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Original Article

Efficacy of acetazolamide and loop diuretics combinatorial therapy in congestive heart failure: A meta-analysis

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Abstract

Acetazolamide, one of the carbonic anhydrase inhibitors, has been known to improve the efficacy of diuretic therapy in patients with in congestion heart failure. The aim this study was to investigate the effectiveness of acetazolamide when combined with loop diuretics in ameliorating diuresis and natriuresis in congestive heart failure using systematic review and meta-analysis. Randomized controlled trials (RCTs) and cohort studies were searched on PubMed, Scopus, and Embase on March 7, 2023, by using combinations of 'acetazolamide', 'heart failure' and along with their respective synonyms. The protocol had been registered on PROSPERO (CRD42023409864). The studies must investigate the effect of oral acetazolamide as the add-on to loop diuretic therapy to be included. Successful decongestion, natriuresis, and diuresis were set as the primary outcomes. The quality of the included studies was assessed using the Cochrane risk-of-bias tool for RCTs and Newcastle Ottawa Scale for observational studies. We identified 1176 titles in the initial search, and further reduced to five studies (three RCTs and two cohort studies) after in-depth screening. A total of 625 patients were recruited in the included studies published from 2015 to 2022. Results from meta-analysis revealed that acetazolamide and loop diuretics combination therapy ameliorated natriuresis (n=4; standardized means difference (SMD): 0.65; 95%CI: 0.07–1.24; p=0.03) and diuresis (n=2; SMD: 0.29; 95%CI: 0.12–0.46; p=0.0009) when compared to loop diuretics alone. Acetazolamide and loop diuretics combinatorial therapy is efficacious in alleviating congestion in heart failure patients.

Keywords: Acetazolamide, carbonic anhydrase inhibitor, heart failure, loop diuretics, decongestion

Introduction

The prevalence of heart failure is high and become a major public health problem that has an estimated effect on 26 million people worldwide with the occurrence of high mortality, morbidity, and hospitalization [1-5]. The hospitalization of heart failure patients is mainly caused by the signs and symptoms of congestion [6]. Congestion in heart failure patients is associated with poor clinical outcomes, extended lengths of stay in the hospital, and elevated mortality rates [7,8].

Several decades ago, the diuretic that was used to achieve decongestion in heart failure was acetazolamide. Acetazolamide acts as a carbonic anhydrase inhibitor that blocks sodium and bicarbonate reabsorption in the proximal renal tubular, promoting fluid excretion [6]. However,

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the use of acetazolamide to treat fluid overload in heart failure patients has been abandoned since the emergence of loop diuretics which are considered to be more potent [9,10]. Differently from acetazolamide, loop diuretics decreased sodium and chloride reabsorption from urine by blocking the $Na^+/2Cl^-/K^+$ cotransporter of the thick ascending loop of Henle [11]. Nowadays, in the occurrence of volume overload, the current guideline by the American Heart Association /American College of Cardiology/Heart Failure Society of America joint committee) recommends the administration of loop diuretics, both in the acute and chronic phases of heart failure [12].

Nonetheless, acetazolamide has a big potential to be used as an adjunct therapy with loop diuretics to alleviate the plasma volume overload among heart failure patients. Acetazolamide inhibits the reuptake of sodium bicarbonate in the proximal tubules of the kidney which increased the supply of sodium to Henle's loop, hence it has a boosting effect on loop diuretics especially in cases of reduced renal blood flow [13]. An observational study in acute heart failure has witnessed that the use of acetazolamide as an add-on therapy improves the efficiency of loop diuretics [14]. Moreover, acetazolamide also inhibits the pendrin system in the distal nephron, which might be a candidate mechanism of diuretic resistance [15]. Despite being supported by growing bodies of evidence for its potential, systematic review and meta-analysis on acetazolamide as adjunct therapy for loop diuretics are still underreported.

Methods

Protocols and registration

Protocols for this present systematic review and meta-analysis were designed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The protocols have been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number: CRD42023409864.

Search strategy

Search for the published records were carried out on March 7, 2023, utilizing the searching feature available on PubMed, Scopus, and Embase. A combination of keywords 'acetazolamide' and 'heart failure' was used, along with the synonyms from the respective keyword. Boolean operators ('OR'/'AND') were employed in the three databases, and the complete keyword combinations have been presented in **Table 1**.

Table 1. Keyword combinations used in each database

Database	Keyword combination
PubMed	("acetazolamide" OR "carbonic anhydrase inhibitor") AND ("heart failure" OR "acute decompensated heart failure" OR "congestive heart failure")
Embase	('acetazolamide':ti,ab,kw OR 'carbonic anhydrase inhibitor':ti,ab,kw) AND ('heart failure':ti,ab,kw OR 'acute decompensated heart failure':ti,ab,kw OR 'congestive heart failure':ti,ab,kw)
Scopus	TITLE-ABS-KEY (("acetazolamide" OR "carbonic anhydrase inhibitor") AND ("heart failure" OR "acute decompensated heart failure" OR "congestive heart failure"))

