Randomized Clinical Trial for The Evaluation of The Effects Of Cholecalciferol Supplementation On The Parathyroid Hormone In Hemodialysis Patients

Effect of Cholecalciferol Supplementation on Parathyroid Hormone in Hemodialysis Patients

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SUMMARY

Introduction. Vitamin D regulates mineral metabolism, playing a crucial role in maintaining adequate bone density. Immunomodulatory, cardioprotective and

antiproliferative effects have been described recently. Its deficiency has been associated with diabetes, cancer and increased mortality. 25OH vitamin D (25VD) is stable (with a half-life of over 2 weeks) and suitable for the evaluation of vitamin D sufficiency. It has been found that levels of 25VD are inversely related to those of the parathyroid hormone (iPTH), and its supplementation has been associated with a decrease in levels of iPTH in patients with Chronic Kidney Disease, although these results have not been uniform in patients on hemodialysis (HD). The usual treatment for secondary hyperparathyroidism in HD with active and analogous forms of vitamin D increases the risk of hyperphosphatemia and vascular calcifications.

The aim of the study is to evaluate whether cholecalciferol supplementation for a period of 12 weeks can normalize decreased levels of 25VD and reduce increased iPTH in HD patients with a vitamin D deficiency. Secondary aims: to evaluate decrease in inflammation, anemia or use of erythropoietin (epo).

Design. Randomized, double blind clinical trial in two arms of HD patients with 25VD deficiency and secondary hyperparathyroidism, one arm to be treated with cholecalciferol supplementation and the other with a placebo, for a period of 12 weeks.

Population. Patients over 18 years of age on HD for more than 3 months and levels of 25VD < 30 ng / ml and iPTH >300 ng/ml , who sign a consent form. Patients will be recruited over a period of one year. Once their consent has been obtained, iPTH and 25VD levels will be measured. Randomization will be achieved by using a table of random numbers at the pharmacy, and neither doctors nor patients will know which group they have been assigned to.

Treatment. Supplementation will consist of one 5000 IU 25VD tablet or placebo during dialysis for a period of 12 weeks.

Monthly monitoring will include: hemoglobin (g/dl), Calcium (mg/dl), Phosphorous (mg/dl), iPTH (ng/ml), epo dose (IU/kg/week), epo resistance (IU/kg/week/g Hb). At the beginning and end of the study the following will be measured: alkaline Phosphatase (IU/ml), PCR (mg/L), 25VD (ng/ml), ferritin (ng/ml) and transferrin saturation, quality of life (SF36).

During the study, doses of calcitriol or paricalcitol will not be modified.

The study will be discontinued if calcemia ≥ 10.5 mg/dL is detected on two occasions.

Size of sample is estimated at 120 patients for a iPTH decrease of 20% in 35% of patients in group treated (assuming 15% follow-up losses). Analysis will be done for Intention to treat for the primary outcome.

Ethical aspects: Authorization has been obtained from the Ethics Committee of the institution as regards Good Clinical Practices, Helsinki Declaration and national regulations. The test will be registered with Cochrane and the Ministry of Public Health.

INTRODUCTION

Vitamin D regulates the metabolism of calcium and phosphorous and plays a crucial role in maintaining adequate bone density. Apart from mineral

metabolism, immunomodulatory, cardioprotective and antiproliferative effects of vitamin D (1,2) have been described recently.

Studies in the general population have found a correlation between deficiency of 25OH vitamin D (25VD) and mortality and morbidity (3). Said correlation was also confirmed in patients with end stage renal disease treated with hemodialysis and peritoneal dialysis (4, 5, 6). 25VD is very stable and has a lengthy half-life (close to 2 weeks) which makes it the optimum metabolite for the measurement and evaluation of vitamin D sufficiency (7).

The synthesis of the active form of vitamin D3 (1,25 (OH) 2 D3) or calcitriol is carried out by means of a second hydroxylation mediated by 1α hydroxylase produced in the proximal tubule of the kidney. The presence of cells that contain 1α hydroxylase capable of synthesizing calcitriol in non-renal sites is significant as renal function deteriorates, but adequate levels of 25VD in the blood are also required (8).

Normal levels of 25VD are considered to be those above 30 ng/ml, moderate deficiency or insufficiency when levels are between 10 and 30 ng/ml, while severe deficiency is when concentration is below 10 ng/ml (9).

It has been found that levels of 25VD are inversely related to those of parathyroid hormone (iPTH) (10), and its supplementation has been associated with a decrease in levels of iPTH in patients with Chronic Kidney Disease (CKD), especially in those with a glomerular filtration rate (GFR) higher than 30 ml/min. The reported results for patients on dialysis have been less consistent. Some studies have reported a decrease in iPTH levels after 25VD supplementation in patients on dialysis as well.

