Fluoride for the Treatment of Postmenopausal Osteoporotic Fractures: A Meta-Analysis

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Abstract. We conducted an effectiveness meta-analysis to determine the efficacy of fluoride therapy on bone loss, vertebral and nonvertebral fractures and side effects in postmenopausal women. A literature search was conducted on MEDLINE, Current Contents and the Cochrane Controlled Trial Registry. Two independent reviewers selected randomized controlled trials which met predetermined inclusion criteria. They independently extracted data using predetermined forms and assessed the methodologic quality of the trials using a validated scale. For dichotomous outcomes, the relative risk (RR) was calculated, and for continuous outcomes, the weighted mean difference (WMD) of percentage change from baseline was calculated. Where heterogeneity existed (determined by a chi-square test) a random effects model was used. Eleven studies (1429 subjects) met the inclusion criteria. The increase in lumbar spine bone mineral density (BMD) was found to be higher in the treatment group than in the control group with a WMD 8.1% (95% CI: 7.15, 9.09) after 2 years of treatment and 16.1% (95% CI: 14.65, 17.5) after 4 years. The RR for new vertebral fractures was not significant at 2 years [0.87 (95% CI: 0.51, 1.46)] or at 4 years [0.9 (95% CI: 0.71, 1.14)]. The RR for new nonvertebral fractures was not significant at 2 years [1.2 (95% CI: 0.68, 2.10)] but was increased at 4 years in the treated group [1.85 (95% CI: 1.36, 2.50)], especially if used at high doses and in a non-release form. The RR for gastrointestinal side effects was not significant at 2 years [2.18 (95% CI: 0.86, 1.21)] but was increased at 4 years in the treated group [2.18 (95% CI: 1.69, 4.57)], especially if fluoride was used at high doses and in a non-release form. The number of withdrawals and dropouts was not different between treated and control groups at 2 and 4 years. Thus, although fluoride has an ability to increase bone mineral density at the lumbar spine, it does not result in a reduction in vertebral fractures. Increasing the dose of fluoride increases the risk of nonvertebral fractures and gastrointestinal side effects without any effect on the vertebral fracture rate.

Keywords: Bone mineral density; Fluoride; Fracture; Meta-analysis; Osteoporosis; Randomized controlled trials

Introduction

Osteoporosis is a condition that results in an increased risk of fractures due to the reduction of bone volume, which is caused by an imbalance between bone formation and bone resorption. It is defined as a disease characterized by low bone mass with microarchitectural deterioration of bone tissue leading to increased bone fragility and consequent increase in fracture risk [1]. Because of the aging of the general population, osteoporosis is a significant public health problem [2]. Furthermore, the burden of osteoporotic fractures, in terms of pain, disability and mortality, represents a large cost to society [3].

Fluoride is known to stimulate osteoblast activity in humans, in contrast to most other drugs used for the
prevention and treatment of osteoporosis, which inhibit bone resorption [4]. Because of this property, fluoride has been used for over 30 years as a treatment for osteoporosis [5]. Histomorphometric studies suggest that although fluoride increases bone mineral density (BMD), there is a corresponding decrease in elasticity and strength of the bone tissue [6], and fluoride is thought to alter the crystalline structure of the bone tissue [7].

The ability of fluoride to increase BMD has been shown in several randomized controlled trials, as well as a recent systematic review by the National Osteoporosis Foundation [8]. However, other studies have demonstrated an increase in periarticular pain due to stress fractures [9,10] and an increase in the nonvertebral fracture rate with fluoride therapy [11]. These side effects are thought to be related to the type and dosage of fluoride [12].

The purpose of this meta-analysis was to examine the effects of fluoride for the treatment and prevention of postmenopausal osteoporosis in women, with emphasis on the effects of different dosages and types of fluoride.

Methods

We used the methodology for meta-analyses described in the Cochrane Handbook, which consists of a structured approach to identifying articles, extracting data, and synthesizing results that minimizes bias [13].

Literature Identification

We searched MEDLINE from January 1966 up to January 1998 (Appendix), the Cochrane Controlled Trials Register (CCTR), Issue 1, 1998 and Current Contents back for 6 months prior to January 1998, using the sensitive search strategy for randomized controlled trials (RCTs) recommended by the Cochrane Collaboration Musculoskeletal Group [14]. The key words used for this search are described in the Appendix and included fluoride, monofluorophosphate, fluoridation, osteoporosis, fractures, bone density and bone loss. Since not all trials are indexed on these electronic data bases, we conducted a hand search of the reference sections of each of the articles retrieved by these searches. We also contacted experts in the field of osteoporosis for help in identifying additional missed studies, unpublished studies, conference proceedings and abstracts.

Eligibility Criteria

According to an a priori protocol, we included studies which fulfilled the following eligibility criteria: we only considered randomized clinical trials involving women with primary osteoporosis in which the intervention was fluoride in any form or dosage. Acceptable control groups included calcium and vitamin D combinations, if they were given in equal doses to both the control and treatment groups. Outcome measures included vertebral or nonvertebral fractures, BMD (at any site), pain or height. The selection of outcome measures was based on the consensus report of OMERACT 3 (outcome measures in rheumatology), which defined a potential core set of outcomes for osteoporosis [15]. Biochemical markers were not considered as outcomes for this meta-analysis [16]. Where possible, toxicity was analyzed by considering total withdrawals due to adverse reactions and withdrawals for system-specific side effects. Individual patient and overall measures of side effects were tabulated, including gastrointestinal side effects (nausea, vomiting, gastritis, diarrhea, gastrointestinal irritation or bleeding) and musculoskeletal side effects (pain and stress fractures). Withdrawals and dropouts were analyzed both overall and for those due to side effects.

For practical reasons, studies published in languages other than English, French or German were not included in the analysis but they were retrieved for further translation. For duplicate or complementary reports of the same trial, the most complete results were used.

Quality Assessment

Two independent reviewers (D.H., S.M.), using a validated quality assessment instrument [17], assessed the methodologic quality of each trial including the quality of randomization, masking and reporting of withdrawals. The score was given as follows: if the study was described as randomized, 1 point; if the study was described as double-masked, 1 point; if there was a description of withdrawals and dropouts, 1 point, if the method of randomization was described and appropriate, 1 point; if the method of double-masking was described and appropriate, 1 point; if the method of randomization was not appropriate or if the method of masking was not appropriate, deduct 1 point. Differences were resolved by consensus. If needed, a third reviewer was consulted (V.W.). Quality assessment was not used as a criterion for including studies.

Data Extraction

Two independent reviewers extracted the data from the original articles (D.H., S.M.). In case of disagreement, a third reviewer (V.W.) helped reach consensus after consulting the original article. Data extraction was performed using a pre-established form which included aspects of the study design and methodology, intervention characteristics, participant characteristics, adverse events, outcome measures and quality assessment.

Where possible, the mean percent of baseline and the corresponding standard deviation were extracted. In several studies these values were not directly available. Letters were sent to three authors for additional data, and one author of two trials replied [11,18]. Some data was extracted from graphs when numerical data was not