Original Article

Efficacy of Oral Acetazolamide as Add-on Diuretic Therapy in Decongestion in Patients with Heart Failure: A Study Protocol for a Randomized Controlled Trial

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Abstract

Background: *Acute heart failure is a common clinical syndrome leading to hospital admission, with few evidence-based therapies for managing congestion. This trial aims to assess the efficacy of acetazolamide combined with loop diuretics in achieving decongestion among patients who fail to respond to oral diuretics and progress to acute decompensated heart failure in the absence of injectable furosemide.*

Methods: *This single-center, double-blind randomized controlled trial with a 1:1 allocation ratio aims to evaluate 130 patients admitted to the infusion ward. Participants will receive standard furosemide treatment and be randomized to either oral acetazolamide (250 mg twice daily) or placebo for 3 consecutive days. The primary objective is to assess the efficacy of combined oral acetazolamide and furosemide therapy in achieving decongestion. The prespecified secondary outcomes include the following: N-terminal pro-B-type natriuretic peptide levels on day 30, readmission rates within 3 months, health-related quality of life as assessed by the Heart Failure Quality of Life Questionnaire at 3 months, and changes in weight, creatinine levels, urinary sodium excretion, potassium levels, and hematological indices from the complete blood count on day 3 of the trial.*

Conclusion: *Diuretic resistance commonly occurs in patients with heart failure, underscoring the urgent need for innovative interventions that can effectively address the limitations of current diuretics, including diuretic resistance and electrolyte imbalances, while enhancing their efficacy in this patient population.*

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Introduction

Cardiovascular disease remains the first killer in Western countries, and its burden continues to be extremely high.[1] Heart failure (HF) is a debilitating chronic disease and a heterogeneous clinical syndrome stemming from cardiac overload and injury, resulting in considerable morbidity and mortality, poor functional capacity, reduced quality of life, and high financial costs.[2,3] Acute heart failure (AHF), as a clinical syndrome characterized by the rapid onset or worsening of HF symptoms, is among the most common causes of hospital admission, particularly in patients older than 65, and its pathophysiology and management are less understood compared with chronic HF.[4,5]

Fluid management is crucial to relieving volume overload and hospital admission control.[6,7] Patients with HF currently face new challenges due to diuretic resistance as a growing clinical problem.[8] Loop and thiazide diuretics are the primary diuretic therapy choices. Other nephron tubular sites for diuretic blockage have not been commonly utilized and could, thus, serve as other targets for intervention.[6]

Patients with HF often have multiple electrolyte imbalances, such as hyponatremia, hypokalemia, and hypochloremia.[9] Chloride was recently identified as crucial to HF pathophysiology, and its strong prognostic value has been the subject of much attention.[9-11] The observations in a contemporary advanced acute decompensated heart failure (ADHF) cohort conducted by Grodin JL et al[12] suggested that serum chloride levels at admission were independently and inversely associated with mortality. In the chloride theory, chloride plays a critical role in controlling the reabsorption of electrolytes and water in the kidneys through the renin-angiotensin-aldosterone system and in distributing body fluids among different compartments.[11] Thus, based on this hypothesis,[13] chloride manipulation, including the use of acetazolamide,[14] may be an essential therapeutic target in HF treatment.[11]

Acetazolamide, a carbonic anhydrase inhibitor that inhibits sodium absorption in the proximal tubule, is a potent chloride-reabsorbing diuretic that also aids in lowering blood potassium levels. This agent greatly modulates serum electrolytes (eg, hypochloremia correction) and provides the necessary stability for administering mineralocorticoid receptor antagonists.[11]

In this randomized controlled trial (RCT) in Iranian patients with signs of volume overload without intravenous diuretics, we aim to determine whether oral acetazolamide can improve the efficacy of loop diuretics, potentially leading to more natriuresis. Urinary sodium excretion is considered a measure of diuresis, and increased natriuresis is deemed a measure of congestion relief. We also aim to evaluate the quality of life in patients with HF through a questionnaire.

This study protocol discusses the rationale and detailed methodology of the trial with a prespecified approach.

Methods

This study is a single-center, double-blind RCT with a 1:1 ratio to evaluate the effects of oral acetazolamide on diuresis and decongestion in Iranian patients with HF. The research will be conducted on HF patients whose congestion symptoms persist despite oral diuretics and necessitate temporary hospitalization in the infusion ward for intravenous diuretic administration. The infusion unit is a dedicated section for patients with HF failing to respond adequately to oral diuretics and requiring short-term treatment with injectable furosemide.

