

Efficacy of Pamidronate in Complex Regional Pain Syndrome Type I

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ABSTRACT

Objectives. Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy (RSD), is a painful, disabling disorder for which treatment is difficult. The aim of this study was to determine the efficacy of pamidronate in a double-blind randomized placebo-controlled trial.

Methods. Patients referred to our regional multidisciplinary pain management center who fulfilled the International Association for the Study of Pain criteria for CRPS Type I were enrolled in the study over a 2-year period. Patients were administered, intravenously, either pamidronate, 60 mg as a single dose, or normal saline. Patients' pain scores, global assessment of disease severity scores, and functional assessment (SF-36) scores were documented at baseline and at 1 and 3 months.

Results. Twenty-seven patients (18 female, 9 male; average age 45 years) were recruited, of whom 14 received pamidronate and 13 received placebo. Overall improvements in pain score, patient's global assessment of disease severity score, and physical function (SF-36) score were noted in the pamidronate group at 3 months, and improvements in role physical (SF-36) score were noted at 1 and 3 months. There was variability in pamidronate response among individuals.

Conclusions. Pamidronate may be a useful treatment option in the management of patients with CRPS Type I. Although treatment response was variable, the majority of patients improved. Early administration in tandem with other treatment measures is recommended.

Key Words. CRPS; Therapy; Pamidronate; Bisphosphonate

Introduction

Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy (RSD), is a painful debilitating disorder usually affecting a peripheral limb and may follow a relatively minor injury [1]. CRPS Type I has a broad etiology, occurring after an initiating noxious event or a cause of immobilization. CRPS Type II follows a nerve injury [2,3]. The hallmarks of these conditions include continuing pain, allodynia, or hyperalgesia disproportionate to the inciting event, evidence at some time of edema, abnormal

sudomotor activity, and the exclusion of other conditions that would otherwise account for the degree of pain and dysfunction.

Treatments to date have included analgesics (both systemic and topical), a variety of neuro-pathic agents, physiotherapy, sympathetic and other regional nerve blocks, acupuncture, transcutaneous electrical nerve stimulation, and psychotherapy—all with mixed and generally unfavorable results [4–6]. More invasive therapies, including spinal cord stimulation, have shown promise [7]; however, such therapies are expensive, require significant expertise, and are limited to highly selected patients in tertiary care centers.

In recent years, bisphosphonates have been promoted as potential therapeutic agents, with several studies reporting positive results [8–11]. Bisphos-

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phonates are potent antiosteoclastic agents, and it has been postulated that osteoclast hyperactivity is the dominant mechanism involved in the localized osteoporosis seen in CRPS [9]. Furthermore, bisphosphonates have been reported as having significant analgesic efficacy in a number of bone-related pathologies, including Paget's disease [12], metastatic cancer [13], myeloma [13], acute vertebral fracture [14], and refractory rheumatic conditions [15], suggesting additional analgesic mechanisms [16].

We report our experience on the efficacy of intravenous (IV) pamidronate in a randomized, double-blinded, placebo-controlled trial in a cohort of CRPS Type I patients.

Methods

Patients referred to our regional multidisciplinary pain management center who fulfilled the international Association for the Study of Pain (IASP) criteria for CRPS Type I [3] were enrolled in the study over a 2-year period (Jan 1998–Jan 2000). Patients were randomized to receive either IV pamidronate (pamidronate disodium, disodium amonohydroxypropylidene bisphosphonate), 60 mg as a single infusion (treatment group), or placebo (normal saline infusion, control group). Pain scores (visual analog scale [VAS]), patient's global assessment of disease severity scores, and functional assessment (SF-36) scores were documented at baseline and at 1 and 3 months. Background analgesia continued throughout the study, and doses were held stable throughout the 3-month treatment period. Analgesics used included paracetamol (4g/day), codeine phosphate (120–180mg/day, as monotherapy and in combination with paracetamol), and paracetamol (325mg)/dextropropoxyphene (50mg) combination (maximum 8 per day). Both the patients and the investigators were blinded until completion of the study. The study was approved by the Canterbury Ethics Committee.

Statistical Analysis

Changes in pain scores and patient's global assessment of disease severity scores were analyzed using the nonparametric Mann-Whitney test. Functional assessment (SF-36) data were analyzed by repeated-measures analysis of variance, with time and allocated group as factors. The appropriateness of a parametric analysis of this data was confirmed by visual inspection of residual plots from the analyses.

Results

A total of 40 consecutive patients over the 2-year study period, who met the IASP criteria for CRPS Type I, were approached to participate, of whom 27 were enrolled. The main reason for refusal was concern over randomization to the placebo arm. These patients tended to be younger and employed.