Among the effects of vitamin D not related to mineral and bone metabolism we can find those related to inflammation, angiotensin renin system, arterial pressure and cancer (11). Some studies suggest that it could be through inflammation that 25VD might influence erythropoiesis, thus explaining the association reported in recent observational studies (12, 13). It has been reported that the decrease of 25VD and the higher levels of C reactive protein (CRP) were associated independently with less hemoglobin in individuals with kidney disease not requiring dialysis (14, 15, 16, 17), and that higher doses of erythropoietin are needed in patients on dialysis.

For decades secondary hyperparathyroidism has been treated with active forms of vitamin D (calcitriol) and analogous forms of vitamin D (paricalcitol) (8,9).

The use of calcitriol is associated with a risk of phosphorous increase and of vascular calcifications. While these effects are less significant with paricalcitol, the cost is several times higher which makes it unaffordable for many countries and many patients.

There are not enough randomized clinical trials that confirm the possibility of treating secondary hyperparathyroidism with cholecalciferol (28-31). This is a drug with minor side effects and low cost so it would be very advantageous for all patients, both in developing and developed countries.

AIMS

The aim of the study is to evaluate whether cholecalciferol supplementation for a period of 12 weeks can normalize decreased levels of 25VD and reduce increased iPTH in HD patients with a vitamin D deficiency. A secondary aim is to

evaluate whether this treatment will reduce anemia or the need for erythropoietin in this population.

Specific Aims

1. Primary aim: to analyze whether it is possible to normalize levels of 25VD and reduce high levels of lPTH
2. Secondary aim: to evaluate whether it is possible to improve renal anemia in hemodialysis patients with a 12-week course of cholecalciferol
3. Secondary aim: to investigate whether cholecalciferol supplementation in HD patients is associated with hypercalcemia and hyperphosphatemia

METHODS

Design. Randomized, double blind clinical trial in two arms of chronic HD patients with vitamin D deficiency and secondary hyperparathyroidism, one arm to be treated with cholecalciferol supplementation and the other with a placebo, for a period of 12 weeks.

POPULATION

Criteria for inclusion: Age 18 or over, signed informed consent form, CKD with regular dialysis treatment for at least 3 months, levels of 25VD < 30 ng / ml and iPTH >300 ng/ml, stable doses of calcitriol or paricalcitol over the last 30 days. Criteria for exclusion: Congestive heart failure class lll or lV or unstable angina

or myocardial infarction or stroke during the previous 3 months, active malignant neoplasm, use of any trial medication, life expectancy lower than 6 months, corrected calcemia ≥ 10.5 in the 2 months prior to recruitment, intake of cholecalciferol or ergocalciferol in the 2 months prior to recruitment, prospective move to another city or transfer to PD in the following 6 months.

Patient recruitment. Patients will be recruited over a one-year period when the study will be explained to them, and samples will be taken to assess whether they fulfill the criteria for inclusion in the trial. Once iPTH and 25VD testing has taken place, eligible participants will be requested to sign an informed consent form, and will be told that they will be treated either with cholecalciferol or a placebo. They will be assigned to one of the arms using a table of random numbers at the pharmacy of the institution, stratified in two subgroups according to vitamin D levels: below 15 ng/ml or between 15 and 29.

Randomization. Once approval has been received from the Ethics in Research Committee and the consent form has been signed, patients will be assigned to one arm by using a table of random numbers, according to a number from 0 to 9 which will be drawn at random at the time the patient is included. For purposes of randomization, one fixed number will be skipped from the starting point which is only known by the person who does the randomization at the pharmacy, using a starting point selected initially on the table. Notification of the arm allocated will arrive in sealed envelopes with the medication to be taken (either cholecalciferol or the placebo) which will be administered orally during dialysis.

The laboratory that prepares the medication and the placebo will send them to the pharmacy labelled as medication A and B. Then the pharmacy of the

institution will send the tablets to the patient, neither the doctors nor the patient knowing what arm he has been assigned to. The medication will be administered by the nurse during dialysis.

It will not be necessary to make changes to the dietary intake of vitamin D as dairy products, which are the main source of dietary vitamin D, are strictly limited in the diets of these patients.

Treatment: Supplementation will consist of one 5000 IU tablet of 25VD or placebo taken during dialysis for a period of 12 weeks. A nurse from the team will ensure access to the medication by being in permanent contact with the pharmacy. Monthly follow-up of the patients in the study will include evaluation of laboratory tests as well as normal clinical controls during dialysis (weight, arterial pressure and intra-dialysis hypotension events), and monthly report of dosage of erythropoietin (IU/kg/week) for the calculation of the index of resistance to erythropoietin (IU/kg/week / g of Hb).

Laboratory testing to be done monthly will include: hemoglobin (g/dl), Calcium (mg/dl), Phosphorous (mg/dl), and iPTH (ng/ml). At the beginning and at the end of the study the following will be measured: Alkaline Phosphatase (IU/ml), CRP (mg/L), ferritin (ng/ml), transferrin saturation, and 25VD (ng/ml).

