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Rapid Communication

# The successful use of pamidronate in an 11-year-old girl with complex regional pain syndrome: Response to treatment demonstrated by serial peripheral quantitative computerised tomographic scans

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ABSTRACT

Complex regional pain syndrome (CRPS) is a disorder that can cause significant functional morbidity. While it usually presents in adulthood, it has also been reported in children. Multiple treatment modalities have been reported with mixed success. Bisphosphonate therapy has been shown to be effective in adult patients, but there are limited data in children. We report the successful use of intravenous pamidronate therapy in diminishing pain, improving function, and restoring bone mass in an 11-year-old girl with CRPS of her left lower limb following a tibial fracture. Previous treatment with intense physiotherapy and regional sympathetic blockade had not improved her symptoms. Pain improved within weeks of the first pamidronate infusion, with subsequent improvement in function. The benefit in pain reduction and function was sustained during the 2-year treatment regime. Improvement in bone mass and density was demonstrated by dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computerised tomography (pQCT). pQCT scans showed marked improvement in bone size and geometry and muscle bulk on the affected side. No adverse affects were reported. We conclude that intravenous pamidronate was associated with reduced pain, a return of function, and recovery of bone and muscle parameters in a child with CRPS. Before definitive conclusions can be drawn, a randomised controlled trial similar to those undertaken in adults previously is required to fully validate this approach.



## Introduction

Complex regional pain syndrome (CRPS), or reflex sympathetic dystrophy (RSD) as it was previously known, is a disorder characterized by regional pain, discolouration, oedema, temperature changes, and decreased function. It often follows trauma to the affected area such as fracture [1]. There is now an increasing understanding that CRPS may be due to an abnormal local inflammatory response to trauma in the affected part [2]. Underlying bony changes are recognized as a consequence of this disorder, with X-rays showing localised osteopenia [3]. While it was previously considered a disorder of adult life, there is increasing awareness that it occurs in the paediatric age group, with a recent review showing that it generally affected older children (median age of 13 years) and females in this age group [1].

A variety of treatment strategies have been trialled in CRPS. Physical therapy remains the cornerstone, with evidence of success in the majority of paediatric patients [4]. For recalcitrant cases, regional anaesthesia to cause sympathetic blockade is widely used, yet evidence for its efficacy remains limited [5]. Calcitonin has also been reported with variable evidence for any positive benefits [3]. Between 25% and 77% of children with CRPS have been reported to require psychological intervention [4,6].

There are four randomised controlled trials of bisphosphonates in adults with CRPS, using a variety of bisphosphonates, both oral and intravenous [7], as well as a number of smaller reports using predominantly intravenous pamidronate [8,9]. These have all shown some benefit in improving symptoms, suggesting that bisphosphonates have a role in the management of this condition. There has been no report of bisphosphonate treatment of CRPS in a child less than 13 years of age.

Here we report the use of intravenous pamidronate in an 11-year-old girl with CRPS following tibial fracture. Dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computerised tomography (pQCT) were used to assess the bone phenotype of the subject and her skeletal response to treatment. pQCT allowed for more detailed analysis of the bony phenotype as well as providing data that more closely relates to functional outcomes [10].

## Methods

pQCT using the XCT-2000 (Stratec Medical Systems, software version 6.0) was performed on the right and left tibiae at the 4%

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**Table 1**
DXA scan results – numbers in table represent *Z* score for height for each value.

| BMD *Z* scores for height | Baseline | 10 months | 19 months | 24 months | 6 months after cessation |
|---|---|---|---|---|---|
| Total body | −3.2 | −2.9 | −2.3 | −1.9 | −1.7 |
| Femoral neck: left | −3.5 | −2.1 | −1.0 | −0.7 | −0.6 |
| Femoral neck: right | −1.9 | −1.5 | −0.8 | −0.5 | −0.2 |
| Lumbar spine: L2–L4 | −2.4 | −1.6 | −1.5 | −1.1 | −0.1 |
| Height *Z* score | 0.37 | 0.34 | 0.40 | 0.73 | 1.08 |

BMD – bone mineral density.