Of the 27 recruited patients, 13 were randomized to the placebo arm (control group) and 14 received pamidronate (treatment group). The mean age of participants was 45 years (range: 30–60 years), with 9 males and 18 females. A lower limb was affected in 13 cases, and an upper limb was affected in 14 cases. Disease duration ranged from 3 months to 6 years (average: 21.6 months). There were no significant differences in age, sex, or duration of treatment between the two groups. All patients completed the 3-month study.

The overall pain score was significantly lower ($P = 0.043$, Figure 1A) and the percent change in VAS pain score was significantly greater ($P = 0.048$, Figure 1B) in the treatment group at the 3-month assessment period than in the placebo group. There was an overall improvement at 3 months in the patient's global assessment of disease severity score in the treatment group that was not seen in the control group (Table 1). No significant differences in pain score or in global assessment of disease severity score were seen, however, between the two groups at 1 month.

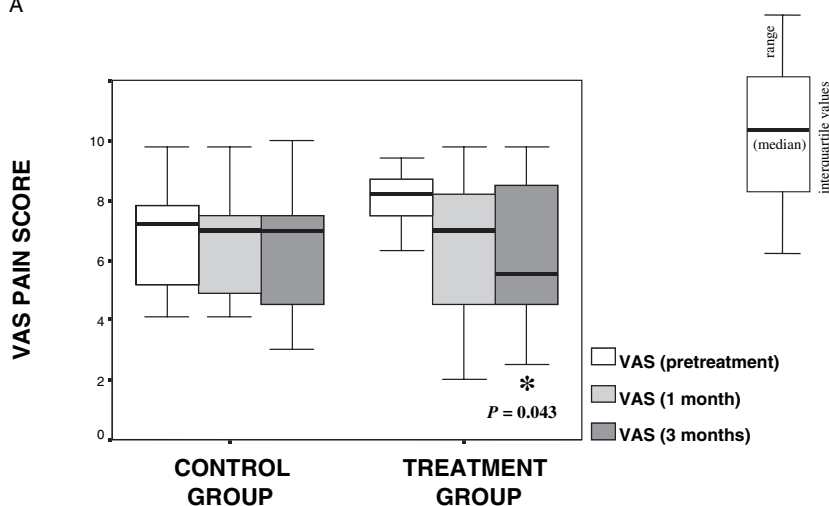
Regarding functional assessment (SF-36), patients in the treatment group had significantly higher scores than those in the placebo group in physical function at 3 months ($P = 0.047$) and in role physical at 1 and at 3 months ($P = 0.008$ and $P = 0.04$, respectively). There were no differences in other functional indices between the two groups. There was no correlation between analgesic use (type, dose, frequency) and treatment response.

In the assessment of individual responses within the treatment group, there was substantial variability, ranging from marked to minimal clinical improvement. The pamidronate therapy was well tolerated. Five patients in the treatment group and two in the control group experienced minor influenza-type symptoms, and two patients in the treatment group experienced mild infusion site reactions (erythema and discomfort). All symptoms resolved within 6–48 hours.

Discussion

CRPS Type I, formerly known as RSD, is a challenging condition both in diagnosis and

A



B

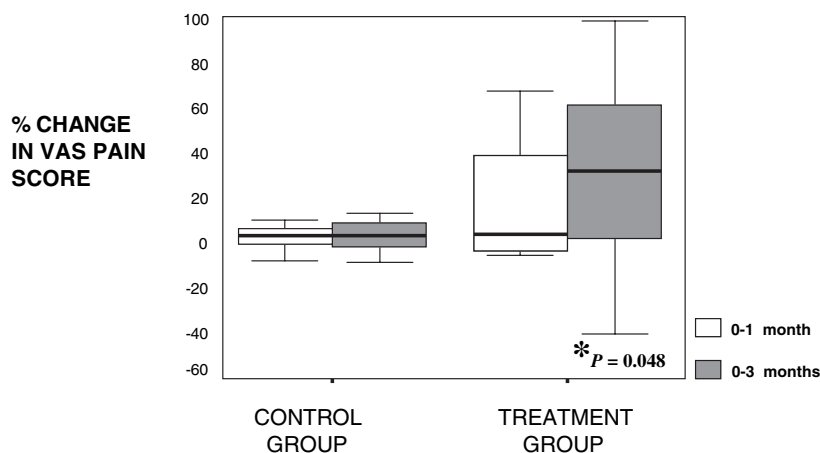


Figure 1 A) Boxplot comparing change in VAS pain score between control and treatment groups. B) Boxplot comparing percentage (%) change in VAS pain score between control and treatment groups.

management. The revised IASP criteria [3] are broad and reflect the heterogeneous nature of the condition. The mechanisms of pain in CRPS are complex and poorly understood, with a number of models promoted; it is likely that both peripheral and central mechanisms operate in the evolution of CRPS [17]. Most authorities agree that early

recognition and treatment are integral to successful management.