Patients who, according to expert opinion, do not experience effective relief from congestion with oral diuretics, will be admitted to the infusion unit for weekly furosemide injections. Eligibility criteria for this trial are presented in Table 1 and Table 2.

This study will employ acetazolamide tablets (250 mg) and placebos manufactured by the Iran Daru Pharmaceutical Company, as well as 20 mg vials of furosemide. Patient medical information will be documented. Clinical assessments will include the calculation of the EVEREST score at baseline and on the third day.[15] Weight and laboratory indices will be measured at baseline and on the third day with standardized scales and laboratory kits. Blood pressure will be measured at baseline and daily before furosemide injection by a qualified nurse with the

Table 1. EVEREST score calculation

Sign/Symptom	0	1	2	3
Dyspnea	None	Seldom	Frequent	Continuous
Orthopnea	None	Seldom	Frequent	Continuous
Fatigue	None	Seldom	Frequent	Continuous
JVD (cm H2O)	≤6	6–9	10–15	≥15
Rales	None	Bases	To<50%	To>50%
Odema	Absent/trace	Slight	Moderate	Marked

JVD, Jugular venous distention

Table 2. Eligibility criteria

Inclusion Criteria	
	1. Earn at least 8 points from the EVEREST score (See Table 1.) 2. Adult patients (≥18 y) 3. A major clinical sign of volume overload, including edema, ascites confirmed by abdominal ultrasound, or pleural effusion confirmed by chest X-ray or chest ultrasound without using intravenous furosemide 4. Maintenance treatment with oral furosemide as a loop diuretic ≥20 mg for at least 1 month 5. Using SGLT2i drugs, including canagliflozin, dapagliflozin, and empagliflozin, for at least 1 month
Exclusion Criteria	
	1. Systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg 2. eGFR<20 mL/min/1.73 m2 3. Using any diuretic agent except mineralocorticoid receptor antagonists, including spironolactone and eplerenone 4. Simultaneous diagnosis of acute coronary syndrome, characterized by typical chest pain in addition to an increase in troponin levels >the 99th percentile or electrocardiographic changes indicating ischemia or hospitalization as unstable angina

SGLT2i, Sodium-glucose co-transporter 2 inhibitor; eGFR, Estimated glomerular filtration rate

same blood pressure cuff. Patients will undergo follow-ups for clinical events up to day 90. The study protocol has been developed in accordance with the Standard Protocol Items for Clinical Trials (SPIRIT) guidelines for random-ized clinical trial protocols.

The primary objective is to determine the efficacy of combination therapy involving oral acetazolamide and fu-rosemide, a loop diuretic, in improving congestion in patients at baseline and on the third day. An indicator of this objective will be the measurement of the urinary sodium-to-creatinine ratio at 2 PM on these specified days.

The prespecified secondary objectives consist of assessing N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels on day 30; determining the hospitalization rate within 3 months; comparing the quality of life between the 2 groups at the end of the third month; evaluating changes in weight, creatinine levels, urinary sodium excretion, potassium levels, and hematological indices in the complete blood count (CBC) on the third day of the trial; and filling out the Iranian Heart Failure Quality of Life (IHFQoL) Questionnaire at the end of the third month. The questionnaire consists of 16 questions organized into 5 dimensions, and its validity and reliability have been confirmed (Kornbach's α coefficient= 0.922). The questionnaire offers total scores ranging from 20 to 66, with higher scores indicating a better quality of life. The 5 dimensions of this survey encompass the severity of disease symptoms (items 1, 2, 3, 4, and 6), physical limitations (items 7-1 to 7-6), mental limitations (items 5, 9, and 11), social aspects (items 8, 10, 12, and 13), self-care (items 14 and 15), and the patient's overall satisfaction (item 16).[16]

This 1:1 ratio parallel RCT will feature 1 intervention arm and 1 comparator arm.

Intervention: Injectable and oral furosemide will be administered in the infusion ward based on the specialist's prescribed dosage on day 0. Oral furosemide administration will continue for 3 days. The specialist will determine the prescribed dose of the injectable and oral furosemide based on the patient's previous visits and hospitalizations to minimize symptoms. The intervention group will receive a 500 mg acetazolamide tablet on day 0, followed by 250 mg twice daily for 2 days and 250 mg on the third day.

