Bisphosphonate use in acute and chronic spinal cord injury: a systematic review

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CRD summary
This review assessed the use of bisphosphonates to prevent bone loss in patients with acute and chronic spinal cord injury and concluded that there was insufficient evidence to recommend their use. Given some potential biases in the review process and the suboptimal quality and variation within included studies, the extent to which the authors’ conclusion is reliable is unclear.

Authors' objectives
To evaluate the use of bisphosphonates on post-treatment sublesional bone mineral density in patients with traumatic spinal cord injury.

Searching
MEDLINE (1966 to December 2008) and Web of Knowledge (1955 to December 2008) were searched. Search terms were reported. Bibliographies of identified publications and review articles were also searched. Only English language articles were eligible for inclusion.

Study selection
Eligible studies were randomized controlled trials (RCTs), non-randomised trials and case control studies of patients with traumatic spinal cord injury who had received bisphosphonate therapy to optimise bone health. The primary outcome was bone mineral density measurement at sublesional sites by dual-energy x-ray absorptiometry. Three older studies that reported histomorphometric outcomes were reviewed but will not be further discussed in this abstract.

Patient characteristics were variable with included studies reporting both acute and chronic spinal cord injury at varying levels. Where reported, males represented a higher proportion of the study population. Interventions included alendronate (three studies), pamidronate (two studies), zoledronate (one study) and etidronate (one study). Different dosing regimens were used and additional supplementation with calcium and/or vitamin D was variable. Measurement sites for bone mineral density varied between the studies.

The authors do not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using a modified established checklist. Scores were allocated based on an assessment of randomisation, allocation concealment, similarity of groups at baseline, specification of eligibility criteria, blinding, presentation of primary outcome, and intention-to-treat analysis. The maximum score possible was 21; studies were assessed as poor (7 to 11), fair (12 to 16) or good (17 to 21).

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Data were collected on numbers and/or means with standard deviations to enable the calculation of treatment differences between baseline and follow-up.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Because of significant heterogeneity between the included studies and the relatively small sample size of the studies, a narrative approach was taken. Differences between the studies were examined using tables and text.
Results of the review
Seven studies were included in the review (n=168 patients); six were RCTs (n=144 patients) and one was a quasi-experimental study (n=24 patients). Five of the studies were rated fair and two were rated as poor. Follow-up varied between six and 24 months.

Acute spinal cord injury: Bone mineral density declined at a slower rate in patients given alendronate (70mg weekly), commencing within 10 days of spinal cord injury and continuing for 12 months. There was a 17.6% (p<0.001) difference in total hip bone mineral density and 7% (p<0.001) difference in total body leg bone mineral density between the intervention group and the control group. Patients receiving a single dose of 4 or 5mg of zoledronic acid at 10 to 12 weeks after spinal cord injury had attenuated bone loss at the proximal femur for six months and at the femur shaft for 12 months, although the effect at the proximal femur did not persist. In the group given etidronate, bone mineral density was maintained near baseline only in the two patients who were ambulatory. Patients receiving intravenous pamidronate also had attenuated bone mineral density loss, but this was not demonstrated to persist at 24 months.

Chronic spinal cord injury: Bisphosphonates use in chronic spinal cord injury improved bone mineral density loss relative to pre-treatment values, although statistical significance was only reported as achieved in two of nine bone mineral density parameters. In a study of patients with acute and chronic spinal cord injury given alendronate (10mg daily) plus elemental calcium for 24 months, there was a statistically significant treatment effect over those given calcium alone (distal tibia -2.0% versus -10.8%; p=0.017), but generally no reparation of bone loss relative to bone mineral density before spinal cord injury.

Authors’ conclusions
Data were insufficient to recommend routine use of bisphosphonates for fracture prevention in patients with acute or chronic spinal cord injury.

CRD commentary
This review addressed a clear research question, supported by potentially reproducible inclusion criteria. The database search was limited to two sources. Specific language limitations were included and no apparent attempts were made to locate unpublished material, so language and publication bias could not be ruled out. It was unclear if appropriate methods to minimise reviewer error and bias were applied for study selection, data extraction and study quality, representing a potential threat to the reliability of findings.

Validity was assessed using a systematic checklist and this revealed concerns about the potential risk of bias in the selected studies. There was considerable heterogeneity between the included studies and the sample sizes were relatively small, so a narrative synthesis was appropriate.

In light of the potential limitations highlighted, the authors’ cautious conclusion is appropriate but its reliability is unclear.

Implications of the review for practice and research
Practice: The authors stated that there are insufficient data to recommend routine use of bisphosphonates for fracture prevention in patients with acute or chronic spinal cord injury.

Research: The authors stated that future research should define risk factors connected with low-energy fractures in the spinal cord injury population, evaluating whether the modest effect of bisphosphonates on bone mineral density in spinal cord injury leads to fracture risk reduction. Future study designs should address minimising variation within the study population and in outcome measures. Research on the potential risks of bisphosphonates in women of reproductive age is warranted.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.