There have been a multitude of proposed treatments for CRPS Type I, with few achieving consistently positive results when assessed in a randomized, double-blinded, placebo-controlled setting [4–6]. Such studies are limited to relatively small numbers of patients due to the low incidence and poor recognition of this condition.

Notwithstanding this, our small treatment cohort experienced significant benefits from a single 60-mg pamidronate infusion, which were not seen in a control cohort treated with a sham infusion, in a randomized double-blind setting. This effect was sustained at 3 months. Modest improvements were noted in a number of patients at the first assessment (1 month), but these did not reach statistical significance in the group as a whole except in functional status (role physical, SF-36). Background therapy was kept to a

Table 1 Patient's global assessment of disease severity

	Pretreatment	1 month	3 months
Control Group			
Median	5.8	4.6	5.3
Interquartile range	(4.1–7.8)	(4.0–7.6)	(4.0–7.0)
Treatment Group			
Median	7.6	6.9	5.3
Interquartile range	(5.4–9.3)	(5.0–8.4)	(4.5–8.0)
P value	0.11	0.23	0.026

Patients were asked to rate the severity of their condition on an arbitrary scale (0–10; 0 = no disease activity, 10 = maximal disease activity) at pretreatment and at 1 and 3 months posttreatment.

minimum, with only standard analgesics allowed. Additional therapies (physiotherapy/reactivation exercises, cognitive-behavioral approaches) were withheld during the course of the study. This, and concern regarding the placebo arm, was the main reason potential patients (13/40) declined to participate. We considered whether this might affect the generalizability of our results; however, these patients tended to be younger and employed, and the majority responded to subsequent pamidronate infusion(s) given outside the trial setting.

Another potential weakness of the study was that the treatment group had greater pain and disease activity scores at baseline than the control group. Patients were randomly assigned prior to their baseline assessments, and thus, were not matched according to pain severity. There was significant variability in the response within the treatment group; however, it showed an overall improvement that was not seen in the control group, whose indices did not change substantially. We do not believe the different baseline levels invalidate our findings; however, larger future studies are recommended.

Our results are consistent with other published studies [8–11] demonstrating the potential benefit of bisphosphonate therapy. There are, however, some differences in the magnitude and consistency of response, particularly in comparison with the Varenna et al. study [11], which found dramatic and uniform responses following intravenous clodronate in their treatment group. The reasons for this are speculative but may include their study cohort having substantially shorter disease duration and further efficacy with repeated treatments. There may also be differences in efficacy among different bisphosphonate drugs.

Despite our positive findings, we would be cautious in promoting this treatment as a panacea for CRPS patients; we noted substantial inter-individual variation in response in our treatment group, ranging from dramatic to minimal benefit. We did not identify any standout predictors for a positive response in our treatment cohort.

These findings are consistent with our more recent clinical experience, where we have found modest benefit in the majority of patients with a sustained response in those receiving repetitive treatments. Ideally, such treatment should be combined with physical therapy and a coordinated cognitive-behavioral approach, particularly in those more severely affected. Pamidronate infusions are well tolerated and easy to administer;

several patients reported minor infusion site reactions and mild flu-like symptoms that settled within 6–24 hours.

The mechanism of analgesic effect of bisphosphonates remains speculative. They are potent inhibitors of osteoclastic activity; they may also play a role in modifying inflammatory cytokines (e.g., interleukin-1) and other systemic factors (e.g., prostaglandin E₂) involved in sensitizing painful nociceptors and low-threshold mechanoreceptors [18,19]. If, as proposed, peripheral mechanisms predominate in the early phase of the illness, with central mechanisms dominating in later phases [17], early treatment with pamidronate would appear optimal. Despite this theoretical consideration, several of our patients with established disease of several years duration responded to pamidronate, perhaps reflecting the heterogeneity of this condition. Our policy is to trial it in most patients regardless of disease duration, but we recommend early diagnosis and treatment.

A number of therapeutic questions remain including: which (if any) bisphosphonate is the superior agent, what are the optimal dosing regimens, what is the efficacy of repeated treatments, what is the characterization of treatment responders, and what is the optimal integration of bisphosphonate therapy with other treatment approaches?

In summary, our study has shown significant benefit to a cohort of patients with CRPS Type I following a single 60-mg pamidronate infusion, demonstrating superior pain relief and functional outcome versus placebo at 3 months. However, we believe these results should be interpreted with caution in view of the relatively low number of patients studied and the heterogeneity of response. Further larger controlled studies are needed to validate these findings. Our current practice is to give the majority of our CRPS patients a trial of pamidronate therapy and to continue if they respond positively.

This study adds to a growing body of evidence suggesting a role for bisphosphonates in this difficult and potentially debilitating condition.

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