CHLORTALIDONE AND BUMETANIDE IN ADVANCED CHRONIC KIDNEY DISEASE: HEBE-CKD TRIAL

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RESEARCH PROTOCOL

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FABIO SOLIS JIMENEZ M.D.

PRINCIPAL INVESTIGATOR

LUCIA MONSERRAT PÉREZ NAVARRO

RESEARCH ASSOCIATE

RAFAEL VALDEZ ORTIZ M.D. PhD

RESPONSIBLE INVESTIGATOR

HOSPITAL GENERAL DE MEXICO "DR. EDUARDO LICEAGA"

NEFROLOGY DEPARTMENT

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1. BACKGROUND

1.1 INTRODUCTION

Nowadays, chronic kidney disease (CKD) is considered a public health problem due to its marked increase in prevalence and incidence that currently far exceeds estimates made in previous years. (1) One of the main features of CKD is volume overload, which is accentuated as the disease progresses and confers multiple complications that directly impact the morbidity and mortality of patients suffering from it. (2)

The treatment of choice for volume overload, decrease extracellular fluid (ECF) and control of hypertension in CKD, is the use of diuretics, manly loop diuretics. (3) However, adaptive changes in the distal nephron secondary to prolonged use of loop diuretics, may decrease its effectiveness, so it is necessary to change the treatment for a more potent diuretic such as Bumetanide, or add another diuretic that acts at a different site from the nephron, as thiazide diuretics. (4)

Although the effect of thiazides on advanced CKD has been studied, most studies are observational and there are no randomized clinical trials with adequate statistical power that strongly recommend the use of thiazides in these patients. (5)

Although renal function replacement therapy is the treatment of choice in patients with stage 5 chronic kidney disease of the KDIGO classification (ERC-5), approximately 15% of them prefer not to undergo dialysis and remain in conservative treatment in order to reduce symptoms and improve the quality of life. (6) (7) Recently, the tendency to recommend replacement therapy to all patients with CKD-5 has been questioned because all the evidence focuses exclusively on improving survival, leaving aside the quality of life and decisions based on patient preferences. (8) (9) While it is true that patients who choose to be treated with hemodialysis live longer, there are studies that show that patients who prefer conservative treatment have a lower rate of hospital visits, admission and days of hospital stay, which means improvement in quality of life and reduction of treatment costs (10) However, up to a third of patients have symptoms despite conservative treatment, of which the majority described as disabling, are secondary to volume overload. This indicates that the current treatment may be insufficient. (11)

IMPACT OF VOLUME OVERLOAD ON ERC

Patients with CKD who suffer from volume overload have an increased risk of mortality from all causes compared to those patients with CKD who do not suffer from it. (12) This is explained by the high cardiovascular risk that these patients have, since volume overload has been associated with the development of ventricular hypertrophy (13), hypertension and endothelial damage, (14) which

results in up to 38% of the deaths are attributed to atherothrombotic cardiovascular events and 24.3% to arrhythmias. (15)

It has also been shown that the treatment focused on reducing volume overload directly impacts, in addition to reducing all the aforementioned complications, to improve the quality of life of the patient with CKD. (16)

DIURETIC RESISTANSE

One of the biggest limitations with the use of diuretics to treat volume overload in CKD is diuretic resistance. This is defined as the inability to achieve the desired therapeutic reduction of edema when effective doses of the drugs are used. (17) There are multiple mechanisms that explain the development of diuretic resistance, most include alterations that modify the pharmacokinetics of diuretics and that can be resolved by increasing the dose above those recommended in patients who do not have CKD. (18)

Another mechanism described is the development of adaptive changes in the distal nephron, triggered by the chronic use of loop diuretics. (19) Under normal conditions up to 25% of filtered sodium is reabsorbed in the thick ascending portion of the loop of Henle (site of action of loop diuretics) and 5-10% in the distal contoured tubule (site of action of thiazide diuretics). (20) However, in patients who use loop diuretics chronically, unusual amounts of sodium reach the distal contoured tubule, causing epithelial cell hyperplasia and consequently a greater sodium reabsorption at this level, which decreases the therapeutic effect of loop diuretics. (21)

