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Trial Design

Home Bioelectrical Impedance Analysis Management System in Patients With Heart Failure: Rationale and Study Design

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ABSTRACT

Body fluid monitoring and management are essential to control dyspnea and prevent re-hospitalization in patients with chronic heart failure (HF). There are several methods to estimate and monitor patient's volume status, such as symptoms, signs, body weight, and implantable devices. However, these methods might be difficult to use for reasons that are slow to reflect body water change, inaccurate in specific patients' condition, or invasive. Bioelectrical impedance analysis (BIA) is a novel method for body water monitoring in patients with HF, and the value in prognosis has been proven in previous studies. We aim to determine the efficacy and safety of home BIA body water monitoring-guided HF treatment in patients with chronic HF. This multi-center, open-label, randomized control trial will enroll patients with HF who are taking loop diuretics. The home BIA group patients will be monitored for body water using a home BIA device and receive messages regarding their edema status and direction of additional diuretics usage or behavioral changes through the linked application system once weekly. The control group patients will receive the usual HF management. The primary endpoint is the change in N-terminal prohormone of brain natriuretic peptide levels from baseline after 12 weeks. This trial will provide crucial evidence for patient management with a novel home BIA body water monitoring system in patients with HF.

Keywords: Heart failure; Electric impedance; Monitoring, physiologic; Telemedicine

INTRODUCTION

Heart failure (HF) is a chronic condition punctuated by acute decompensated episodes. Each acute decompensated event results in further organ damage; myocardial and renal damage occurring during such episodes may contribute to progressive left ventricular and/or renal dysfunction.[1,2] Increasing frequency of acute events with disease progression leads to higher rates of hospitalization and increased risk of mortality.[3]

The main symptoms of HF are shortness of breath and swelling, which are the main causes of emergency room visits and hospitalizations.[4,5] After discharge, body water monitoring and management of patients with HF are very important to prevent HF aggravation and re-hospitalization. There are several methods of body fluid monitoring in patients with HF. Previously, monitoring pulmonary artery pressures using a wireless implantable hemodynamic monitoring system and multi-parameter monitoring via implanted electrical devices (e.g., Implantable cardioverter defibrillator, cardiac resynchronization therapy with defibrillator) were expected to improve clinical outcomes and were recommended in HF guidelines.[6] However, it is no longer actively recommended in the recent guidelines, and clinical evidence might be also insufficient as GUIDE-HF trial failed to satisfy the primary endpoint.[7,8] Moreover, these modalities have limitations of invasiveness, high cost, and require significant medical providers' efforts. Other body water monitoring methods are signs and symptom monitoring and body weight-based monitoring.[7] However, signs such as weight gain and edema or symptoms such as dyspnea due to worsening heart failure are not recognized until just 7 days and 3 days, respectively, before the hospitalization event.[9]

Bioelectrical impedance analysis (BIA) can be a novel method for body water monitoring in patients with HF.[10,11] BIA is a noninvasive, reproducible, and relatively inexpensive method to estimate fluid status.[12] Home BIA monitoring has the potential benefit of continuous water monitoring for edema control in patients with HF. In this study, we will evaluate the feasibility of treatment using home BIA and a linked application system in patients with HF.

STUDY DESIGN

This study is a multi-center, prospective, open-label, randomized clinical trial conducted at Korea University Guro Hospital and Soonchunhyang University Bucheon Hospital (Seoul, Korea). The study protocol was approved by the Institutional Review Board (IRB) of Korea University Guro Hospital (IRB number: 2021GR0130) and Soonchunhyang University Bucheon Hospital (IRB number: 2020-12-039). The objective of this study is to evaluate the efficacy and safety of the treatment using home BIA and a linked application system in patients with HF.

Trial population

Adult patients with a prior diagnosis of HF will be eligible for the study regardless of left ventricular ejection fraction (LVEF) on echocardiography. Patients should be receiving loop diuretics for HF symptom control. Patients who cannot measure BIA and those who have edema caused by other diseases which could affect the results of body composition will be excluded. The specific inclusion and exclusion criteria are demonstrated in **Tables 1** and **2**. A total of 40 patients who met the inclusion criteria without exclusion criteria will be randomized in a 1:1 manner for home BIA monitoring or control group. Patients will continue to receive the optimal medical therapy for HF.

