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Recommendations

Bisphosphonates for treatment of Complex Regional Pain Syndrome type 1: A systematic literature review and meta-analysis of randomized controlled trials versus placebo

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ABSTRACT

Objectives: Complex Regional Pain Syndrome Type 1 is a severely disabling pain syndrome with no definite established treatment. We have performed a systematic literature review and meta-analysis of all randomized controlled trials to assess the benefit of bisphosphonates on pain and function in patients with Complex Regional Pain Syndrome Type 1.
Methods: A systematic literature search was performed in the Medline, Embase and Cochrane databases. Two authors selected independently blinded randomized trials comparing bisphosphonates to placebo on short-term (J30 to J40) and medium term pain (M2–M3), safety and function in patients with CRPS 1. The methodological quality of the studies was analyzed. Data were aggregated using the method of the inverse of the variance.
Results: 258 articles were identified. Four trials of moderate to good quality comprising 181 patients (90 in the bisphosphonate group and 91 in the placebo group) were included in this meta-analysis. Short-term pain Visual Analog Scale was significantly lower in the bisphosphonate group versus the placebo group (SMD = −2.6, 95%CI [−1.8, −3.4], $P < 0.001$), as well as the medium term Visual Analog Scale pain (SMD = −2.5, 95%CI [−1.4, −3.6], $P < 0.001$). There were more adverse events in the bisphosphonate group (35.5%) than in the placebo group (16.4%) with a relative risk of 2.1 (95%CI [1.3, 3.5], $P = 0.004$) and a number needed to harm of 4.6, (95%CI [2.4, 168.0]) but no serious side effects.
Conclusions: Our results suggest that bisphosphonates reduce pain in patients with Complex Regional Pain Syndrome type 1. Other studies are needed to determine their effectiveness.

1. Introduction

Complex Regional Pain Syndrome type 1 (CRPS 1) is a disorder characterized by pain, swelling, and vasomotor disorders skin changes leading to a severe disability for which the therapeutic management remains a challenge [1]. The precise causes of this syndrome remain largely unknown [2]. The classic therapeutic strategy comprises pharmaceutical treatments, physical care and loco regional blocks. Local anesthetic sympathetic blockade and calcitonin used in CRPS 1 do not appear to be effective [3].

Bisphosphonates, antiosteoclastic agents, have been reported as having significant analgesic efficacy in a number of bone-related pathologies including Paget's disease [4], metastatic cancer [5], myeloma [6], acute vertebral fracture [7], and refractory rheumatic conditions [8].

Bisphosphonates seem have an analgesic efficacy in CRPS 1 [9,10]. But in CRPS 1, enhanced osteoclastic activity has never clearly been demonstrated [11,12]. This raises the question of the mode of action of bisphosphonates in this pathology. The demineralization observed in CRPS 1 [13] is probably more related to local tissue hypoxia, so the antiosteoclastic action of bisphosphonate could not explain the potentially antalgic effect in CRPS 1. A potential mechanism of pain in CRPS 1 may be the activation of two main groups of acid-sensing nociceptors (TRPV1 and ASICs) [14] resulting of a local acidosis, secondary at the hypoxia following micro-vascular disturbances [15] observed in this pathology. Bisphosphonates could act on this pathway by decrease proton

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concentration of the bone microenvironment [9] and provoke an antalgic effect.

Bisphosphonates have the ability to prevent the dissolution of hydroxyapatite crystals in an acidic environment. It is also one of their first described pharmacological effects [16], this may explain their efficiency in CRPS 1. Bisphosphonates also have the ability to inhibit the growth, migration and activity of mononuclear cells derived from the bone marrow [17–19]. Many studies have shown that bisphosphonates decrease the production of tumor necrosis factor α and other pro-inflammatory mediators [20,21]. There are a lot of possible mechanisms of action which can explicate that bisphosphonates can work in CRPS 1.

During the past few years, several trials were carried out to compare the efficacy of bisphosphonates and placebo in CRPS 1 [22]. A Cochrane review [3] concluded that the effectiveness of bisphosphonate to reduce pain is of low quality of evidence. But they did not include the results of the recent randomized controlled trial with good methodological quality and correct power from Varenna et al. [23]. Therefore, we performed a systematic literature review and meta-analyses in order to obtain a numerical conclusion necessary for an objective evaluation of bisphosphonates efficacy about pain, function and safety in CRPS 1.