STUDIES ON THIAZIDES AND CKD

In the decade of the 90's the first controlled clinical trials were conducted on the use of thiazide diuretics, loop and its combination. The first of them in the year 1994 analyzed 10 patients with glomerular filtration rate (GFR) <15 mL / min / 1.73m2 and showed that the combined use of a loop diuretic and a thiazide increases its natriuretic effect compared to the individual administration (22) The following year a similar study was carried out in patients with a mean GFR of 39 in which the same result was shown. (23)

It was until 2005 when the first clinical trial was conducted following a double-blind model. In this study, 7 patients were randomized to receive 60 mg of furosemia a day or hydrochlorothiazide 25 mg per day for 30 days and it was found that individual use of hydrochlorothiazide significantly increased natriuresis and decreased an average of 15 mmHg of blood pressure in a month of follow-up, without finding benefit of combined use. (24) In 2012, the same work team led by Dussol and collaborators, carried out a similar study but with a sample of 23 patients and a 3-month follow-up, reporting contrasting results with the previous trial, since in the latter they did find benefit from combined use of both diuretics. (25) In 2014, studies began with chlorthalidone, a molecule that is called thiazide-like because, although it does not have the chemical characteristics of this pharmacological family, it has the same mechanism of action. (26) The first was a pilot study, in which 14 patients with uncontrolled hypertension and GFR between 20 - 45 mL / min / 1.73m2 were recruited, 50 mg of chlorthalidone was given and

followed up for 12 weeks. It was found that these patients decreased 10.5 mmHg of blood pressure, lost 1.5 liters of water and 1.2 kg of weight. (27) Subsequently, a study was conducted where 60 patients with uncontrolled hypertension and GFR <60 mL / min / 1.73 m2 were recruited and a dose of 25 milligrams of chlorthalidone was administered for 8 weeks. At the end of the follow-up, a decrease in systolic blood pressure of 19 mm and a weight reduction of 0.88 kg was found. (28)

PROBLEM STATEMENT

Chronic kidney disease is a growing health problem. In the disease, as the deterioration of renal function progresses, the volume overload becomes more evident and in advanced stages it implies high morbidity and mortality, because it causes respiratory distress, uncontrolled arterial hypertension, heart failure and peripheral edema. Nowadays, the treatment of volume overload in patients with advanced CKD is limited to the prescription of loop diuretics, which although they are useful drugs in the early stages, as the disease progresses and with its constant use, they decrease its effectiveness due to diuretic resistance. This means that the current treatment is insufficient.

JUSTIFICATION

Since the volume overload treatment options in patients with advanced chronic kidney disease are limited, it is necessary to seek treatment options different from those currently recommended.

In this sense, thiazide diuretics promise to be a viable option for the treatment of volume overload in these patients because they inhibit the loop diuretic resistance mechanism created with prolonged use of diuretics.

Unfortunately, the current evidence regarding the use of thiazide diuretics in advanced chronic kidney disease is not conclusive, so it is necessary to perform more studies with the appropriate methodology, in order to improve morbidity, mortality and quality of life in these patients.

HYPOTHESIS

If, the combination of chlorthalidone and bumetanide is more effective as a treatment for volume overload in patients with advanced CKD than the use of isolated bumetanide, then, patients with CKD and volume overload who receive treatment for four weeks with chlorthalidone and bumetanide , will have a decrease in the percentage of total body water greater than 10% compared to those who only receive bumetanide and placebo.

OBJETIVES

To evaluate the effect of bumetanide versus bumetanide plus chlorthalidone as a treatment to reduce volume overload in patients with advanced CKD.