Comparator: The control group will receive a placebo equivalent to acetazolamide in addition to standard therapy with intravenous furosemide on the first day and oral furosemide for 3 consecutive days.

Before the start of the study and on the third day, the patient's urine sodium-to-creatinine ratio, potassium, venous blood gas, CBC, and weight will be measured.

In the event of acidosis (serum sodium bicarbonate<20 mmol/L) or hypokalemia (serum potassium<4 mmol/L), 8 mL of NaHCO3 8.4% and 40 mmol of potassium chloride will be injected, respectively, based on a specific protocol taken from the ADVOR trial.[15]

In the instance of systolic blood pressure below 90 mm Hg or mean arterial pressure below 65 mm Hg, the drugs will be held and then resumed after recovery.

In the circumstance of acetazolamide-induced agranulocytosis or thrombocytopenia as rare but potential adverse events, the drug will be discontinued, and the patient will be under close bone marrow monitoring (Figure 1).

Safety oversight will be conducted by the Data and Safety Monitoring Board (DSMB), comprised of individuals possessing the requisite expertise.

Avoidance of conflicts of interest: The DSMB operates independently of the steering committee and the authors of the study. The board will convene weekly to evaluate safety and efficacy data from each arm of the study. Every DSMB member will be granted complete access, including access to personal information and the random allocation of each participant, via secure usernames and passwords within the electronic database. Additionally, the DSMB members will receive official weekly reports from the Clinical Events Committee (CEC). Subsequently, the DSMB will

