A Randomized Double-Blinded Superiority Trial to Compare the Efficacy of Vitamin D3 and Calcium versus placebo in Prevention of Hip Fractures in Elderly Women

L. Fagotti[1], M. Balbino[2], T. Bispo Gonzalez Truffa[3], C. Susanna[4], J. Calvo- Marin[5], JC. M Fuentes B[6], JM. Carrasco Rueda[7], LG. Villares da Costa[8*]

* Corresponding author: Rua da Consolação 2825, apto 184 – Cerqueira Cesar. Zip code 01416-001 São Paulo - SP.

Rest of author's affiliation at the end of the manuscript.

Abstract:

Basal Background and Aim: *The role of vitamin D plus calcium to protect against hip fracture in postmenopausal women remains controversial. Two major studies on this subject presented diverse outcomes; they implemented different doses of Vitamin D and Calcium, and they studied different populations. One study found evidence that Calcium plus Vitamin D do protect against fractures; the second study failed to demonstrate such protection. The aim of the present study is to test the hypothesis that a higher dose of vitamin D plus calcium is effective in reducing hip fractures in non-osteoporotic elderly women when compared to placebo.*

Methods: *This will be a randomized, double-blinded superiority, multicenter trial involving three centers in São Paulo, Lima and Mexico City. After a three-month run-in period, 7176 participants will receive Calcium + Vitamin D or Placebo. The primary outcome is the occurrence of hip fractures assessed by the pelvic radiographic image; secondary outcomes include other fractures, the variation of Bone Mass Density, and the adverse effects rate.*

Conclusion: *There is an increase in morbidity, mortality, and costs resulting from hip fractures since it is an important risk fact following accidents. A possible lack of benefit inside the active group drives more attention to an eventual over-prescription of those substances. Therefore, further studies including a phase II trial with different exclusion criteria could be desirable to confirm these findings and help to reduce the incidence of hip fractures.*

INTRODUCTION

Each year, more than 350.000 women are hospitalized due to hip fractures, which provides an economic burden of about $3 billion per year only in the US. Hip fractures results in high morbidity and mortality worldwide, and it is also an important risk factor for a subsequent fracture [1]. Vitamin D deficiency is common among elderly people and may contribute to the occurrence of hip fractures in this population. The supplementation of Vitamin D for postmenopausal women is a common practice and can increase the hip mineral density [3]. Studies have suggested that taking Vitamin D as a supplement might prevent bone loss in the proximal femur and reduce the risk for hip fractures [3,4]. However, this supplementation was found to be unlikely in preventing fractures when the patient received between 400 IU to 800 IU Vitamin D daily with co-administration of 1200mg of Calcium [4].

The present study proposes a multicentric evaluation of the real benefit of supplementation of calcium and a higher dose of Vitamin D for the prevention of fractures in non- osteoporotic postmenopausal women.

Aims of the study

In this randomized double-blinded trial, we will evaluate the occurrence of hip fractures in postmenopausal non-osteoporotic women over 70 years old. The subjects will be randomized to receive either Vitamin D 1200 IU plus Calcium 1200 mg each day or placebo, in a two-year follow-up. A physician will diagnose clinically and radiologically the presence of hip fractures. Secondary outcomes will include the occurrence of other fractures, like appendicular and vertebral fractures, the variation of Bone Mass Density (BMD), the variation of serum Vitamin D and the cumulative adverse effects rate.

METHODS

Study design

We will conduct a randomized double-blinded superiority trial in elderly women with no diagnosis of osteoporosis. The patients will be recruited from tertiary care hospitals in three different cities: Mexico DF, Lima, and Sao Paulo.

Eligibility

We will include non-osteoporotic elderly women due to the higher risk of falls and due to the controversial evidence regarding the benefit of vitamin D plus calcium supplementation in prevention of hip fractures in such population. This stratum is associated with significant morbidity, mortality, and costs [1].

Inclusion Criteria
- Elderly women over 70 years old;
- Agreement with the double-blinded trial design and with the provided written informed consent;
- Normal Bone Mineral Density (T-score > -1 SD) or osteopenia (T-score between -1.0 and -2.5 SD);

Exclusion Criteria
- Presence of osteoporosis (T-score < -2.5 SD)
- Use of corticosteroids;
- Occurrence of primary cancer with bone metastasis in the same limb of the fracture;
- Presence of severe kidney and liver chronic disease;
- Impossibility of walking.

