Evidence-Based Practice Group Answers to Clinical Questions

“Bisphosphonates as Treatment for Complex Regional Pain Syndrome (CRPS)”

A Rapid Systematic Review

By

WorkSafeBC Evidence-Based Practice Group

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Clinical Services – Worker and Employer Services
About this report

Bisphosphonates as Treatment for Complex Regional Pain Syndrome (CRPS)

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About the Evidence-Based Practice Group
The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Objective

To determine whether there is evidence to support the efficacy and/or effectiveness of bisphosphonates as treatment for Complex Regional Pain Syndrome (CRPS).

Methods

- A comprehensive, systematic literature search was conducted on November 8, 2017.
- The search was done on commercial medical literature databases, including Cochrane Database of Systematic Reviews® (2005 to November 8, 2017), ACP Journal Club® (1991 to October 2017), UK York University Database of Abstracts of Reviews of Effects® (1st Quarter 2016), Cochrane Central Register of Controlled Trials® (November 2017), UK NHS Health Technology Assessment® (4th Quarter 2016), UK NHS Economic Evaluation Database® (1st Quarter 2016), BIOSIS Previews® (1969 to 2008), Embase® (1974 to 2017 November 07), Medline Epub Ahead of Print®, Medline In-Process & Other Non-Indexed Citations®, Medline Daily Update® and Medline® (1946 to Present), that are available through the OVID® interface.
- The following keywords combination were employed in this literature search:
  1. (complex regional pain syndrome) OR crps OR causalgia OR (reflex sympathetic dystrophy) OR (Sudeck atrophy) OR algodystrophy OR (post-traumatic vasomotor syndrome) OR (complex regional pain syndrome type 1) OR (complex regional pain syndrome type 2) OR (complex regional pain syndrome type I) OR (complex regional pain syndrome type II) OR algoneurodystrophy OR (painful post traumatic osteoporosis) OR (transient migratory osteoporosis) OR (painful post traumatic dystrophy) OR (shoulder-hand syndrome) OR rsd
  2. bisphosphonates OR alendronate OR pamidronate OR etidronate OR clodronate OR tiludronate OR neridronate OR olpadronate ORibandronate OR risedronate OR zoledronate
  3. 1 AND 2
- No limitations, such as on the language or year of publication, were employed in any of these searches.
  o Two hundred and ten\(^{(1-210)}\) published studies were identified through these searches.
- A manual search was also done on the references of the retrieved articles with the purpose of identifying further relevant primary studies.
  o No further study was identified through this manual search.
Results

- Literature search:
  - Upon examination of the titles and abstracts of the 210\(^{(1-210)}\) studies identified via the literature searches, forty-three studies\(^{1,2,3,4,5,7,8,17,28,34,35,38,44,48,54,57,65,69,78,82,86,91,95,96,110,117,120,122,124,126,141,153,155,157,161,166,181,184,185,186,188,189,199,206}\) were thought to be relevant and were retrieved in full for further appraisals.