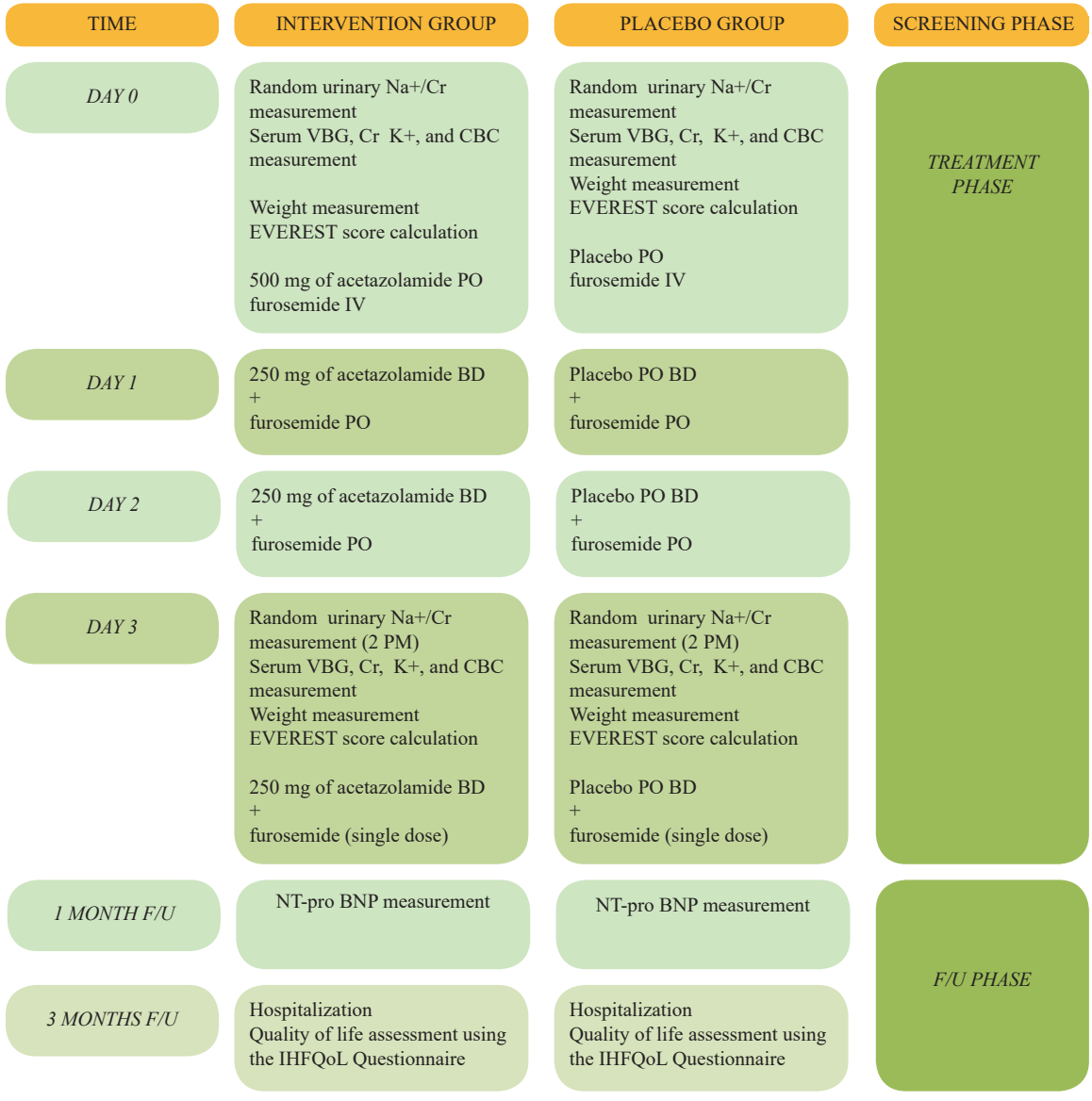

Figure 1. The image depicts the study flowchart
Na+/Cr, Sodium/creatinine ratio; VBG, Venous blood gas; Cr, Creatinine; K+, Potassium; CBC, Complete blood count; PO, Orally; IV, Intravenous; BD, Twice daily; NT-proBNP, N-terminal pro B-type natriuretic peptide; F/U, Follow-up; IHFQoL, Iranian Heart Failure Quality of Life

offer its recommendations to Tehran Heart Center, with a specific focus on the infusion ward and the study's principal investigator.

In terms of criteria for halting the study due to safety concerns, the DSMB will conduct analyses once 25% and 50% of the target population have been recruited. The goal is to assess whether there is a statistically significant increase in the primary endpoint, rehospitalization due to ADHF, or significant changes in CBC and acidosis in the intervention arm compared with the control group. This assessment will be based on a P-value threshold of 0.01. Early termination due to safety concerns will be considered if there is an absolute 10% excess in life-threatening infections or ketoacidosis, with a 2-sided P value of 0.025. The decision to terminate the study early due to safety concerns will be contingent upon the absence of counterbalancing efficacy improvements, as determined by the DSMB's discretion.

The criteria for early study termination due to safety concerns in the intervention arm will also encompass an excess in the primary endpoint, rehospitalization due to ADHF, or significant changes in CBC and acidosis, with a P-value threshold of 0.01. The DSMB will promptly communicate any safety concerns or other oversight issues to the study's principal investigator.

Based on the ADVOR trial,[15] the occurrence rates of the primary endpoint in the intervention and control groups were 42.2% and 30.5%, respectively. The prespecified significance threshold for all the primary and secondary endpoints was a P value of less than 0.05. Statistical type Π (β) error and study power were considered at 20% and

80%, respectively, in calculations. The hypothesis was considered 2-tailed. Attrition was considered 10%, and the total sample size was calculated for the primary objective with the G power 3.1 statistical software. Consequently, the total number of patients who will be included in the study will be 130, with each arm consisting of 65 patients.

Randomization will be conducted by an independent expert using a concealed centralized web-based system based on a computer-generated randomization sequence and using permuted block sizes of 3. In total, 130 patients will be randomized in a 1:1 ratio to furosemide plus acetazolamide (the intervention arm) or furosemide plus placebo (the control arm).

The tablets will be identified by a trained expert with separate codes (1 and 2) in order to blind the study participants and their caregivers, investigators, and outcome assessors.

The normality will be tested with the Kolmogorov-Smirnov test. Quantitative variables with normal distribution will be reported as mean±standard deviation and will be compared using the independent ANOVA test. Variables with non-normal distributions will be reported with medians and interquartile ranges (IQRs). Qualitative variables with reported frequencies and percentages will be compared, and the $\chi 2$ or Fisher exact test will be used to compare the 2 groups. For multivariable analysis, binomial logistic regression will be conducted to evaluate the influence of the baseline variables on the primary outcome. The effects of acetazolamide on relieving congestion with relative risk and the corresponding confidence interval will be calculated and reported. Additionally, if there are missing data in each group, primary analyses will be performed via 2 complementary strategies: sensitivity analysis according to the intention-to-treat principle and the per-protocol analysis. Analyses of the primary outcome will be conducted in advance to determine any interactions between age, sex, diabetes mellitus, and ischemic cardiomyopathy.