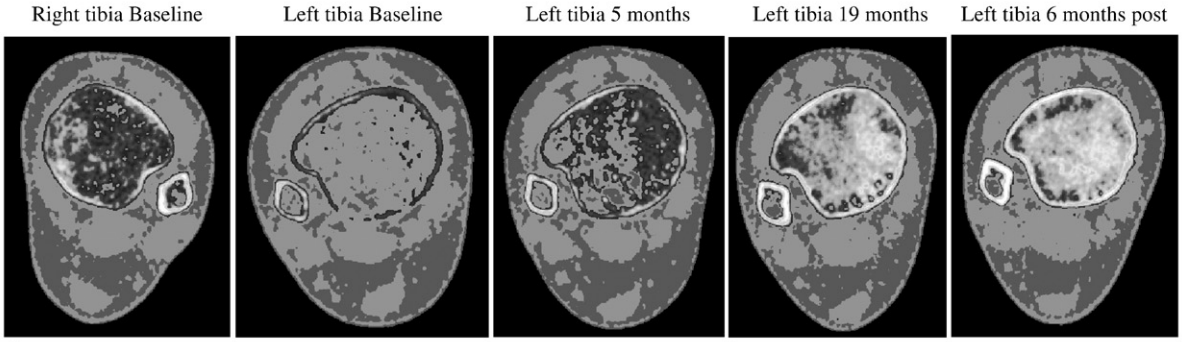
distal site to assess trabecular volumetric bone mineral density (vBMD) and the 65% distal site to assess cortical vBMD, while also assessing bone size (cortical thickness, bone cross-sectional area) and the stress–strain index (SSI) [11]. Muscle cross-sectional area at 65% of the site was also calculated. Age-matched standard deviation (SD) scores were generated from these data using normative values kindly provided by Moyer-Mileur et al., University of Utah.

Total body, AP spine (L1–L4), and dual proximal femur DXA scans were performed using a Lunar Prodigy (GE Lunar Radiation Corp, Madison, Wisconsin, USA; software version 8.60). The patient was positioned, scanned, and analysed according to standard manufacturer recommendations. Raw data were converted to SD scores based on previously published normative data [12]. SD scores are reported taking into account height to avoid bone size confounding the areal bone mineral density scores.

## Case report

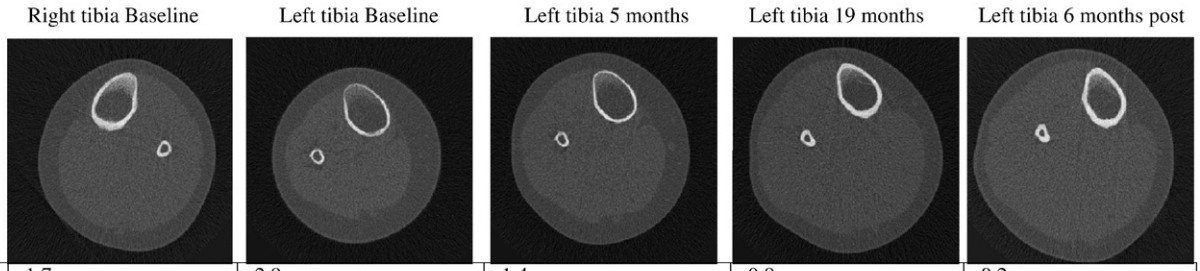
An 11-year-old girl sustained a fracture to the left distal tibia and fibula following trauma. The fracture was managed conservatively with plaster of Paris but was complicated by the development of compartment syndrome requiring surgical decompression. CRPS developed in the left leg, as evidenced by pain and by changes in skin temperature and colour. Physiotherapy and regional nerve block provided only minimal symptomatic relief.