Study flow

The study flow is shown in **Figure 1**. Patients who meet the inclusion criteria will be screened and randomized after written informed consent has been obtained. After randomization, patients assigned to the home BIA monitoring group will measure their body fluid composition daily using a home BIA device. The patients measured their body fluid composition at the same time in the morning and entered the study period after a week of practice to master the measurement using a home BIA device. The home BIA monitoring group participants will be notified by text of the adequacy of their fluid status and changes from the previous week. The change of body fluid was analyzed based on the average value of 3 days on Friday, Saturday, and Sunday for the previous week and this week. They may also receive once weekly instructions on appropriate behaviors (e.g., avoid salty food, be aware of symptom changes, doctor appointments, etc.) or on the use of additional diuretics (furosemide 20–80 mg/day) if needed based on the body fluid status analysis. In addition, if the patient did not measure the BIA for 3 consecutive days, the system automatically sent a push notification. The contents of the message

Table 1. Inclusion criteria

Criteria
Patients willing and capable of providing informed consent, and who agree to follow the study protocol
Age >20 years
Prior diagnosis of HF regardless of LVEF
Patients taking loop diuretics for HF symptom control
Patients who have a smart-phone and can use applications

HF = heart failure; LVEF = left ventricular ejection fraction.

Table 2. Exclusion criteria

Criteria
Having implanted materials that could interfere with the BIA (e.g., Pacemaker, ICD, CRT)
Unable to stand alone
Being pregnant
Having serum creatinine levels of >5 mg/dL or nephritic syndrome or undergone dialysis
The presence of systemic diseases such as hypothyroidism, decompensated LC, and SLE
Having active cellulitis, severe varicose veins, lymphedema, or deep vein thrombosis

BIA = bioelectrical impedance analysis; ICD = implantable cardioverter defibrillator; CRT = cardiac resynchronization therapy; LC = liver cirrhosis; SLE = systemic lupus erythematosus.

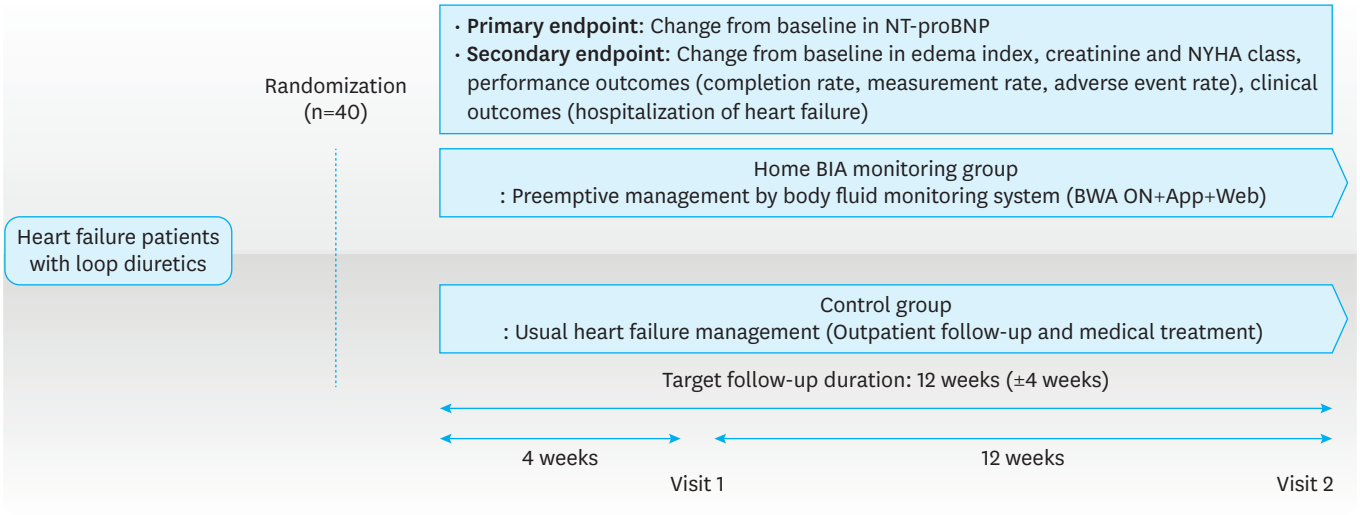

Figure 1. Study flow.
NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; BIA = bioelectrical impedance analysis.

were prepared by the investigators in advance using an algorithm according to the state and change of the edema index defined as extracellular water/total body water (**Supplementary Table 1**). The control group patients will be treated with the usual HF management including general HF education.