Blinding

This study will assess the double-blinded method in which the trial participants, health care providers, investigators, data collectors, and outcome assessors will be blinded. The subjects will be randomized to receive a single pill of Vitamin D (1200 IU) daily plus 1200mg Calcium or placebo. To keep the study group assignment hidden after allocation, the Vitamin D, and the placebo pill will be manufactured by the same pharmaceutical laboratory and will be identical in shape, color, and taste. The pills will be dispensed in identical containers labeled with codes generated by the pharmaceutical laboratory, and the timing of administration will be the same for both groups; the pharmaceutical laboratory will know which code corresponds to Vitamin D and placebo. Also, the same third company that randomized the study groups will conduct the statistical analysis. They will contain the DSMB (data safety and monitoring board) to perform an interim analysis during the study, evaluating any safety risks to the study subjects. The DSMB and the pharmaceutical laboratory will be the only parts of the study that will stay unblinded. We intend to test the blinding method, by asking the study subjects about their study group assignment, and comparing their responses to what would be expected by chance.

The unblinding process will happen in exceptional circumstances such as the intake of pills at home by a child, or when an event of a suspected/unsuspected acute adverse reaction occurs. In this case, the investigator will report any other unblinded event to the DSMB and the Principal Investigator using a case report form.

Adherence

Some strategies will be proposed to increase adherence and prevent dropouts. The adherence will use a system of assessments (questionnaires and counting pills) made by the research team periodically and also based on well-informed participants.

The investigators will perform a run-in period of three months, a period in which the adherence of the patients will be tested.

The first dose of the study medication will be taken at the site under the guidance of a group of health-care professionals; the consecutive doses will be taken at home. The same group will provide a briefing about the importance of the daily intake and the benefits and adverse effect of the medication.

The site team will call the patient on day 30 and 60 of each cycle (± 3 days) and will ask about the intake behavior based on the Morisky-Green questionnaire (MMAS-4). On day 90 of each cycle (± three days) the patients must bring the remaining pills to the site and a new blister will be dispensed. The adherence of treatment will be calculated at this moment, based on the number of pills returned, in days, since the last count, and considering the interruption due to adverse events.

The individual's adherence is expected to be above 80%. The subjects that are non-adherent to the treatment according to the protocol must be carefully interviewed and reminded about the purpose and conduct of the study.

The completion of the form "Daily Oral Medication" is mandatory: reporting date and time that the medication was taken at home, and if any problem occurred (missed pills, lost pills, adverse events, etc.). Interruptions in the treatment for more than 30 days will not be allowed, and a discussion between the investigator and sponsor must occur to decide the best way to deal with the case. If the staff does not foresee a minimal chance of adherence, the patient will be eliminated from the study and included in the statistical analysis as "Missing at Random".

Subjects that are non-adherent to the treatment according to the protocol must be helped to cope with side effects. They will be interviewed and reminded about the purpose and importance of the study. The investigator has the autonomy to discontinue a patient from the study in case of continued non-adherence occur (e.g., patient with more than 30 consecutive days without drug intake despite previous actions mentioned to enhance adherence).

Sampling

The referral of patients to the clinical trial will rely on a stratified probability sampling method. A heterogeneous population of patients enrolled in different medical ambulatories will generate groups of patients (strata). Each of the three cities will have a hospital engaged in the data collection process. A team member will receive, enroll, and obtain a random sample of individuals. Once involved, the patient will continue the treatment with her original doctor; however, this specialist will go blinded regarding the treatment this patient receives.

Recruitment

Recruitment period will last 12 months and will be followed from the beginning to the completion in the three cities: Mexico DF, Lima, and Sao Paulo. All patients meeting eligibility criteria in any of the tree centers will be invited to enroll in the study. A physician responsible for referring the patients to our study and collecting the informed consent will be chosen from four different medical ambulatories: Obstetrics and Gynecology, Endocrinology, Internal Medicine and Geriatrics. Written information will be given at the recruitment to help educate the patient on the purpose and methods of the study.

Intervention

After consenting, participants will be allocated to one of the two arms (active intervention or placebo) and will receive a complete physical examination and first evaluation of serum vitamin D and calcium levels.

Additionally, for each participant the evaluators will perform a bone densitometry to assess BMD.

Once eligibility is confirmed, the intervention for all patients will be randomized in one of the two arms:

1. Treatment Arm: Participants will be given a blister of 90 pills containing a combination of vitamin D 1200 UI + Calcium 1.200 mg every three months for a total period of two years. When the blister runs out, the patient will receive a refill and the evaluators will perform a questionnaire to measure adherence.

2. Placebo Arm: Participants will receive a placebo pill. Due to the blinding process, patients will get an identical (size, shape, taste) pill, similarly to the one that was given in the active treatment arm.