SPECIFIC

- To assess the effect of pharmacological intervention as an antihypertensive treatment
- Describe the clinical and biochemical characteristics of the population in zero time, at the week and at the end of the treatment.
- Compare the baseline clinical and biochemical variables, during the follow-up and at the end of the study, according to the type of treatment assigned.
- Evaluate the change in volume overload with the intervention using bioimpedancemetry vectors
- To assess the effect of treatment on cerebral natriuretic peptide (BNP).
- Evaluate the occurrence of adverse effects with the treatment implemented.

METHODOLOGY

STUDY DESING

Randomized, double-blind, placebo-controlled clinical trial.

POPULATION AND SAMPLE SIZE

A statistical power analysis was performed to estimate the sample size, based on data from the study entitled "Parallel-group 8-week study on chlorthalidone effects in hypertensives with low kidney function" published in the journal Hypertension in 2014 (n = 60). The effect size of the study was 0.5 considered as medium using the Cohen criteria (1988). With an alpha = 0.05 and power = 0.80, the projected sample size needed with this effect size was calculated in GPower 3.1.9.2 considering an ANOVA test of repeated samples between factors, resulting in n = 32 for this simple comparison between the groups.

Therefore, our proposed 32 + 8 sample size will be more than sufficient for the main objective of this study and should also allow for expected attrition and meet our additional objectives of controlling possible mediating factors / moderators / subgroup analysis, etc.

SELECTION CRITERIA

- Patients over 18 years of age.
- Glomerular filtration rate <30 ml / min determined by the CKD-EPI formula.
- Residual uresis of at least 100ml per day.
- Without replacement treatment of renal function (peritoneal dialysis or hemodialysis).
- Patients who after explaining in detail the benefits of renal replacement therapy, do not wish to undergo it.

- Current treatment with a loop diuretic for at least one month prior to contact.

- That they sign informed consent and agree to participate in the study.

EXCLUSION CRITERIA

- Patients with suspected or documented infection

- Sulfate allergy

- Established diagnosis of heart failure with reduced ejection fraction (less than 40%).

- Cognitive disorders

- Other comorbidities that compromise renal flow (malignant neoplasia, liver failure and respiratory failure.)

- Pregnant patients

ELIMINATION CRITERIA

- Patients who do not attend a follow-up consultation

- Patients who during the follow-up request to start renal replacement therapy

- Patients who, during follow-up, begin dialysis or hemodialysis due to dialysis emergency

DEFINITION OF VARIABLES

VARIABLE	CONCEPTUAL DEFINITION	OPERATIONAL DEFINITION	VARIABLE TYPE	MEASUREMENT SCALE	INDICATOR
Age.	Time that has lived a person or another living being counting from birth.	Its measurement will be established in years based on the years completed at the time of patient selection.	Quantitative discrete.	Years.	It will be considered number of years. Mean ± SD
Gender	Set of people or things that have common general characteristics.	It will be established based on physical examination.	Qualitative dichotomous.	Man, woman.	Absolute and relative frequency of the population in 2 gender categories (male and female).
Systemic blood	It is the pressure exerted by the blood	It will be established based on the sphygmomanometer socket. It will	Continuous quantitative	mmHg	Absolute and relative

pressure	against the walls of the arteries as the heart pumps blood to your body	be considered hypertensive one whose values are greater than 140/90 mmHg			frequency of patients with HTAS Mean ± SD
Edema of pelvic limbs	Accumulation of fluids at the subcutaneous interstitial level	It will be established according to patient clinic Grade I: minimum Grade II: 15 seconds Grade III: 1 minute Grade IV: 2 to 5 minutes	Qualitative ordinal	Clinic based on Godette	Grade I: minimum Grade II: 15 seconds Grade III: 1 minute Grade IV: 2 to 5 minutes
Serum creatinine	Creatinine is an organic compound generated from the degradation of creatine, which is a useful nutrient for muscles.	Creatinine measurement is the simplest way to monitor kidney function.	Quantitative continues.	mg/dl.	Mean ± SD