(a) Tibia 4% Site




| | | | | | |
|---|---|---|---|---|---|
| Tibia 4% (trabecular) vBMD | -0.6 | -3.3 | -2.0 | 2.3 | 3.3 |

(b) Tibia 65% Site




| | | | | | |
|---|---|---|---|---|---|
| Tibia 65% (cortical) vBMD | -1.7 | -2.9 | -1.4 | -0.8 | -0.2 |
| Tibial 65% CSA | 1.8 | 1.2 | 0.8 | 1.0 | 0.8 |
| Tibial 65% cortical thickness | -1.8 | -3.9 | -3.4 | -2.1 | -1.6 |
| Stress strain index | 0.9 | -1.6 | -1.2 | 0.0 | 0.4 |
| Muscle CSA | -0.1 | -1.2 | -0.5 | 0.2 | 0.3 |

vBMD – volumetric bone mineral density; CSA – cross sectional area.

**Fig. 1.** pQCT scans with *Z* scores for selected measurement parameters listed underneath.

*Background history*

Our subject had a past history of tetralogy of Fallot requiring surgical repair as an infant. Since infancy, she had been completely asymptomatic from a cardiac perspective with normal cardiac function and no limitation on physical capacity. At 10 years of age, she sustained a traumatic fracture of her right wrist that healed with no complications. She was otherwise well, active, and on no medications. She had a dietary calcium intake of approximately 1000 mg daily. At initial presentation, she had reached Tanner stage 2 pubertal development and was premenarchal.

*Initial assessment*

The patient was first seen by the Bone and Mineral Service 4 months after the initial injury. She required crutches to weight bear, had muscle wasting of her left leg, and significant ongoing pain (revised Faces Pain Score [13] of 7), leaving her unable to attend school. Serum calcium, phosphate, magnesium, alkaline phosphatase, parathyroid hormone, and 25-hydroxy vitamin D levels were within normal limits (data not shown). Bone mineral density (BMD) by DXA showed generalised osteopenia (Table 1). Femoral neck BMD was lower on the left than the right (Table 1). pQCT also showed differences at baseline between her affected left lower limb and her non-affected right side (Fig. 1), with marked muscle wasting on the left side.

*Treatment/progress*

Intravenous pamidronate (10 mg/100 ml of normal saline and infused over 4 hours) was commenced at 0.5 mg/kg for the first dose then 1 mg/kg at 2 monthly intervals for 2 doses. After 6 months of treatment, pain had completely resolved and the subject was fully ambulant without the need for crutches. With this, the infusion regimen was changed to 1.5 mg/kg at 3 monthly intervals for 5 doses. An increase in symptoms in the month leading up to her next infusion was reported before the last two doses on the 3 monthly regimen. Infusions were therefore changed back to second monthly for 3 further doses of 1 mg/kg. Over a 24-month period, the subject received a total of 11 treatments before treatment was suspended with the absence of pain and normalisation of mobility and BMD. While on pamidronate, intensive physiotherapy, using activities such as trampolining, treadmill, exercise bike, and hydrotherapy, continued.

During therapy, bone density, size, shape, and SSI improved (Table 1 and Fig. 1), with reduction in side-to-side differences. Muscle cross-sectional area also improved in the affected leg. There were no fractures while on therapy and mineral homeostasis remained normal.

At review 6 months after cessation of treatment, pain had returned, although still significantly less than pretreatment pain levels. The subject was also still able to walk 20–30 min/day. She had reached Tanner stage 3, with menarche achieved 3 months after cessation of treatment. Growth also continued unimpeded (Table 1).

## Discussion

This report is the first of a patient younger than 13 years with CRPS successfully treated with bisphosphonates with reduction in pain, improvement in function, and normalisation of bone density and strength. While it is difficult to firmly establish cause and effect, both physical therapy and regional sympathetic nerve blockade had been trialled without success. The extent of reduced mobility was reflected in the baseline pQCT and DXA scans that showed marked sarcopenia and disuse osteopenia in the affected limb.

