The effectiveness of dapagliflozin versus furosemide in controlling blood pressure in uncontrolled hypertension with subclinical fluid retention in chronic kidney disease

Introduction

Background

Hypertension is a common problem encountered in clinical practice. Chronic hypertension leads to impaired kidney function and reduced efficiency, ultimately resulting in chronic kidney disease (CKD). It is found that hypertension is the second most significant cause contributing to the development of CKD, following diabetes. Besides impairing kidney function, chronic hypertension also poses a significant risk factor for cardiovascular diseases if not adequately managed.[1]

Uncontrolled hypertension (UCH) is a condition where blood pressure levels cannot be controlled within appropriate limits even with patients receiving treatment through lifestyle adjustments and appropriate medication, including at least four drug groups. UCH is frequently encountered in patients with CKD, especially in the advanced stages of the disease. A study was conducted on CKD patients under follow-up care at the Bhumibol Adulyadej Hospital. Data collection found that approximately 42.3% of CKD patients before undergoing renal replacement therapy had UCH.[2] Such patients require appropriate management of hypertension to delay the progression of kidney disease.

The main cause of UCH in CKD patients arises from the increased activity of the renin-angiotensin system (RAS) and sympathetic nervous system (SNS), leading to salt and water retention in the body.[3] This results in fluid overload, which, when assessed solely through physical examination, lacks precision in evaluating the body's fluid status, leading to inadequate correction of fluid overload.[4] Consequently, the management of UCH becomes challenging. Bioimpedance spectroscopy (BIS) has been introduced as a more accurate tool for assessing the body's fluid status, aiding in the management of high blood pressure in CKD patients with UCH.[5]

A study by LanC found that Sodium-glucose Cotransporter-2 inhibitors (SGLT2i); Empagliflozin, effectively reduce blood pressure in elderly Chinese patients with an average SBP of 157-159 mmHg, achieving the target goal of 83.9%.[6] This is attributed to the SGLT2i's efficacy in diuresis and reducing fluid overload in the body.[7]

Dapagliflozin, another SGLT2i, is the only drug currently approved by the Food and Drug Administration, Thailand for use in CKD patients to delay kidney deterioration. This medication is of interest for further study, particularly regarding its efficacy in reducing blood pressure in patients with treatment uncontrolled hypertension.

Hence, this study aims to compare the efficacy of Dapagliflozin with Furosemide in controlling blood pressure in CKD patients with treatment uncontrolled hypertension using BIS for fluid status assessment. The study will be conducted on stage 3 and 4 CKD patients at the Bhumibol Adulyadej Hospital, including evaluating its efficacy in delaying kidney deterioration, and reducing cardiovascular events.

Literature review

High blood pressure is commonly found in patients with chronic kidney disease (CKD), and it has been observed that CKD patients in the late stages receiving renal replacement therapy have high blood pressure as the second leading cause, following diabetes. The incidence of high blood pressure has significantly increased, from 30.6% in 2019 to 38.9% in 2019, when compared to 2016.[8]

The definition of hypertension is systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, as measured in healthcare settings.[9]

A study by Thanakitcharu assessed the fluid status of CKD patients before renal replacement therapy using Multi-frequency bioelectrical impedance analysis (MF-BIA) compared to physical examination. It found that although physical examination results were normal, there was fluid overload in the body, with percentages in stages 1-2, 3-4, and 5 CKD patients being 70.6%, 41.7%, and 61.5%, respectively.[4]

Verdalles' study found that extracellular volume expansion (ECV) is one of the causes of RHT, particularly in CKD patients before renal replacement therapy. The study utilized the bioimpedance spectroscopy technique (BIS) to assess fluid overload in the body and treated it with diuretics. After 6 months of treatment, systolic blood pressure decreased by 21.4 ± 7.1 mmHg, total body water (TBW) decreased by 1.9 ± 1.1 liters, and extracellular volume (ECV) decreased by 1.1 ± 1 liter.[5]

Currently, the recommendation is to use SGLT2i to delay kidney deterioration in CKD patients with a glomerular filtration rate (GFR) of ≥20 mL/min/1.73 m².[10] SGLT2i reduces blood sugar levels by promoting its excretion in urine and decreases sodium reabsorption in the proximal tubule, resulting in increased sodium excretion and reduced blood pressure.[11]

Ohara's study compared the efficacy of Furosemide, Dapagliflozin, and Tolvaptan in diuresis using BIA to measure body fluid volume before and after treatment for 7 days. All three groups significantly reduced body weight, and urine output increased. However, there were differences in extracellular water (ECW) changes, with Furosemide showing the greatest change (-12.5 ± 1.3%), followed by Dapagliflozin (-8.4 ± 1.7%) and Tolvaptan (-7.4 ± 1.5%).[7] However, there have been no studies comparing the effectiveness of controlling high blood pressure with the use of these medications.