Assessment

For the correct evaluation of the primary outcome, we will confirm the occurrence of hip fractures through medical records of the patients. If the fracture occurs in a medical center outside the sites, the investigators should look for the correct date and localization of the fracture in the discharge summary medical report.

We will consider recurrent fractures; these particular patients will remain in the risk set until the last interval finishes (i.e. last failure time or censorship). Secondary fractures, due to diseases like tumors or avascular necrosis, will censor the patient, without counting as a real event. A previous fracture, before the admission in the study, will remain ignored in the analysis.

The secondary outcomes will be the occurrence of other fractures, such as appendicular and vertebral fractures. We will follow the same procedures described for the primary outcome.

We will use the Discovery DXA System by Hologic ® in two different times for the evaluation of BMD: when the patient enters the study and after two years of follow-up.

In respect to the variation of the levels of serum vitamin D, we will collect a blood sample at three different time points: at the beginning of the intervention, and after the first and second year of follow-up. For the assessment of the blood sample, we will use the ADVIA Centaur Vitamin D Total Assay by Siemens ®

We will monitor for the safety and risks of the intervention and will control for the cumulative adverse effects of treatment. Our primary concern will be the assessment of nephrolithiasis, hypercalcemia, vitamin D toxicity, gastrointestinal symptoms, suspension related to adverse drug effect, hospitalization and death.

Data collection

For the info registration, each of the three participation sites (Sao Paulo, Mexico DF, and Lima) will be equipped with a PC that runs iDatabase 2® software, which will tabulate the events and clinical variables collected in the Data Collection Form. A password will protect the document file and the team leader will be the one responsible for its safety and confidentiality.

Data will be gathered and processed from a periodic evaluation of the participants. This will be achieved by scheduling a medical consultation every three months and a phone call every 30 days.

Randomization

Patients will be randomized in blocks of four, six or eight subjects and stratified according to the status of the BMD, which can be normal or osteopenic. We will perform allocation concealment to each block and stratum. The lists of computer generated random numbers will be obtained using the software randomization.com [13]. The website will provide the sequence for each block and stratum in the study.

Sample size calculation

The small STATA 13.1 software was used to perform the sample size calculation. Based on two previous studies with a similar design [2,3], we estimated the mean of hip fracture incidence to assess the proportion of the analysis of the primary outcome obtaining a fracture rate of 2.22% in the treatment group, 2.92% in the control group and a global fracture frequency of 2.57%. Using a survival analysis technique we estimated a total of 322 events needed, and considering an alpha error probability of 0.05 and power of 80%, the sample size was calculated on 12918 observations or 6459 observation per year along two years. Using a dropout rate of 10% we obtained a final sample size of 7176 observations per year, which means a total of 14352 participants in two years. Finally, we'd have 2392 participants for each of the three centers, which will be distributed amongst two sites of each country.

Statistical analysis plan

Periodic The total number of participants will be equally distributed between the three sites involved. Baseline characteristics will be analyzed based on respective distributions. Continuous variables will be handled with paired t-tests for normally distributed data or signed-rank test and Friedman test for not normally distributed data. Categorical data will be processed with chi-squared or exact Fischer tests.

Kaplan-Meyer curves will examine the primary outcome. The total number of critical events will be reported, as well as person-time of follow-up. Comparisons will be represented with hazard ratios and nominal 95 percent confidence intervals from Cox proportional hazards models, stratified according to age group, race, and prior fracture. The report will provide Kaplan-Meyer survival curves by groups, as well as the numbers at risk at regular interval times. We will try to draw our conclusions critically dependent on the statistical assumptions of this approach. The primary outcome will be analyzed in a time to event basis according to the intention-to-treat principle.

Two interim analysis are planned, focusing on safety issues when 33% and 66% of data are collected. The O'Brien-Flemming approach for alpha spending will be adopted. The level of significance will be set at 0.05 and 95% confidence intervals will be estimated.

Outcome

To evaluate the difference in effectiveness between Vitamin D plus Calcium and placebo on the reduction of hip fracture events in non-osteoporotic elderly women, we consider the occurrence of hip fracture in a period of two years of follow- up as the primary outcome. A radiographic image will define the diagnosis of the hip fracture. The clinical background of the patient will also be considered for assuring that the fractures were not caused by pathological factors such primary bone tumors or bone metastasis. In this case, the patient will be excluded. A past history of previous fractures of the hip will be ignored, but a new fracture diagnosed in a previously operated hip will be counted. For patients presenting more than one fracture (a hip fractures and a vertebral fracture), only the hip fracture, which is potentially more harmful, will be considered.