The study protocol and signed patient informed consent will be approved by the Iran National Committee for Ethics in Biomedical Research (the code of ethics: IR.TUMS.THC.REC.1402.016) and will adhere to the ethical guidelines outlined in the 1975 Helsinki Declaration. The study's principal investigator will explain the study goals, each investigational therapeutic strategy, and the potential risks and benefits of participating in the trial to the patients or their next of kin if the participants are not conscious or able to make decisions. A written informed consent form will be signed by the patients or their next of kin. During and after the trial, the researchers ensure that adequate medical care is provided to the participants whenever any adverse event or complication associated with the trial occurs. Any adverse events or complications arising from this study will be promptly disclosed to the participants, who will be closely monitored and appropriately managed free of charge.

The study was registered at the Iranian Registry of Clinical Trials (IRCT) on 2023/07/08 (the registration reference: IRCT20230527058306N1).

Discussion

This randomized, double-blind parallel-controlled trial will provide evidence of the effectiveness of oral acetazolamide in improving the efficacy of loop diuretics and decongestion in Iranian patients with HF.

Acetazolamide, a carbonic anhydrase inhibitor, is present in the proximal tubule of the nephron and red blood cells. It usually works to reabsorb sodium, bicarbonate, and chloride.[17] By the inhibition of carbonic anhydrase, these substances are excreted instead, eliminating excess water and decreasing intracranial, intraocular, and blood pressure.[17]

Available dosages of acetazolamide are 125 mg and 250 mg of immediate-release tablets and 500 mg of extended-release capsules. Intravenous administration of acetazolamide is also available.[18]

Acetazolamide can lead to various general and specific side effects. Patients may experience fatigue, nausea, vomiting, abdominal pain, diarrhea, paresthesia, black stools, decreased libido, tinnitus, and taste alterations. There are also reports of patients developing depression or a bitter or metallic taste. Less commonly, there is a risk of developing metabolic acidosis, hyponatremia, and hypokalemia. Kidney stones, albeit uncommon, can also be seen. Rare side effects, such as Stevens-Johnson syndrome, aplastic anemia, agranulocytosis, toxic epidermal necrolysis, and fulminant hepatic necrosis, also exist.[19,20]

Acetazolamide is administered for the treatment of central sleep apnea and Marfan syndrome, as well as the prevention of high-dose methotrexate nephrotoxicity and contrast-induced nephropathy in non–FDA-approved indications, and the treatment of glaucoma, idiopathic intracranial hypertension, altitude sickness, periodic paralysis, epilepsy, and congestive heart failure in FDA-approved indications.[21]

Several studies have investigated the impact of acetazolamide administration and suggested a potential benefit, especially in combination with loop diuretics, in the treatment of fluid overload in heart failure.[22-24] Kataoka et al[25] administered acetazolamide to patients with both ADHF and chronic HF and observed that chloride levels increased and remained stable for a minimum of 60 days. In another RCT conducted by Verbrugge et al,[7] acetazolamide was added to low-dose loop diuretics in the treatment arm, enhancing effectiveness. Additionally, the ADVOR trial will examine the hypothesis that adding intravenous acetazolamide to loop diuretics could improve decongestion and clinical outcomes in ADHF.[22,23]

The salient limitation of our study is the use of the urine

sodium-to-creatinine ratio as a surrogate for 24-hour urine collection since the participants are not hospitalized and are seen in an outpatient heart failure clinic setting. Furthermore, due to financial constraints, we are unable to utilize NT-proBNP as an entry criterion and have, thus, employed alternative criteria. Another noteworthy consideration is the sample size: it would be beneficial to increase the sample size in order to obtain more reliable results.

Conclusion

HF is a multifaceted and life-threatening syndrome with a high social and economic burden. Entering the acute phase is a common complication experienced by patients with HF. There is an urgent need to find novel interventions that effectively and safely overcome the shortcomings of existing diuretics, such as diuretic resistance and electrolyte abnormalities, and improve their performance in patients with ADHF.

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