Biphosphonates for the therapy of complex regional pain syndrome I: systematic review

CRD summary
The review assessed the effectiveness of biphosphonates for the treatment of CRPS 1 patients with bone loss. It concluded that very limited available data suggested that biphosphonates had the potential to reduce pain associated with bone loss in CRPS 1 patients. The conclusions reflect the limited data presented and are appropriate.

Authors' objectives
To assess the effectiveness of biphosphonates in the treatment of complex regional pain syndrome 1 (CRPS 1) patients with bone loss.

Searching
MEDLINE, EMBASE (both from inception to April 2007), Cochrane Central Register of Controlled Trials (Issue 2, 2007), and reference lists of included studies were searched for publications in any language. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) comparing biphosphonates against placebo in patients with CRPS 1 were eligible for inclusion. Outcomes of interest were changes in pain intensity (assessed with a visual analogue scale (VAS) of 100 mm) and function and quality of life.

The mean age of patients was 51.7 years. Biphosphonates considered were: alendronate (7.5 mg intravenous in one study; 40 mg/daily orally in another); pamidronate (60 mg intravenous, one study) and clondronate (300 mg intravenous, one study). The duration of exposure was varied (ranged from a single infusion to eight weeks).

Outcomes reported included changes in pain intensity, function and quality of life, bone mineral content, hydroxyprolin/kreatinin ratio, and a number of side effects. In most patients, CRPS 1 was situated in the lower extremity. The most frequent cause of CRPS 1 was trauma and fracture.

Two reviewers independently assessed the studies for inclusion. Disagreements were resolved by discussion or by a third reviewer.

Assessment of study quality
Study quality was assessed based on a modified criteria used by ter Riet and Kessels, and considered aspects of validity, data description and analysis and compliance. Each item was scored out of 4, with 1 meaning appropriately addressed, 2 partially addressed, 3 inappropriately addressed and 4 not addressed. Two reviewers independently assessed study quality using a standardised form. Disagreements were resolved by consensus or through arbitration by a third reviewer.

Data extraction
Two reviewers independently extracted outcome data at baseline and follow-up for each group. Data from studies reporting pain assessment using a visual analogue scale were extracted to calculate mean differences. The authors did not state how any disagreements were resolved.

Methods of synthesis
Study results were described narratively where interventions and outcome measures were varied. However, results of comparable studies (those with similar outcomes and timing of assessments) were combined by calculating a pooled mean visual analogue scale difference using the variance weights method. Statistical heterogeneity was not formally assessed, but clinical and methodological differences were described in the text.

Results of the review
Four RCTs were included (n=118). Sample sizes were small (range: 20 to 39). Follow-up ranged from two weeks to 12
months. All of the included studies were rated as moderate quality.

Biphosphonates, compared to control, were associated with a significant improvement in joint mobility (two RCTs of alendronate) and physical function (one RCT of pamidronate).

Biphosphonates, compared to control, were associated with a significant reduction in pain intensity (one RCT of alendronate and one RCT of pamidronate): mean visual analogue scale difference was 22.4 mm after four weeks and 21.6 mm after 12 weeks of follow-up (confidence intervals and p-values were not reported). A number of side effects were reported in the review.

**Authors' conclusions**

Although biphosphonates were shown to have the potential to reduce pain in CRPS 1 patients with bone loss, the evidence was insufficient to recommend biphosphonates for the treatment of CRPS 1.

**CRD commentary**

The review question was clear with respect to study design, participants, interventions and outcomes. Relevant databases were searched without language restriction, thus minimising the possibility of language bias. Relevant studies may have been missed as no attempts were made to search for unpublished literature. Potential for reviewer bias and error was minimised through duplicate study selection, data extraction and quality assessment. Characteristics and quality of the individual studies were presented clearly. Methods used to synthesize results were appropriately justified, but results of statistical pooling were incompletely reported. Conclusions of the review were derived from a small number of studies with small sample sizes. The authors’ conclusions are appropriate given the limited data presented.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that further large, high quality RCTs of the effect of biphosphonates in CRPS 1 management were needed. Measures of outcomes in future trials should include improvements in function and quality of health status, pain, return to work and side effects.

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