A secondary outcome will include the differences in the evolution of bone mass density (BMD) measured by densitometry at baseline and the end of the observation (two years). The BMD will be dichotomized into three categories: normal, osteopenic and osteoporotic and will be considered as a surrogate outcome associated with the risk of occurrence of fractures. Elderly population has several problems with oral intake medication. Therefore, the necessity of controlling and guarantee the effect of Vitamin D must be assessed by another outcome. We will evaluate the levels of Serum analysis of 25-hydroxyvitamin D (25(OH)D) at the baseline, 12 months and 24 months of follow-up and as well as the adverse effects reported by participants or evaluated by health professionals.

Intention-to-treat analysis

We will keep the premise that "once randomized, always analyzed". The intention is to maintain the groups according to randomization. Patients will keep the original groups, either Vitamin D or Placebo, inclusive the dropouts. The statistical approach to missing data will be described in the respective part of this paper.

Missing data

As we believe that the dropouts may probably reflect association with socioeconomic status and health concern, we expect most of the missing cases as missing at random (MAR). Therefore, we suppose both groups should have similar dropout rates. The highest assumed margin for missing information is 5%. The value comes from a preliminary study that observed an average of 496 patients that either withdrew or lost their follow-up among almost 17,000; or a 2.9% rate loss.

As we deal with a large dataset, we will adopt the multiple imputation approach. About five (or more) datasets will be created, each with slightly different imputed values. The analysis will be conducted on each data set using the standard software.

Budget and funding

We will perform a multicenter study in tree cities of tree different countries of Latin America (Mexico DF, Lima, and Sao Paulo). The number of participants will be continuously monitored in each center along two years of study. The total cost of this trial is high and justified by the budget that was estimated based on primary topics of the study methodology. The impact of services on the trial's budget is inevitable. Therefore, we expect to obtain financial aid for the questionnaires, documents, printing, number of pills needed to cover the planned treatment, laboratory tests applied to the subjects, personnel fees, meeting costs, and supplies.

The funding plan is based on the request of support of international and government institutions that provide grants for the development of investigation initiatives and the negotiations with pharmaceutical companies who would offer the treatment and placebo pills for a low or free cost ensuring the quality and feasibility of the product provided.

Ethics

Our primary concern is to offer the best of care to all the patients. No women should go without prevention of fractures; however, we found a controversy in the literature, from where our main question arose. The doubt was a result of conflicting findings in Jackson's and Chapuy's papers concerning the eventual benefit of the association of Calcium and Vitamin D in the prevention of hip fractures in elderly women. The first author found no prevention in the occurrence of the fractures; however, the second did. We will evaluate normal to osteopenic women, and only the active group will receive Calcium supplementation.

The IRB submission will be done locally by each site center, in the three sites of the study. The research coordinator will be responsible for the IRB submission.

Registration and Confidentiality

After approval, this trial will be registered at Clinicaltrials.gov. All researchers involved in this study will be trained and certified to protect subject private health information. Data will be de-identified accordingly in electronic forms and all other statements planned in the protocol.

DISCUSSION

The supplementation of Calcium and Vitamin D is routinely prescribed for postmenopausal women, aiming an increase of the bone mineral density. A dose of 1000 UI of Vitamin D might reduce the risk of falling, but a decrease in the occurrence of hip fractures was not demonstrated [14,15]. Our study focused on verifying whether a higher dose of Vitamin D (1200 mg) associated with calcium is more effective than placebo in preventing the occurrence of hip fractures.

We propose a randomization method as well as an intention to treat analysis to investigate a cause-effect relation between the intervention - supplementation of Vitamin D plus Calcium - and the outcome - occurrence of hip fractures. The randomization process is a powerful tool capable of minimizing the influence of external factors, or so-called systematic differences, on the outcome [9]. The fixed block randomization creates a randomization list when all the blocks are put together. This list has a balanced treatment allocation and the patients will remain on the list even if they do not receive one of the allocated treatments. Due to the large number of subjects to be enrolled, and for being an old population prone to a higher morbidity and mortality, the possibility of missing data and poor adherence cannot be ignored. If the center does not enroll the full number of women expected, the block randomization helps to keep in each treatment arm an approximately equal number of patients [10].

The intention to limit the occurrence of bias, especially the occurrence of selection bias, is based not only on a proper randomization but also when the blinding process is assured. A double-blind method was

selected in order to hide the allocated treatment from both patients and investigators. Both can easily find information about the possible benefits of supplementation of Vitamin D and Calcium, which could influence their interpretation about efficacy of the treatment during the study. Considering that we propose a multicenter study, in which differences in clinical practice might affect the attitudes of physicians to the treatment, blinding will avoid the influence of previous knowledge of the treatment allocation, helping the recruitment and adherence process [10].