Serum urea	It is the end result of protein metabolism. It is formed in the liver from the destruction of proteins.	It will be taken at your first consultation, then a week and at the end of the study.	Quantitative continue	mg/dl.	Mean ± SD
Serum sodium	It is the positive ion that is found mainly, outside the cells, in the extracellular fluids of the human body.	It will be taken at your first consultation, then a week and at the end of the study.	Quantitative continue	meq/l	Mean ± SD
Serum chlorine	It has the ability to enter and leave the cells along with sodium and potassium or combined with other major cations such as calcium.	It will be taken at your first consultation, then a week and at the end of the study.	Quantitative continue	mg/dl	Mean ± SD

Serum potassium	It is the positive ion that is found primarily within the cells of the human body. The concentration in the cells is 30 times higher than the extracellular space and serves to maintain the electrical charge of the cell membrane.	It will be taken at your first consultation, then a week and at the end of the study.	Quantitative continue	mg/dl	Mean ± SD
Uric acid	It is a chemical that is created when the body breaks down purines. Most of it dissolves in the blood and travels to the kidneys.	It will be taken at your first consultation, then a week and at the end of the study.	Quantitative continue	mg/dl	Mean ± SD

Albumin	Albumin is a protein that is found in a large proportion in the blood plasma, being the main protein in the blood, one of the most abundant in being.	It will be taken at your first consultation, then a week and at the end of the study.	Quantitative continue	g/l.	Mean ± SD
Glomerular Filtration Rate.	It is the volume of fluid filtered per unit of time from the renal glomerular capillaries into the Bowman's capsule.	It will be taken at your first consultation, then a week and at the end of the study.	Quantitative continue	ml/min/1.73	Mean ± SD
Sodium excretion fraction	Represents the relationship between sodium fractions excreted and filtered by the kidneys	It will be taken at your first consultation, then a week and at the end of the study.	Quantitative continue	mmoL/day	Mean ± SD

Weight	The mass or amount of weight of an individual. It is expressed in units of pounds or kilograms	Weight in kilograms of the patient. The measurement will be done without shoes or heavy clothing, and preferably at least two hours after eating food.	Quantitative continue	Kilograms	Mean ± SD
Height	The perpendicular distance between the transverse planes of the Vertex point and the bottom of the feet.	It will be measured with the subject standing, with the heels, buttocks and the upper back in contact with the scale, with the head in Frankfurt plane.	Quantitative continue	Centimeters	Mean ± SD
Body mass index (BMI kg / m2)	It describes the relative weight for height and is significantly correlated with the total fat content of the individual.	It will be obtained through the measurement of weight and height with the following formula: BMI (kg / m2): weight in kilograms / height in m2	Quantitative continue	kg/m^2	Mean ± SD

Uresis	It is defined as the amount of urine produced in a given time	It will be obtained from the daily collection of urine by the patient on an outpatient basis.	Quantitative continue	Milliliters	Mean ± SD
Ballast	Force that opposes the passage of a current because of a conductor, also given in this vessel by the polarity of cell membranes. Mi of the conductivity of cell membranes	The electrical properties of the body will be analyzed at mono frequency (50 kHz) and the reactance value of the RJL equipment will be taken.	Quantitative continue		Mean ± SD
Phase angle	Tangent arc between resistance and reactance in a series or parallel circuit	The electrical properties of the body will be analyzed at mono frequency (50 kHz) and the phase angle value of the RJL equipment will be taken.	Quantitative continue		Mean ± SD

PROCEDURE

During the period between June and August of the year 2019, patients from the external nephrology clinic of the General Hospital of Mexico will be selected who have GFR less than 30 mL / min / 1.73 m2 estimated by CKD-EPI and will be offered to perform a bioimpedancemetry, where those patients who meet volume overload criteria will be offered to participate in the study.

