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Mini Review

Supplementing Vitamin D in Unselected Elderly People through a Yearly Bolus to Reduce the Risk of Fractures: Is this Practice Effective?

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Abstract

A number of studies have investigated the effectiveness of vitamin D given as an annual dose to unselected elderly people to reduce the risk of fractures, but the results are conflicting. Since new clinical studies have recently been made available, we carried out an updated analysis on this issue.

Our study was aimed at evaluating the effectiveness of this annual dose of vitamin D. Patients were unselected elderly people. Fractures were the end-point of our analysis. The clinical material was represented by observational and randomized studies that included a patient group given the vitamin D annual bolus and a control group given no such supplementation. Our meta-analysis was based on the random-effect model of Der Simonian and Laird. Relative Risk (RR) was our outcome measure.

After a standard PubMed search, we identified 5 clinical studies that met the criteria of our analysis (total number of patients: 115,220). The fracture rates were pooled across the studies. The meta-analytical RR was estimated to be 0.81 (95% confidence interval, 0.59 to 1.13). There was a high degree of heterogeneity in this clinical material.

Our results indicate that the supplementation of vitamin D based on an annual mega-dose does not reduce the incidence of fractures in unselected elderly people.

Keywords: Osteoporosis; Fractures; Vitamin D; Annual bolus; Elderly people

Introduction

The effectiveness of vitamin D supplementation in unselected elderly people has been evaluated by numerous clinical studies [1-7] aimed at improving the clinical outcomes of bone health (e.g. fractures and falls). One important practical criterion to distinguish these supplementation studies from one another is the schedule adopted for the administration of vitamin D.

The great majority of these clinical studies employed a daily administration of vitamin D (or, anyhow, a regular schedule of repeated administrations). According to the systematic review of Newberry et al., [2] and the DIPART pooled analysis of 7 randomized studies [6], the effectiveness of the daily supplementation appears to be controversial. For example, the DIPART analysis [6] indicated that vitamin D given alone in doses of 10-20 microg was not effective in preventing fractures; by contrast, calcium and vitamin D given together were shown to reduce hip fractures and total fractures, and probably vertebral fractures. Conflicting results were shown by other clinical studies as well [2]. So, on the one hand, no firm conclusion can currently be made on the effectiveness of this intervention. More importantly, since the results reported thus far in the literature for the regular regimen of repeated doses are conflicting [1-7], it seems very unlikely that this therapeutic controversy will be settled in the near future on the basis of new analyses of published data and/or new data from original studies.

A quite small subset of the clinical studies focused on vitamin D supplementation employed a single mega-dose of vitamin D (single annual bolus scheme) that has generally been administered to unselected elderly patients in conjunction with the influenza vaccination [2,6]. Also the effectiveness of the annual winter schedule is controversial, but one important advantage in exploring if this dosing schedule works is that the available studies are fewer than in the case of daily administration; therefore this permits an attempt to clarify this question through a new analysis.

The present study was carried out as an original meta-analysis aimed at evaluating if the annual bolus scheme can reduce the incidence of fractures in unselected elderly people in comparison with patients not given any form of vitamin D supplementation.

Methods

Study design. The design of our meta-analysis can be summarized as follows. We firstly conducted a literature search aimed at identifying all clinical studies evaluating the effectiveness of the annual mega-dose in unselected elderly people. The clinical end-point for our analysis was the incidence of fractures. Then, we carried out a standard pair wise meta-analysis to determine the effectiveness of the mega-dose in comparison with no vitamin D supplementation.

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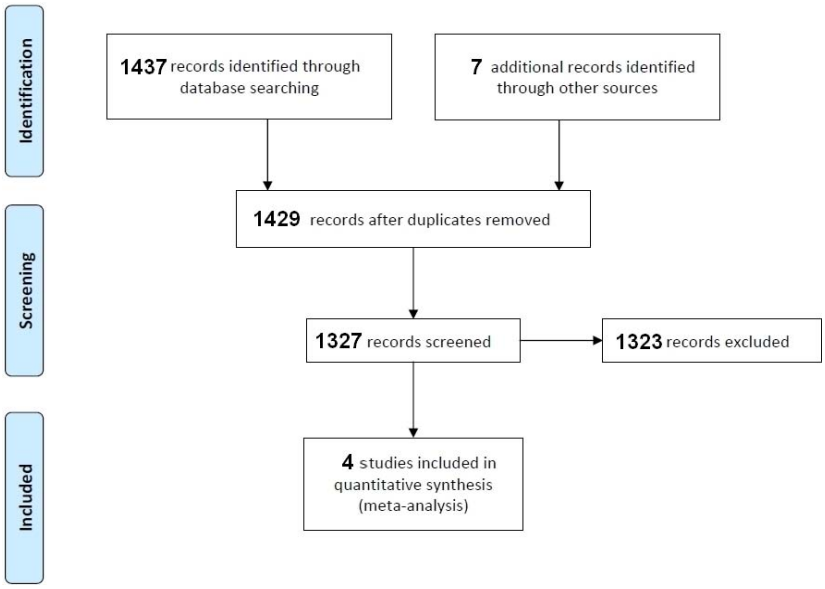

Figure 1: PRISMA diagram of our literature search based on PubMed. Other sources for identification of further articles included EMBASE and Scopus. Last search was run on 25 September 2015. Other sources were represented by the bibliography of screened studies.