The mechanism by which pamidronate improves the symptoms associated with CRPS is unclear. It has been suggested that local acceleration of osteoclast activity may lead to local osteoporosis and bone pain. Therefore, inhibition of these osteoclasts may explain the reduction in symptoms with treatment [14]. However, as inflammation is also postulated as a cause of symptoms, the effect of bisphosphonates on modifying inflammatory cytokines cannot be discounted [15]. Effects on pain nociceptors have also been proposed as a possible mechanism [15]. Until the underlying pathophysiology of CRPS is fully elucidated, the effect of bisphosphonates in this disorder will remain speculative. As with any treatment modality that improves pain, the possibility of a placebo effect exists. While it is difficult to disprove this in a single case report, the positive benefits demonstrated in adult RCT trials, as well as the temporal relationship of the patient's pain increasing before the next infusion, support a positive effect of pamidronate therapy.

The subject experienced a normally timed puberty during the study. The use of age- and height-matched *Z* scores allows for accurate assessment of bone mass accrual over this time. Indeed, her height SD increased over the latter part of the study, but her DXA *Z* scores for height increased also, suggesting that she was accruing bone mass at a rate above that expected for her degree of height gain.

pQCT demonstrated the improvement in muscle and bone that occurred during pamidronate therapy. The recovery seen is likely to represent an interplay between pamidronate and mechanical bone effects from improved mobility, associated with enhanced participation in her physical therapy program. The improvement in cortical thickness seen is consistent with that described for children with bone fragility treated with pamidronate [16]. Pamidronate has also been associated with improved grip strength in children with osteogenesis imperfecta [17]. Separating out a direct bone effect of pamidronate from the secondary bone effects due to enhanced muscle pull as pain settled, and therefore mobility improved, is not possible. However, the right (unaffected) tibia showed minimal change in parameters such as cortical thickness and stress–strain index (data not shown). This suggests that at least some of the cortical improvements in the affected leg were not directly related to pamidronate but rather due to improved muscle mass and force. This is supported by the increase in muscle cross-sectional area seen on the affected side but not on the unaffected side.

The increase in trabecular BMD on 4% site pQCT scan seen both at the 19th month scan and the 6 months posttreatment scans is a reflection of pamidronate therapy and highlights that an increase in BMD seen on DXA does not reflect a uniform increase in bone, which has been demonstrated by previous histomorphometric analysis of patients on pamidronate [18]. A “pamidronate line” represents a horizontal bar of trabecular bone and calcified cartilage that was laid down following a pamidronate infusion [18]. With growth, these lines begin to fall within the 4% scan region on pQCT and do not reflect generalised metaphyseal bone density [19].

Concern exists regarding short-term and long-term safety of bisphosphonate therapy in children [20,21]. As such, children should receive these medications under the supervision of centres experienced in their use. Recognised side effects of intravenous bisphosphonates include acute flu-like symptoms and hypocalcaemia following the first infusion [22], disturbed metaphyseal modelling [23], reduced bone turnover [24], persistence of calcified cartilage in the metaphysis [18], and delayed bone healing in children with osteogenesis imperfecta [25]. Bisphosphonate-related osteonecrosis of the jaw is another potential side effect of this therapy; however, to date, this has not been reported in paediatric patients [26]. Despite these concerns, bisphosphonates are considered the standard of care by many for the management of children with significant bone fragility [27] and are being used increasingly in children with other bone disorders [23,28–30].

With the above risks in mind, the decision to treat this patient was based on her severe symptoms associated with a marked reduction in her quality of life. Careful monitoring of bone and mineral homeostasis was undertaken as well as regular dental review, while bone density was closely monitored as described above. As these compounds cross

the placenta and persist for many years, there is potential for future effects on foetal development even years after the treatment has ceased [27]. However, to date, no adverse effects have been demonstrated in babies born to mothers using bisphosphonate therapy aside from mild hypocalcaemia [31]. Most importantly, no skeletal anomalies have been detected. However, the small number of births to women treated with bisphosphonates means that the risk is still not well understood, and caution is advised. These potential risks need to be weighed up against the possible positive benefits of treatment: in our patient, we felt that the symptomatic benefit outweighed any potential or theoretical side effects.

In conclusion, pamidronate therapy was associated with improvement in pain and functional outcomes in our patient. Bone and muscle parameters on DXA and pQCT scans showed improvement consistent with the clinical findings. A prospective randomised controlled trial similar to those undertaken in adults with the use of a validated pain scale is required to confirm the findings from our report.

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