Once they agree to participate in the study, the consent is signed and through a randomization process carried out through an online program (https://www.graphpad.com/quickcalcs/randomize1.cfm) a group will be assigned. This group will be known as A or B, without the investigator or the patient knowing which will be the intervention and which the control group. Subsequently they will be granted an appointment in order to obtain the initial measurements.

Appointment 1 (day 1): Patients will be scheduled at 8:00 a.m. with 8-hour fast and 24-hour urine collection, to the nephrology service where a brief questionnaire will be made in order to obtain demographic data and personal background of importance for the trial. Anthropometric measurements will be made (weight, BMI size) and blood pressure measurement will be performed after asking the patient to remain in a sitting room and in a quiet environment for 15 minutes, and without having consumed any substance that modifies the pressure taking. Measurements of both arms were taken and the average of both will be recorded.

Subsequently, a bioimpedancemetry study will be carried out again, for which patients were asked to shed any metal object. Finally, they will be given the

corresponding medicine for the first week of follow-up, in closed and labeled packages for the assigned group. That same day, they will be granted a nutrition consultation where they were given nutritional recommendations on the consumption of sodium and water. Finally they were explained by probable side effects and alarm data with which they will be able to go to the emergency department, a new appointment will be scheduled within a period of 7 days and they will be asked to go to the central laboratory where trained personnel will be responsible for carrying out the Sample collection and processing.

Appointment 2 (day 7): The same procedure and measurements were performed, the corresponding medication was granted for the rest of the follow-up. A new appointment was granted within a period of 3 weeks.

Appointment 3 (day 28): The same procedure was performed and the final measurements were taken.

WORKPLACE

Patient recruitment will be carried out in the outpatient department of the nephrology service. The citations of the essay will be carried out in the research section in nephrology and nutrition, located inside the nephrology service. Sampling and processing were performed in the central laboratory. All within the facilities of the General Hospital of Mexico "Eduardo Liceaga".

INTERVENTIONS

Patients will be randomized to two groups (control and intervention), which will be blinded to the patient and the researcher throughout the study and will consist of the following:

1. Control: Bumetanide plus placebo

2. Intervention: Bumetanide plus Chlorthalidone

The initial dose of bumetanide will be 3 milligrams, which will be administered as follows: 2 milligrams at 10:00 a.m. and 1 milligram at 4 p.m.

The initial dose of Chlorthalidone will be 50 milligrams, which will be administered as follows: 50 milligrams at 12 p.m.

After a week of follow-up, if the patients have no adverse effect, the dose of the medication will be increased, as follows:

Bumetanide 4 milligrams, which will be administered as follows: 2 milligrams at 10:00 a.m. and 2 milligrams at 4 p.m.

Chlorthalidone 100 milligrams, which will be administered as follows: 50 milligrams at 12 p.m. and 50 milligrams at 6 p.m.

Unmanaged doses of chlorthalidone to the control group will be replaced by placebo capsules, identical (sight and touch) to chlorthalidone capsules. The placebo will consist of cornstarch (powder).

STATISTICAL ANALYSIS

Data capture will be done in Excel, which will be reviewed and validated by a third party to rule out errors in the capture. Subsequently, the information will be exported to the SPSS statistical program.

Parametric and non-parametric statistics will be performed depending on the distribution of variables. Average and standard deviation will be applied for continuous variables, with Student's t-test, and X2 test for nominal variables, considering a value of $p < 0.05$, with 95% CI as statistical significance.

ETHICAL AND BIOSECURITY

The study is considered to be greater than the minimum risk for the patient, since it was subjected to blood sampling; Each patient will be fully explained that the adverse effects that could occur if they were included in the study were: hypokalemia, hyperuricemia, increased azoa, impaired renal function, hypotension, dizziness, vomiting, even urgent dialysis requirement.

All admitted patients must sign an informed consent where the objective of the study will be described and their participation.

The protocol was approved by the research committee and the research ethics committee in March 2019 and granted the approval number: DI / 19/105-B / 03/018.

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