Baseline BIA will be performed at the date of enrollment. Baseline laboratory results will be obtained on the day of enrollment or within 4 weeks. The follow-up of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels will be measured at visit 2 of the 12-week (±4 weeks) after enrollment. Other laboratory tests will be performed at visits 1 and 2. Drug adherence and the symptom scales of the New York Heart Association (NYHA) functional class will be investigated at every visit.

Body fluid measurement using BIA

Body fluid measurement using BIA includes total body water, extracellular water, intracellular water, and edema index defined as extracellular water of the total body water according to body segments such as the whole body, trunk, right arm, left arm, right leg, and left leg. Body fluid composition of all patients will be measured using a standard BIA device (InBody S10; InBody®, Seoul, Korea) on the day of enrollment and at visit 2. Patients in the home BIA monitoring group will measure their body fluid composition using a home BIA device (BWA-ON; InBody®, Seoul, Korea) at the same time every morning. Daily data on the body fluid composition will be immediately transmitted to the cloud server and analyzed weekly in the investigating control center (**Figure 2**).

Endpoints

The primary endpoint of this study is the change from baseline in the cardiac biomarker of NT-proBNP for the efficacy at the 12-week follow-up. Secondary endpoints are the change from baseline in the edema index defined as the ratio of extracellular water to total body water using BIA, serum creatinine, and dyspnea according to the NYHA functional class, clinical outcomes including hospitalization for HF, cardiovascular death, and unexpected hospital visits, and performance outcomes including the study completion, measurement, and adverse event rates, and the satisfaction questionnaire scores using the 5-Likert scales at the 12-week follow-up.

Statistical analysis

Overall analyses will be based on the intention-to-treat population. Categorical variables will be described as numbers and percentages. Continuous variables will be presented as means and standard deviations. The 2 groups will be compared using the Pearson χ^2 test or Student's t-test. Changes in the NT-proBNP levels will be transformed with a log value and analyzed using an independent t-test. Changes in the edema index and serum creatinine levels will also be compared using an independent t-test. The correlation between NT-proBNP and body water composition will be analyzed using correlation analysis. All p values will be two-sided, and p-values <0.05 will be considered statistically significant.