Treatment goals for UCH in CKD patients before renal replacement therapy, recommended by the Thai Society of Nephrology, include achieving an SBP < 130 mmHg.[9,12,13,14] This involves behavioral modifications such as smoking cessation, limiting sodium intake to less than 2,000 mg/day (sodium chloride less than 5 grams/day), engaging in moderate-intensity exercise for at least 150 minutes per week, and pharmacological treatment with medications such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), calcium channel blockers (CCB), diuretics, and other antihypertensive medications.[3,10]

Currently, SGLT2i use is beneficial in various CKD patient groups, including those with diabetes and a GFR of ≥20 mL/min/1.73 m² (*1A*), those with heart failure or albuminuria with Urine albumin to creatinine ratio (ACR) ≥200 mg/g (*1A*), and those with a GFR of 20-45 mL/min/1.73 m² and a UACR < 200 mg/g. (*2B*)[9]

Research Objectives

Primary objectives

To compare blood pressure change between dapagliflozin and furosemide in controlling blood pressure.

Secondary objectives

To compare the achieving target of blood pressure, fluid status, renal function, and incidence of hospitalized heart failure between dapagliflozin and furosemide.

Materials and methods

Study design and participants

This single-center, non-inferior prospective randomized, open-label study was conducted at Bhumibol Adulyadej Hospital. The study protocol was approved by the Institutional Review Board of Bhumibol Adulyadej Hospital, Directorate of medical service, Royal Thai Air Force. Written informed consent was obtained from all patients or their legally authorized representatives before participation.

Eligible participants were adults aged ≥ 18 years with CKD (GFR-EPI 20-60 ml/min/1.73m^2) with uncontrolled hypertension with fluid retention detected by bioimpedance. Exclusion criteria included patients receiving diuretics or SGLT2i, uncontrolled hypertension with euvolemic status, life expectancy < 12 months (principal investigator's judgment), living-donor transplant scheduled within the next 12 months, cardiovascular disease (dilated cardiomyopathy, valvular heart disease), active infection, current active malignancy, known HIV or active hepatitis B or C, chronic liver disease and/or screening alanine transaminase or aspartate transaminase above 3 times the upper limit of the normal range, pregnancy or breastfeeding and subject has any kind of disorder that compromises their ability to informed consent and/or to comply with study procedures.

Materials

The Body Composition Monitor (BCM; Fresenius Medical Care, Deutschland GmbH Schweinfurt Plant, Hafenstrasse 9, 97424 Schweinfurt/Germany) utilizes the principle of Bioimpedance spectroscopy technique, which involves using frequencies in the range of 5kHz-1MHz and calculating the electrical resistance values of Extracellular water (ECW) and Intracellular water (ICW) using a combination of Cole-Cole plot and Hanai formulae along with a physiologic tissue model, dividing the body composition into three components: extracellular fluid overload, normohydrated lean tissue, and normohydrated adipose tissue, assuming the proportions of normohydrated lean and adipose tissue remain constant. Then, the program calculates the volume of water in these compartments, with reference values being the 10th-90th percentile of body water volume in the normal population matching the patient's gender and age. This can indicate excess water volume in the studied patients. The value indicating fluid retention in patients is determined by overhydration (OH) exceeding 1 liter.

Randomization

The patients were randomly assigned in a 1:1 ratio to receive either Dapagliflozin or Furosemide. The allocation sequence used random numbers in a block of fours.

Procedures

Participants were selected for the research study based on inclusion and exclusion criteria. Patients were informed about the study details and provided consent to participate. Basic data of research participants were collected through interviews, echocardiograms, Bioelectrical Impedance Analysis (BIS), and dietary sodium restriction guidance of less than 2 grams per day. Patients were randomly assigned into two groups. The experimental group received a daily dose of 10 milligrams of dapagliflozin, while the control group received an initial dose of 20 mg/day of furosemide with dosage adjustment based on BIS assessment. Blood samples were collected, and variables related to the research outcomes were recorded over 6 months. Body fluid status was assessed using BIS monthly during months 1-3 and month

6. Outcomes at 6 months were evaluated through echocardiograms and laboratory tests. Statistical analysis was conducted on the obtained results, shown in Figure 1.