  - After reviewing the above forty-three articles in full, twenty two\(^{2,4,8,34,35,44,45,57,65,69,82,86,95,96,117,120,153,157,161,181,185,186,206}\) studies were eliminated from further discussions, due to a combination of factors, such as irrelevancy, a lack of data or data/primary studies, or where data/studies presented were found to be subsequently covered by more recent articles/reviews.
  - Another three\(^{48,141,199}\) systematic reviews (level of evidence 1. Appendix 1) will not be discussed further due to the fact that the primary studies included in these systematic reviews will be appraised individually below\(^{48,141,199}\), as well as the reviews’ improperly conducted meta-analysis (presenting with very high level of heterogeneity\(^{48}\)), and their unclear interpretation of the results of network meta-analysis\(^{199}\).
  - As such, there were a final eighteen\(^{1,3,5,7,17,28,38,54,78,91,110,122,124,126,155,166,184,188}\) relevant studies appraised and summarized below.
  - Table 1 summarizes data available from six\(^{5,17,126,155,184,188}\) randomized/controlled trials (R/CTs) (level of evidence 1. Appendix 1) that are relevant to the objective this study. Although all of these R/CTs provided some evidence on the efficacy and/or effectiveness of different bisphosphonates in reducing pain among patients diagnosed with CRPS, particularly among those with signs of osteopenic or osteoporotic changes in the affected extremity, it should be noted that all of these trials consisted of small sample sizes, used different diagnostic criteria of CRPS, and where the effect of co-intervention(s) cannot be excluded. As well, “appropriate” dosages of bisphosphonates were not clearly defined, potential conflict(s) of interest associated with funding of the studies cannot be excluded\(^{153}\) and, overall, these studies were of low-medium quality since the influence of bias cannot be excluded.
  - Table 2 summarizes the case report-case series (level of evidence 5. Appendix 1) identified in this systematic review. Similar characteristics, such as radiologically established osteopenia as inclusion criteria for treatment, an early stage of CRPS at the start of treatment and unclear role of co-intervention, were also observed/reported in these case report-case series.
There are concerns regarding osteonecrosis of the jaw (ONJ) in patients who take aminobisphosphonates. ONJ is hypothesized to occur as the direct result of microtrauma on bone that is both hypovascular and hypodynamic and thus less able to meet an increased demand for repair and remodelling. The first generation of bisphosphonates (etidronate, tiludronate and clodronate) are not nitrogen-containing and these compounds have not been considered to cause ONJ. Alendronate, isedronate, pamidronate, zoledronic acid and ibandronate all contain nitrogen within a side chain. The nitrogen-containing bisphosphonates, especially the intravenous forms (zoledronate and pamidronate), have been associated with ONJ\(^{166}\). The probability of developing ONJ after IV administration of bisphosphonates was reported to be 5.48% within a 6-year period\(^{28}\). It should be noted that a case of osteonecrosis of the jaw associated with bisphosphonates infusion (zoledronate and pamidronate) in CRPS patient has also been reported\(^{28}\).