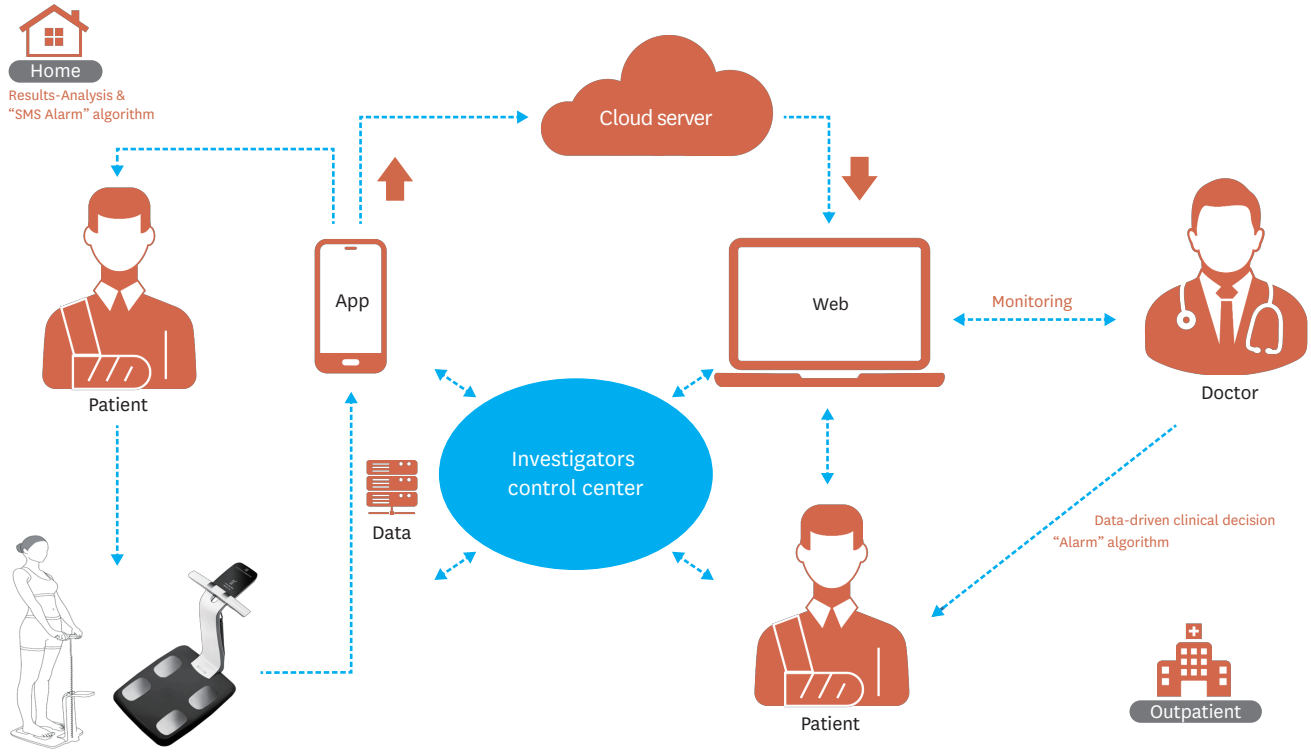

Figure 2. The management of HF using home BIA and linked application system.
HF = heart failure; BIA = bioelectrical impedance analysis.

DISCUSSION

This study is designed for a pilot trial based on the hypothesis that continuous body water monitoring using BIA can reflect the change of extracellular volume status in patients with HF in advance. The primary goal of this trial is to verify the feasibility of home BIA body water monitoring-guided HF treatment with useful support based on data from the patient's body water status.

BIA has been used as a method of measuring volume status non-invasively.[13] Estimation of water status by BIA has been validated in patients with liver and kidney disease.[14,15] Recently, obtaining more accurate body water measurement has been possible by reflecting both intracellular and extracellular water using multiple frequencies, and it is possible to accurately measure body water even in patients with unusual body water conditions such as those of patients with heart failure status.[13,16,17] Previous studies showed that BIA is a valuable tool in the early diagnosis of dyspnea from acute decompensated HF.[18] Furthermore, Martínez et al. found a significant correlation between the NYHA functional class for dyspnea and bioimpedance parameters by BIA.[19] Despite HF symptoms and signs due to worsening HF not being recognized until just 7 days and 3 days before hospitalization events, respectively, the changes of bioelectrical impedance are detected approximately 2 weeks before HF hospitalization.[9] This is the key benefit of body water monitoring using BIA.

Among various parameters from BIA data, most notably, the edema index, which represents the ratio of extracellular water to total body water measured by BIA, can be a surrogate for extracellular volume status.[13,20] The edema index was proven to have a 6-month prognostic value in patients with acute decompensated HF, and a higher edema index was significantly correlated with B-type natriuretic peptide (BNP) and HF-related re-hospitalization.[21] A small randomized controlled trial also showed that edema index-based HF management decreased acute HF events in a 6-month follow-up duration.[22]

To reduce HF re-hospitalization events, many trials have investigated various modalities for monitoring patients with chronic HF after discharge. Using biomarkers, particularly BNP or NT-proBNP-guided treatment for HF with reduced ejection fraction, produced insufficient results in previous studies.[23,24] Hemodynamic-guided HF management using implantable pulmonary artery pressure monitoring showed beneficial effects in patients with HF with NYHA functional class III and a history of recent HF hospitalization.[25] However, a recent larger-scale trial did not demonstrate a significant efficacy of hemodynamic-guid-

ed HF management in patients across the spectrum of ejection fraction and symptom severity.[8] Implantable device monitoring is invasive and expensive, and there is insufficient evidence for benefits such as reducing HF hospitalization and mortality.[6,26]

Although the efficacy has only been proven in small-scale studies to date, BIA provides easy measurement and is non-invasive and cost-effective; thus, continuous body water monitoring using a home BIA device may be a promising therapeutic option in patients with chronic HF.

CONCLUSION

The current pilot study will evaluate the efficacy and safety of home BIA body water monitoring-guided HF treatment in patients with HF. We believe that the results of this study will provide supportive evidence for this novel fluid overload monitoring modality in patients with HF.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Examples of the message direction using an algorithm for extra-diuretics in home BIA group

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Kong MG, Kim EJ; Data curation: Moon I, Seo HS, Suh J, Choi JY, Na JO; Formal analysis: Min Gyu Kong; Funding acquisition: Kim EJ; Investigation: Kong MG, Moon I, Seo HS, Suh J, Choi JY, Na JO; Methodology: Kong MG; Project administration: Kong MG, Kim EJ; Resources: Kim EJ; Supervision: Kim EJ; Writing - original draft: Kong MG, Kim EJ; Writing - review & editing: Kim EJ.

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