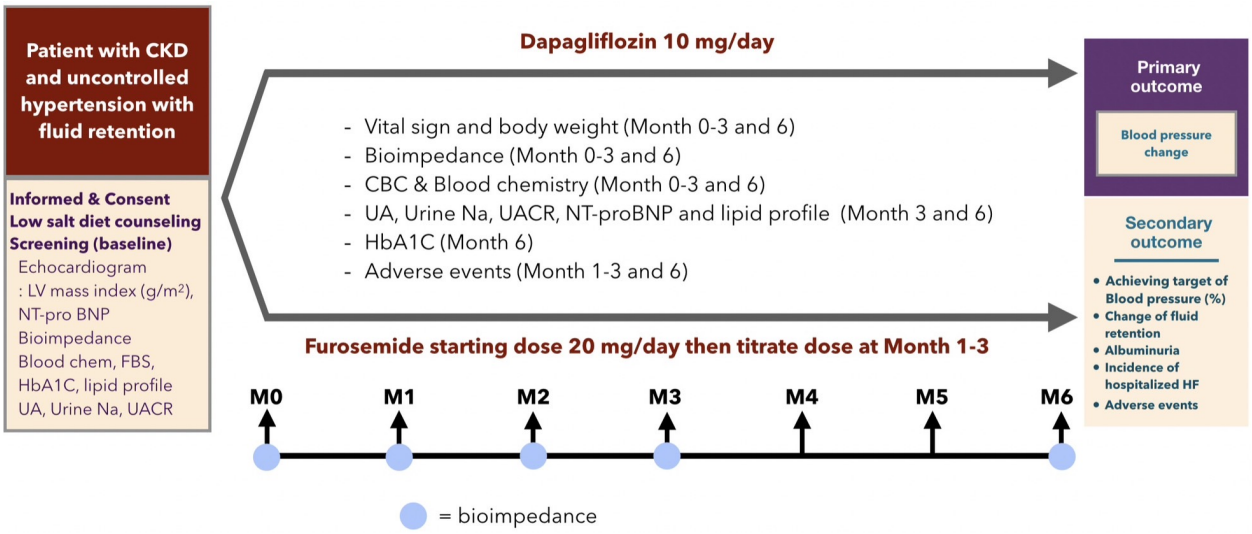

Figure 1. Research protocol.

Outcomes

The primary outcome was to compare blood pressure change between dapagliflozin and furosemide in controlling blood pressure.

The secondary outcome was to compare the achieving target of blood pressure, fluid status (assessed by ECW, ICW, and ECW/Total body water), renal function (eGFR, UACR), cardiac function (change in LV mass index, NT-pro BNP), and incidence of hospitalized heart failure between dapagliflozin and furosemide.

Safety

Side Effects and Risks

1.) Side Effects of furosemide

The observed side effects include low blood pressure, electrolyte abnormalities (hyponatremia, hypokalemia, and hypomagnesemia), and acute kidney injury.

2.) Side Effects of dapagliflozin

After initial medication, a decrease in GFR was observed due to the drug's mechanism, with subsequent stabilization of kidney function. Other potential side effects include genital infections, ketone acidosis, and dehydration-induced kidney injury.

Prevention or Management Standards

1.) Prevention strategies for furosemide side effects involve close monitoring of vital signs, body fluid status assessment, and electrolyte levels in at-risk patients, with corrective measures taken if side effects occur.

2.) Prevention and management strategies for dapagliflozin side effects involve close monitoring of vital signs, body fluid status assessment, and electrolyte levels, with vigilant observation for dehydration. Temporary discontinuation of the medication during prolonged fasting or illness, maintaining the cleanliness of the genital system, and corrective measures if side effects occur.

Study Discontinuation

Study discontinuation may be warranted if a participant experiences drug allergies or side effects deemed severe by the investigating physician, such as normoglycemic diabetic ketoacidosis (DKA) or bloodstream infections originating from urinary tract infections, among others.

Statistical analysis

Continuous data were presented as means with standard deviation (SD) or medians with interquartile range (IQR) and compared using the Student’s t-test or Wilcoxon Rank-Sum test, as appropriate. Categorical data were presented as proportions and compared using Fisher’s exact test. An alpha level of ≤ 0. 05 was deemed statistically significant for all tests. This study used program R version 4.2.1 for data analysis.

Sample size

From the study by V lase et al., it was found that Furosemide can reduce SBP in uncontrolled hypertension patients by 32 mmHg[15], and from the study by Micheal A Weber et al., SGLT2i (dapagliflozin) can reduce SBP in hypertension patients by 11.9 mmHg[16].

Calculation of non-inferiority in continuous data using a significance level of 0.05, a power of the test of 0.8, the standard deviation of the outcome of 7 mmHg, the non-inferiority limit of 7 mmHg, and a dropout rate of 10%, with a minimum sample size of at least 15 participants per group, totaling at least 30 participants.

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