**Summary**

At present, there are some, high-level/low-quality as well as low-level/low-quality studies providing some evidence on the efficacy and/or effectiveness of bisphosphonates as treatment for CRPS. However, it should be noted that there are heterogeneity within the criteria employed in diagnosing CRPS and the type, dosage and duration of bisphosphonates used, and the potential effect(s) of co-intervention(s) cannot be discounted. It should be noted that the use of bisphosphonates is associated with side effects and the potential side effect in the form of osteonecrosis of the jaw cannot be discounted as part of CRPS treatment.
Table 1. Summary of the randomized/controlled trials identified.

<table>
<thead>
<tr>
<th>Ref. (CRPS criteria)</th>
<th>N (interventions / controls)</th>
<th>Drugs (dosage, admin)</th>
<th>Duration</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Side effects</th>
<th>Results</th>
<th>Co-intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (Kozin)</td>
<td>20 (10/10)</td>
<td>Alendronate, 7.5 mg, IV</td>
<td>3 days; after 14 days open labelled for all participants for 3 days</td>
<td>VAS (spontaneous pain and tenderness), arbitrary score for motion (0-4) assessed by MDs, circumference (skin labelling), bone mineral content</td>
<td>2x before treatment, 2 and 4 weeks</td>
<td>3 controls with fever</td>
<td>Interventions: spontaneous pain, tenderness, swelling was statistically significant decreased from baseline, also when compared to first 14 days of control group and from week 2 to 4. Improvement of motion. Controls: no relevant symptomatic changes after first of 14 days follow up, but response to open alendronate therapy given afterwards.</td>
<td>Physiotherapy</td>
</tr>
<tr>
<td>Treatment</td>
<td>Study Number</td>
<td>Study Type</td>
<td>Dose and Route</td>
<td>Duration</td>
<td>Primary Outcomes</td>
<td>Secondary Outcomes</td>
<td>Interventions</td>
<td>Notes</td>
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<td>Clodronate, 300 mg/d, IV</td>
<td>188 (Budapest)</td>
<td>10 days</td>
<td>VAS, clinical global assessment (0-3), efficacy verbal score, hydroxyprolin/kreatinin ratio</td>
<td>Before RX, 40 days, 90 days, 180 days, (phone: 9 and 12 months)</td>
<td>3 controls with asymptomatic hypocalcemia</td>
<td>Significant differences in all clinical variables. Pooling results of all 32 patients after clodronate: 30 patients significantly improved</td>
<td>none</td>
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<tr>
<td>Alendronate, 40 mg/d, orally</td>
<td>126 (IASP and Harden)</td>
<td>8 weeks, 4 weeks nontherapeutic period, 8 weeks open extension</td>
<td>VAS, tenderness, edema, joint mobility and N-telopeptide</td>
<td>4, 8, 12, 16, 20, 24 weeks</td>
<td>1 control dropout due to GI side effect</td>
<td>Alendronate group marked and sustained improvement on pain, pressure tolerance, joint mobility, N-telopeptide</td>
<td>physiotherapy</td>
<td></td>
</tr>
<tr>
<td>Pamidronate, 60 mg, IV</td>
<td>155 (IASP)</td>
<td>Single infusion</td>
<td>VAS, global assessment of disease severity score, SF-36</td>
<td>1, 3 months</td>
<td>5 interventions and 2 controls with influenza typed symptoms and 2 controls with infusion site reaction</td>
<td>Improvement in pain score, patient’s global assessment of disease severity score and physical function in intervention group at 3 months. Improvement in physical function at 1 and 3 months.</td>
<td>NSAIDs and acetaminophen</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Intervention</td>
<td>Duration</td>
<td>Outcome Measures</td>
<td></td>
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<tr>
<td>Budapest</td>
<td>82 (41/41)</td>
<td>Neridronate, 100 mg, IV</td>
<td>IV, 4x over 10 days</td>
<td>VAS pain, joint volume or local oedema, pain evoked by passive motion, allodynia, hyperalgesia, McGill Pain Questionnaire, SF-36 functional status and no of NSAID or acetaminophen tablets taken weekly</td>
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<td></td>
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<td></td>
<td></td>
<td>Before randomization, before infusion, day 10, 20, 40</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>MSK concerns mainly polyarthralgia on 12 (29.3%) neridronate and 5 (12.2%) placebo. Fever was reported by 9 (21.9%) neridronate and 1 (2.4%) placebo.</td>
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<td></td>
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<td></td>
<td>Significant different on pain score starting day 20. At 40 days, ≥ 50% VAS score decrease was obtained in 30 (73.2%) neridronate vs 13 (32.5%) controls McGill Pain Questionnaire significant differences between groups for sensory and affective items were observed at day 40. SF-36 showed at day 40 significant differences for all items except for role limitations due to emotional problems, vitality and general health.</td>
<td></td>
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</tbody>
</table>

NSAID and acetaminophen
| 17 (unclear) | 14 (7/7) | Clodronate, 100mg, IV and IM | IV and IM for 2 weeks. Then all patients were subjected to IM clodronate 100 mg/weekly for 3 months. | VAS pain (0-100) and joint examination | before, after one week and after 3 month | None reported | Clodronate reduces pain significantly in both groups after one week RX, pain reduction significantly higher in patients treated with IV. After 3 months, different in pain not significant. Rapid reduction of pain in IV group was associated to a rapid reduction of hyperhidrosis, edema and joint stiffness after one week of therapy. | NSAID, supplemental calcium and Vitamin D, physical therapy |
Table 2. Summary of case report/series identified in this systematic review.