Blinding supports the internal validity of the trial and protects the randomization process. However the tradeoff is an increase in the study costs, which are already high. The difficulties for the assessment of the possible adverse effects such as hypercalcemia and vitamin D toxicity must be considered. If the interim analysis undertaken after 33% of patients reports problems with the safety of the patient, the fixed sample size for this study will be no longer valid. The screening for kidney stones, gastrointestinal and heart diseases is recommended in a recent meta-analysis [4]. A dose of 1200 UI of Vitamin D is appropriate for this study, since doses greater than 800UI daily have never been tested for this purpose [4]. The administration of 1200mg of Calcium was used following the current Osteoporosis Foundation Guidelines [5].

A good internal validity is not the only prerogative for a solid RCT. The external validity plays an important role when we dealing with public health issues such hip fractures and primary care for elderly patients. The inclusion of the tree different centers is part of our strategy in increase the external validity of the trial. Multicenter clinical trials are helpful to diminish biases and methodological pitfalls that might occur in small single-center trials. We believe that such methodology will create a more heterogeneous sample of subjects and will provide a sufficient power to detect smaller treatment effects. We also expect a positive impact of different leaders from varying backgrounds and expertise in conclusions and investigation for pitfalls [11]. However there are some factors that might affect the generalization of our findings [12]. The discontinuation of the treatment due to poor adherence, presence of comorbidities or prolonged time of treatment must be considered when dealing with elderly patients. Patients with osteopenia might face a deterioration of the bone quality during the study and osteoporosis may occur, which is an excluding factor.

Potential limitations

Different ingestion of calcium: people might be ingesting different quantities of calcium each day, due to their diets. This can influence results of the study. A questionnaire can be applied at the beginning of the study asking about participant's diets. Moreover, subjects will be informed about the importance of maintaining their diets to increase similarity of diets between participants, as well as the credibility of results.

Regarding our budget, this will be a very expensive trial, mainly because of the number of subjects and pills needed, follow-up period and staff. A detailed description of costs will be given to those interested in sponsor us. Likewise, if our study doesn't show benefits from the association between both vitamin D and calcium, national health systems all over the world will save financial resources with population's health. Instead, if the benefit exists, elderly women will have improved health and much less money will be spent on fractures management.

Adherence: can be jeopardized due to long follow-up period and to the number of pills that participants will have to ingest. To avoid limitations in adherence, a run-in period of 3 months will occur. Patients will be well-informed of the importance of the trial and their roles in the study to improve population's health. The first dose will be ingested at the site under guidance and talks. Participants will achieve 15 dollars for each visit. Phone calls will occur on day 30 and 60 of each cycle. Finally, new blister of pills will be dispensed on day 90 and calculation based on number of pills returned in days since the last count.

Effect of treatment: if results are clinically significant, with a lower occurrence of hip fractures in the active group, this can be due to calcium alone instead of the association. Even though, there are meta-analysis in the literature [6,7] that show higher benefit when calcium is associated with vitamin D, rather than calcium alone.

Future perspectives

We expect a reduction in the occurrence of hip fractures in healthy postmenopausal women undergoing Calcium plus Vitamin D. Considering this positive outcome, global campaigns should be performed to decrease the clinical and economic burden of hip fractures in elderly women. The combination of calcium and vitamin D protects the bone from fractures and might slow down bone loss in postmenopausal women [8]. However, a possible lack of benefit inside the active group drives more attention to an eventual over prescription of those substances. In this sense, a phase III trial with different exclusion criteria would be the next step to confirm this finding.

CONCLUSION

A multicenter randomized controlled trial is our strategy, thought to address the occurrence of hip fractures in postmenopausal women with normal or osteopenic status of bone mineral density. Prescription of vitamin D plus calcium is a common practice with controversial benefits. Due to progressively ageing of the population, there is an urgent need for clarification about the effectiveness associated with supplements for non-osteoporotic elderly women, in order to improve general health conditions and quality of life.

Author Affiliations

1 Fellow in Orthopedics Department, Ortenau Klinikum, Gengenbach, Germany.
2 Anesthesia Department, Hospital Universitário - Universidade de São Paulo.
3 Clinical Research Coordinator
4 ABC Medical School, Santo André-SP, Brazil.
5 Hospital Mexico, Caja Costarricense del Seguro Social.
6 Backus MAPFRE Lima, Peru - Medical Auditor.
7 Faculty of Medicine , Universidad San Martín de Porres, Lima, Peru.
8 MD, PhD Department of Anesthesia, Hospital Israelita Albert Einstein, São Paulo - SP, Brazil.

Conflict of interest and financial disclosure

National The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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