminate the sensitization that characterizes CRPS. Only case studies have shown phenoxybenzamine and labetalol to be effective; no RCT has investigated this medication in CRPS (2C+).

IVRB with ketanserin was reported superior to placebo in pain reduction in an RCT (9 of 16 patients had signs of RSD) (2B+, evidence level is weak because of small number of patients in only one study).

IV Anti-TNF-α Antibodies

TNF-α signaling has been reported to contribute to the development of nociceptive sensitization in a tibia fracture animal model of CRPS type 1.[96] Case studies showed effectiveness of infliximab, the monoclonal antibody against TNF-α, in 2 CRPS patients but RCT failed to demonstrate the benefit of this medication (2B–).

In summary, many IV medications have been used in treating CRPS along with traditional therapies.[97] Most of the IV therapies were followed by a standard physical therapy protocol. Several case series have reported effectiveness of several IV medications, but most of these studies lack control groups or placebo for comparison. On the basis of the level of evidence reviewed, we recommend the following strategies:

1. IV bisphosphonates to reduce pain associated with bone loss in patients with CRPS type 1 (evidence level 1B+/2C+); IV immunoglobulin (IVIG) for refractory pain cases of CRPS (2B+/2C+); IV ketamine infusion in some refractory patients (2B+/2C+); IVRB with ketorolac (when used with lidocaine) may be considered for short-term pain reduction in CRPS patients (2B+/2C+); IVRB lidocaine at 5 mg/kg/h may be effective in reducing thermal pain in particular (2B+/2C+).
2. Treatments that lack sufficient evidence or different randomized controlled trials yielded conflicting results: IV magnesium (2B±); IVRB with clonidine, phenoxybenzamine, or labetalol (2C+).
3. Not recommended: IV methylprednisolone and parecoxib (2B–/2C+); IV 10% mannitol (2B–); IV regional block with guanethidine, reserpine, or droperidol (2A–/2B–); IV TNF-α antibodies (2B–).

Because most studies on IV therapies for CRPS are not of high quality,[87] further studies on standard RCT quality are required. Whether recommendations can be made regarding the preferred drug based on the acuity or chronicity of CRPS remains debatable. Currently, it is not clear whether bisphosphonates or other drugs are preferable in acute or chronic CRPS. ■

DISCLOSURES

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