The measuring of hemoglobin will be done by Siemens Healthcare Diagnostics' Advia 2120 haematological analyzer using the cyanmetahemoglobin method modified without cyanide, with Siemens controls and calibrators. Dosing of vitamin D, iPTH and ferritin will be done by Siemens Healthcare Diagnostics' Advia Centaur XP analyzer using the chemiluminescence method, with BIORAD controls and Siemens calibrators.

Other measures will be taken as follows: for calcium, by the Arsenazo III endpoint method, for phosphorous, by the UV phosphomolibdate method, for alkaline phosphatase, by the kinetic technique of paranitrophenol phosphate, for iron, by the endpoint ferrocin method, for transferrin, by the immunoturbidimetric method maximized with PEG, and for reactive C Protein, by the immunoturbidimetric method maximized with latex. All of these will be done by Siemens Healthcare Diagnostics's Advia Chemistry 1800 autoanalyzer with BIORAD controls and Siemens calibrators.

Both prior to the start of the study and after it has ended, quality of life will be evaluated using SF36 auto-administered protocol.

During the 12 weeks of the study, doses of calcitriol or paracalcitol must not be modified. The study will be discontinued in those patients who present levels of calcemia ≥ 10.5 mg/dL on two occasions.

Operational Definitions: 25VD levels are considered normal when above or equal to 30 ng/ml, and severe deficiency (SD-25VD) when below 10 ng/ml. Anemia is defined as presenting levels of Hb below 10g/dl or the need for epo. It is classified as mild anemia when patients have no anemia or require doses of epo below or equal to 2000 IU per week, and, failing this, very mild anemia. Ferritin is considered to be high when over 500 ng/ml. Measurements of all analytes will be done with Siemens equipment at the CASMU laboratory.

Security Measures

Patients will be evaluated for early detection of side effects, particularly in relation to increases in calcemia and fosfatemia. Both calcium and phosphorous will be measured monthly.

If it were necessary to open the blinding, it will be requested from the person in charge of assigning the medication at the pharmacy.

Calculation of sample size

It was estimated, by using free access epidemiological calculator Open Epi (to be found at http://www.openepi.com/v37/SampleSize/SSCohort.htm), that necessary sample size to show a lPTH decrease of 20% in 35% of patients in the group treated (information we found in a previous observational study) is 102, and assuming a 15% loss of follow-up, a sample size of 120 was decided on. This size is more demanding than the 50 patients needed to demonstrate the correction of 25VD in 50% of patients.

Expected Results

Primary end point: A difference in the percentage of patients normalizing levels of 25VD of at least 45% of the group treated vs placebo.

Percentage of patients of at least 30% in the group treated vs placebo presenting a decrease of 20% from previous levels of lPTH.

Secondary end point: Percentage of patients with an increase in Hb or a decrease in resistance to erythropoietin

Ethical Aspects

Authorization has been obtained from the Ethics Committee of the institution. The study will be carried out following Good Clinical Practices, the Helsinki Declaration and national and Mercosur regulations, according to the Ottawa Declaration.

The test will be registered in the Cochrane and WHO Clinical Trials Register, and authorization and registration will be requested from the Uruguayan Ministry of Public Health.

Data Analysis and Statistics

Reference demographic data will be collected related to: age, gender, race, cause of kidney disease, length of time on dialysis, presence of diabetes and use of active forms of vitamin D.

Clinical data will be taken from electronic medical records of dialysis (SISDIA): body weight, height, body mass index, monthly average of systolic and diastolic arterial pressure pre-dialysis, and monthly average percentage of inter-dialysis weight increase.

Both clinical information and laboratory data will be entered in a case report form (CRF) which will be attached as Annex 1.

Laboratory test data will be collected in Table 1 Schedule of measures.

TABLE I. SCHEDULE OF MEASURES

	Time 0	week 4	week 8	week 12	week 16
25VD					
iPTH					
Ca					
P					
Alkaline Phosphatase					
Hb					

CRP					
Ferritin					
Sat Transferrin					
SF36					
Mean SAP					
Mean DAP					
Mean inter-dialytic weight gain					
Number of hipotensive events					

The information obtained from patients' CRFs will be entered in a database which will be treated as confidential. Sensitive data will be kept confidential and patients' identity will remain anonymous during the whole procedure.

In order to ensure the quality of the information, all data entered will be checked by a second member of the research team prior to statistical analysis.

Statistics

Continuous variables with normal distribution will be compared using Student's test for independent or dependent samples as appropriate and will be presented as the mean ± standard deviation. Categorical variables will be compared using Chi square test for paired or independent samples as appropriate

Feasibility

The execution of the study will not involve any costs for the patient nor for the institution. The medication and the placebo will be supplied by Laboratorio Celsius. Costs of laboratory testing for the study as well as of the laboratory

technician will be financed by CSIC if funding is approved, and, if not by Laboratorio Celsius.

Funds

They will be allocated to laboratory expenses for the measured analytes according to the schedule, to medication and the placebo, and to cover human resources for the execution of the study, data input, pharmacy handling, statistical analyses and preparation of report.

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Version December 7th, 2015