<table>
<thead>
<tr>
<th>Ref. (CRPS criteria)</th>
<th>N</th>
<th>Drugs (dosage, admin)</th>
<th>Duration</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Side effects</th>
<th>Results</th>
<th>Co-intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (unclear)</td>
<td>1</td>
<td>Zoledronic acid (4 mg; IV)</td>
<td>once per month for 3 months</td>
<td>VAS pain reduction at 7 days, and 1 month include swelling.</td>
<td>7 days, 1 month and 3 months</td>
<td>Not available</td>
<td>VAS pain reduction at 7 days, and 1 month include swelling</td>
<td>No data</td>
</tr>
<tr>
<td>1 (unclear)</td>
<td>1</td>
<td>Pamidronate (90 mg; IV)</td>
<td>One time IV followed by oral up to 9 months</td>
<td>VAS pain</td>
<td>2 days and 9 months</td>
<td>Not available</td>
<td>Pain disappeared at 2 days, oedema smaller. At 9 months doing well.</td>
<td>No data</td>
</tr>
<tr>
<td>91 (unclear)</td>
<td>1</td>
<td>Pamidronate (60 mg; IV)</td>
<td>IV twice over a week</td>
<td>Pain, RTW</td>
<td>2 days and 1 week</td>
<td>Not available</td>
<td>Pain reduced by half in 2 days. RTW (unclear when)</td>
<td>No data</td>
</tr>
<tr>
<td>3 (unclear)</td>
<td>2</td>
<td>Risedronate (2.5 mg per day and 35 mg per week; oral)</td>
<td>Oral daily and weekly for 15 months</td>
<td>Pain and osteoporotic changes</td>
<td>One, 9, 15, and 30 months</td>
<td>Not available</td>
<td>At 1 month significant bone pain reduction; at 30 months no pain and marked osteoporotic improvement</td>
<td>No data</td>
</tr>
<tr>
<td>38 (unclear)</td>
<td>2</td>
<td>Pamidronate (60 mg; IV)</td>
<td>Single infusion</td>
<td>Pain and osteopenia</td>
<td>24 hours and 1 month</td>
<td>Not available</td>
<td>24 hours pain much improved; 1 months less osteopenia</td>
<td>No data</td>
</tr>
<tr>
<td>122 (Doury’s)</td>
<td>11</td>
<td>Pamidronate (30 mg; IV)</td>
<td>In 500 ml saline over 4 hours, daily for 3 days</td>
<td>VAS pain and physicians global assessment (PGA)</td>
<td>One and 3 months</td>
<td>Transient fever, brief hypocalcemia and brief perioral paraesthesia</td>
<td>Significant decrease of VAS pain and PGA assessment at 1 and 3 months. 3 of 6 who had stopped working had RTW at 3 months.</td>
<td>None</td>
</tr>
<tr>
<td>78 (Budapest)</td>
<td>12</td>
<td>Neridronate (100 mg; IV)</td>
<td>Every 3rd day for 4 times within 10 days from 1st infusion</td>
<td>Qol, joint function, pain</td>
<td>Before, at 3 and 6 months</td>
<td>Not available</td>
<td>After 3 months 8 (12) showed good results. After 6 months, results observed at 3 months were conformed.</td>
<td>No data</td>
</tr>
</tbody>
</table>
### Bisphosphonates as Treatment for Complex Regional Pain Syndrome (CRPS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Treatment Duration</th>
<th>Pain Assessment</th>
<th>Adverse Events</th>
<th>Clinical Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>54 (Doury’s)</td>
<td>23</td>
<td>Pamidronate (1 mg/kg/day; IV)</td>
<td>Either for 3 (for 14), 2 (for 7) or 1 day (for 2 patients) <em>(related to adverse events)</em></td>
<td>Pain: VAS and verbal scale</td>
<td>Before, 7, 30, 60 and 90 days after treatment</td>
<td>Transient fever, venous inflammation, transient hypocalcemia, nausea, lymphopenia, transient hypertension</td>
</tr>
<tr>
<td>110 (Doury’s)</td>
<td>29</td>
<td>Pamidronate (60 mg/day; IV)</td>
<td>3 consecutive days</td>
<td>Complete disappearance of pain and ROM increased by 20°</td>
<td>Days 15 and 45</td>
<td>Fever, diarrhoea</td>
</tr>
<tr>
<td>124 (Budapest)</td>
<td>172</td>
<td>Neridronate (100 mg; IV) or Pamidronate (60 mg; IV) or Clodronate (300 mg; IV) <em>(unclear criteria for drug choice)</em></td>
<td>4 infusions for Neridronate or Pamidronate and 10 infusions for Clodronate <em>(unclear days duration of treatment)</em></td>
<td>Clinical success: ≥ 50% VAS pain reduction at 45-60 days from the beginning of the treatment</td>
<td>45-60 days from the beginning of the treatment</td>
<td>Not available</td>
</tr>
</tbody>
</table>

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WorkSafeBC Evidence-Based Practice Group
www.worksafebc.com/evidence
References


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Bisphosphonates as Treatment for Complex Regional Pain Syndrome (CRPS)

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Appendix 1

WorkSafeBC - Evidence-Based Practice Group Levels of Evidence (adapted from 1,2,3,4)

<table>
<thead>
<tr>
<th></th>
<th>Evidence from at least 1 properly randomized controlled trial (RCT) or systematic review of RCTs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.</td>
</tr>
<tr>
<td>5</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.</td>
</tr>
</tbody>
</table>

References