Literature search

Our literature search was conducted in PubMed (www.pubmed.org) and covered the period from inception (1966) to present time (last query on 30 September 2015). A single search term (namely "vitamin D supplementation AND fracture'") was employed. The PRISMA schematic [8] was adopted to describe the flow leading to the identification of pertinent studies. Although the number of citations retrieved through the first search based on the above keyword was high (more than 1,400), we analyzed all of these articles individually by examining the abstract or, when necessary, their full text. In this way, despite the operational complexity of this approach, we successfully identified the clinical studies that met our inclusion criteria. We thought that there was no simple method of literature analysis that could (more automatically) distinguish the studies employing the mega-dose from the remaining studies employing other dosing schedules.

The inclusion criteria for our analysis were as follows: (i) administration of vitamin D to unselected elderly people (aged ≥ 65 years); (ii) dosing schedule based on a single annual mega-dose of at least 150,000 IU; (iii) information on the incidence of fractures in treated patients and in controls; (iv) randomised and non-randomised design. For each clinical study, we extracted the basic information needed for our analysis as well as the information on the above end-point, expressed as a crude rate.

Meta-analytic methodology

As regards the assessment of methodological quality, two reviewers (AM and ST) applied the Cochrane Collaboration's tool [9] to evaluate the risk of bias in the included studies. This tool assesses six domains (namely: random sequence generation, concealment of allocation, blinding of participants and personnel, incomplete data, selective outcome reporting of outcomes, and other sources of bias). Studies with adequate procedures in all domains were considered to have a low risk of bias.

For our statistical analysis, we employed a standard model of traditional pair-wise meta-analysis [3]. Although two versions of this model (i.e., fixed-effect and random-effect) are available, we chose the random-effect model because we anticipated the presence of heterogeneity in our clinical material. The outcome measure adopted for our analysis was Relative Risk (RR), which was estimated along with its 95% Confidence Interval (CI).

All of our analyses were conducted by using the software package Open Meta-Analyst (version 4.16.12, Tufts University, URL: http://tuftscaes.org/open_meta/).

Results

Our literature search, conducted according to the PRISMA approach (Figure 1), identified 5 studies [10-13] that met the inclusion criteria of our analysis (Table 1). The total number of patients was 115,220. The study by Rossini et al. [10], in which the patients treated in the year 2000 were separately assessed from those treated in 2001, was handled as two separate studies. The analysis of the methodological quality of studies (data not shown) did not provide any important clue to improve the interpretation of our results; of course, the quality scores were much better for randomised studies than for the remaining ones. There were some differences across the studies in the amount of vitamin D contained in the bolus dose (from 150,000 to 500,000 IU), age range, and type of fractures.

Figure 2 shows the meta-analytical values of RR calculated through our meta-analysis (RR, 0.81; 95% CI, 0.59 to 1.13) along with the study-specific values of RR. Heterogeneity in this clinical material was particularly high.

Interestingly enough, the results of the two most recent randomized studies were numerically opposite to those obtained in the three studies published between 1992 and 2001. Furthermore, the randomised study by Sanders et al., [12] showed a paradoxical and statistically significant increase in fractures for the group given

Table 1: Characteristics of the 5 included studies.

Author	Year	Study design	Patients' characteristics	Type fractures	Dosing schedule	Fracture incidence	
						Vitamin D	Controls
Rossini et al. [10]	2000	Quasi experimental*	Women aged ≥65 years	Hip fracture	Annual IM bolus dose of 400,000 IU	173/23156	333/27677
Rossini et al. [10]	2001	Quasi experimental*	Women aged ≥65 years	Hip fracture	Annual IM bolus dose of 400,000 IU	158/24589	315/27303
Heikinheimo et al. [11]	1992	Simplified randomisation according to month of birth.	Unselected elderly people aged ≥85 years	Any fracture	Annual IM bolus of 150,000 to 300,000	56/341	100/458
Sanders et al. [12]	2010	Double-blind randomised	Community-dwelling women ≥aged 70 years	Any fracture	Annual oral bolus of 500,000 IU	171/1131	135/1125
Smith et al. [13]	2007	Double-blind randomised	Unselected elderly people aged ≥75 years		Annual IM bolus of 300,000 IU	306/4727	279/4713

*As pointed out by Rossini et al. [10], risk factors between the two patient groups were not fully balanced in this study; in particular, the control groups were likely to be at increased risk of fractures in comparison with the vitamin D supplementation group. Abbreviations: IM, intramuscular.