2. Methods

This meta-analysis was conducted according to the Cochrane Collaboration guidelines [24].

2.1. Search strategy

Two reviewers (X.R. and M.C.) performed independently an extensive search of PubMed and Embase databases during the summer of 2014. The following key words were used to screen the PubMed database: ((“Diphosphonates”[Mesh] AND “Complex Regional Pain Syndromes”[Mesh]) OR (“Diphosphonates”[Mesh] AND “reflex sympathetic dystrophy”[Mesh])). Key words for searches in the Embase database were: ‘complex regional syndromes’/exp OR ‘reflex sympathetic dystrophy’/exp AND ‘Diphosphonates’/exp. A search with synonyms terms (bisphosphonates, algoneurodystrophy, algodystrophy, shoulder-hand syndrome, Sudeck syndrome, causalgia) not brought any additional article.

This search was completed by a hand search of references from relevant articles, review papers and abstracts presented at the American Society for Bone and Mineral Research annual scientific meetings, the American College of Rheumatology annual scientific meetings, the European League Against Rheumatism annual congress and the French Society of Rheumatology scientific meetings from 2012 until 2014.

2.2. Selection

Inclusion criteria were:

(i) randomized controlled trial;
(ii) evaluating efficacy and/or safety of bisphosphonates;
(iii) adult patients with CRPS 1 according to the international classification criteria [25,26].

Exclusion criteria were:

(i) uncontrolled trial;
(ii) controlled trials without placebo.

2.3. Quality assessment

Two reviewers (X.R. and M.C.) independently assessed the methodological quality of each study included in the meta-analysis using the Jadad score [27]. The Jadad score, ranging from 0 to 5 (a higher score for a higher methodological quality), is a procedure to independently assess the methodological quality (in example randomization, blinding procedures and withdrawals) of a clinical trial.

2.4. Data extraction

Two reviewers (X.R. and M.C.) selected the articles and collected the data using a predetermined form that included study design (randomization procedure, blinding and assessment endpoints), patient characteristics (number, age, gender and disease duration), treatment parameters (name, dosage, route of administration), localization of symptoms and etiology of CRPS 1. When disagreements between both reviewers occurred, a third reviewer (A.B.) was consulted. Authors of included articles were contacted in order to provide unpublished collected data. When the selected articles included an open-label extension phase, data from that were not included in our analysis.

2.5. Outcomes

The following outcomes were extracted from the publications by two independent reviewers (X.R. and M.C.).

Efficacy:

- short term pain: pain Visual Analog Scale (VAS) within 30 to 40 days after treatment onset;
- medium term pain: VAS within 2nd to 3rd month after treatment onset;
- function: Short Form 36 Health Survey (SF36), mobility and pressure tolerance.

Safety: number, severity and types of adverse events [28].

When the outcome measures were recorded in a trial, but not provided in the article, the authors were contacted in order to obtain these missing data. When disagreements between both reviewers occurred, a third reviewer (A.B.) was consulted.

2.6. Statistical analysis

Heterogeneity was tested using the I^2 statistic [29]; $I^2 > 50\%$ indicated significant heterogeneity. The efficacy and tolerance of bisphosphonates were compared with placebo in each study by calculating Relative Risk (RR) and 95% Confidence Interval (95%CI) for binary outcomes (RR > 1 means that the event is more likely to occur in the bisphosphonate group than in the control group). Individual RRs were pooled using the inverse variance method with a random effect model [30]. The Standard Mean Difference (SMD) and 95%CI were calculated for continuous outcomes. The SMD is defined by the difference in mean outcome between groups split by the standard deviation of outcome among participants. Individual RRs and SMDs were pooled using the inverse variance method with a random effect model. Inter-reviewer reproducibility was considered good for a kappa coefficient >0.6 and excellent for a kappa coefficient >0.8 [31]. The meta-analyses were performed using Review Manager 5 (RevMan Version 5.0, Copenhagen, Denmark).

2.7. Sensitivity analysis and heterogeneity assessment

We conducted a sensitivity analysis in order to evaluate the robustness of the meta-analysis by examining the influence of an