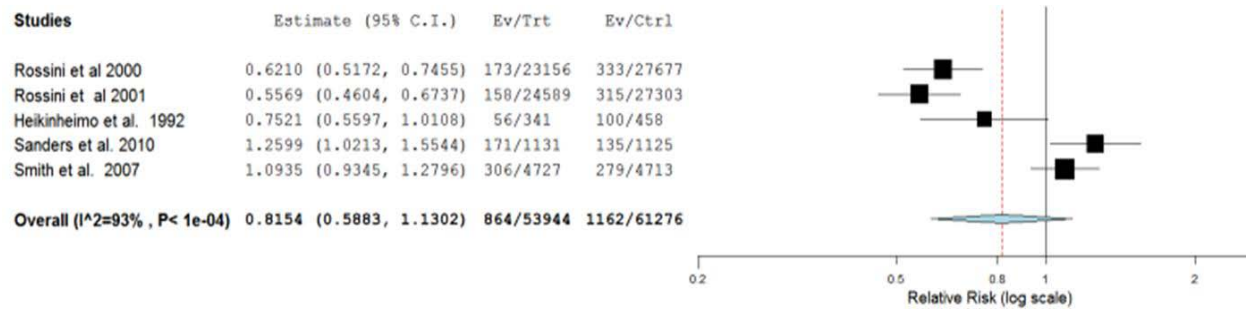

Figure 2: Meta-analysis of 5 clinical studies evaluating the incidence of fractures for patients given the annual mega-dose of vitamin D in comparison with patients not given this supplementation. Relative Risk (RR) was the outcome measure of the analysis. Squares denote study-specific parameters, while diamonds indicate pooled parameters. The vertical dotted line (in red) indicates the meta-analytical value of RR. I2 is a measure of heterogeneity (accompanied by its level of statistical significance). EV: Number of Events (numerator); TRT: Number Of Patients In The Treatment Group; CTRL: Number of Patients in the Control Group.

vitamin D supplementation. Finally, it should be noted that the study by Rossini et al., (which was the only one that clearly favoured the annual mega-dose) had an important limitation (explicitly acknowledged by the authors): the decreased fracture incidence observed in treated women was partly explained because the highest risk individuals were among those not treated [10]. Hence, the "true" advantage (if any) of the mega-dose is very likely to be smaller than the numerical and non-significant finding estimated from our meta-analysis (-18%).

Discussion

Vitamin D supplementation, when given on the basis of different dosing schemes to elderly people selected according to different criteria, is recognized to be an area of difficult interpretation in terms of effectiveness [1-7]. The effectiveness of this intervention is likely to be different depending on whether the population is represented by unselected elderly patients or by elderly patients with vitamin D deficiency; in fact, effectiveness seems to be more likely in the presence of vitamin D deficiency. On the other hand, vitamin D supplementation in elderly people with vitamin deficiency has been shown to significantly reduce the risk of falls according to the systematic review of Leblanc et al., [4]; however, other reports have suggested that this intervention has less clear effects on the risk of fractures or falls or no effect at all., [10].

In an overall framework dominated by an uncertain effectiveness, our study has been focused on a quite specific therapeutic issue because we have restricted our effectiveness analysis according to two criteria: (a) unselected elderly people; (b) dosing schedule based on an annual mega-dose of vitamin D.

Focusing our analysis on this restricted subset has been helpful to reduce the otherwise dominating picture of uncertainty. In fact, in this specific case as well as in a general context, finding "no proof of effectiveness" (as in our analysis) is, in practical terms, a fully informative result because this finding prevents that any recommendation is made in favour of the intervention concerned. Hence, if we specifically consider the administration of the annual bolus dose to unselected elderly people, our meta-analytical results are important because they clearly indicate that this practice cannot presently be recommended. This conclusion is in keeping with that of another recent meta-analysis [14] that differed from ours because it was restricted to randomised studies and included also intermittent dosing regimens. Since, at least in Italy, some regions (e.g. Toscana and Veneto) continue to support the annual bolus of vitamin D by making reference to the Italian study by Rossini et al [10], our results have important practical implications because they suggest that this practice should be disinvested.

There were some limitations in our study. Firstly, the clinical material was quite heterogeneous, in terms, for example, of IU administered, type of vitamin (D2 or D3), and route of administration and so on. Furthermore, the included trials covered a very long time interval spanning from 1992 to 2007. Another limitation is that we designed our analysis on the basis of a single clinical end-point (risk of fractures) and we omitted the analysis of any secondary end-points (e.g. risk of falls).

Nevertheless, since no previous meta-analysis has separately examined the case of the annual bolus, our study bridges a gap in the current literature. We conclude that, in the light of our results, the practice of supplementing vitamin D with an annual bolus dose in unselected elderly people is supported by no proofs of effectiveness and cannot therefore be recommended.

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