Inclusion and exclusion criteria

Inclusion and exclusion criteria in this study adopt the PICOS framework (population, intervention, control, outcome, and study design) [16], which has been presented below: (1) Population: patients who have been diagnosed with heart failure and developing congestion; (2) Control: a single therapy of loop diuretic; (3) Outcome: diuresis, natriuresis, fluid balance, N-terminal pro-B-type natriuretic peptide (NTproBNP), serum chloride concentration, and successful decongestion; (4) Study: randomized clinical trials (RCTs) and observational studies. Studies were excluded if having one of the following criteria: (1) participated by patients with comorbidities that contribute to the congestion such as pulmonary embolism, stage 5 chronic kidney disease, and hypotension; (2) published in languages other than English; (3) not reporting one of the outcomes of interest; (4) acetazolamide was used in combination with add-ons; (5) review articles, case reports, conference proceedings, and abstracts, editorials, commentaries.

Screening and selection of the records

We used PRISMA guideline to guide our screening and selection process which were carried out by two independent reviewers (M.A. and N.H.) [17]. Duplicates were immediately removed once the identified records were imported to Mendeley Desktop v1.19.8. The screening process was then conducted based on the 'Title' and 'Abstract', and selectively reduced by full-text screening according to the predetermined inclusion/exclusion criteria. Discrepancies in the final results were resolved by re-evaluating the articles and discussing them until a consensus was reached. Consultation with the third reviewer (M.I.) was done when the discrepancies persisted.

Data extraction

From the included studies, we collected the studies' characteristics, patients' characteristics, group assignment (acetazolamide versus control), treatment details, and related outcomes. Patients' characteristics included gender (male or female, %) and age (mean ± standard deviation (SD), years old). Treatment details were collected as the dosage and administration frequency and length of the treatment duration. Outcome parameters of diuresis, natriuresis, fluid balance, N-terminal pro-B-type natriuretic peptide (NTproBNP), serum chloride concentration, and successful decongestion were collected. Continuous data and dichotomous data were presented as mean and percentage (%), respectively. Data conversion was only performed for those presented as median, converted to mean using the equation reported previously [18]. Other than that, the difference in units would be resolved by employing standardized means difference (SMD).

Quality assessment

To assess the quality of the included studies we employed Cochrane risk-of-bias tool and Newcastle Ottawa Scale for RCTs and observational studies, respectively. The assessment was performed independently by two reviewers (M.A. and T.F.D.). The studies were rated as having 'low', 'high', or 'unclear' risk of bias according to the criteria in Cochrane risk-of-bias tool for group assignments, blinding, data calculation and interpretation, and other sources of biases. The studies were categorized as 'high quality' if the overall score from Newcastle Ottawa Scale was ≥7 based on the selection, comparability, and outcome criteria.

Data analysis

Meta-analysis was only performed for outcomes that are reported in at least two studies. Forest plots were generated on the software developed by Cochrane Collaborations – RevMan version 5.4.1. SMD and 95% confidence interval (95%CI) were calculated by comparisons of outcomes obtained in acetazolamide versus control groups. SMD, 95%CI, p-value (statistical significance cut-off $p<0.05$), and z-value were used to evaluate the effect of acetazolamide as compared to the control. Heterogeneities in study designs (administration frequency, dosage, and other study settings), as well as the patients' characteristics, were resolved by using random-effect models. A cut-off of $I^2 \geq 50\%$ was used as the heterogeneity indicator [19]. Publication bias analysis using funnel plot was subjected to outcome(s) of interest reported in more than 10 studies [20,21].

Results

Characteristics of the included studies

The literature search and selection process workflow, along with the number of publications obtained from each step, are presented in **Figure 1**. We identified 1176 articles through our systematic search in the three databases. After duplicate removal, 836 articles were excluded in the title and abstract screening and full-text screening phases, respectively, after applying our inclusion criteria. Finally, among the five studies (625 patients) included in our systematic review, involving three RCTs and two cohorts. Moreover, four studies were eligible and included in the meta-analysis (**Figure 1**). One study was not included since insufficient data for the forest plot [22].

Table 2. Characteristics and outcome of the included studies

Author, years (Ref)	Design	Funding institution	Characteristics	Treatment[a]		Outcome
				Experimental	Control	
Verbrugge, *et al.*, 2015 [14]	Cohort	Research Foundation - Flanders; foundation Limburg Sterk Merk	n=9 (exp); 17 (con) Age (years): 67±13 (exp+con) M/F: 40/14 (exp+con) EF <45%: patients with CHF NYHA II-IV	Mean dose: 250 mg ALD + 2 mg LD Follow-up period: 188 days Background therapy: RAB 50%; BB 70%; MRA43%; D 11%; LD 63%	Mean dose: 2 mg LD Follow-up period: 188 days Background therapy: ARB 50%; BB 70%; MRA43%; D 11%; LD 63%	Natriuresis
Imiela and Budaj, 2017 [24]	RCT	Centre of Postgraduate Medical Education	n=10 (exp); 10 (con) Age (years): 73.0±8.6 (exp); 71.2±14.4 (con) M/F: 8/2 (exp); 9/1 (con) EF <50%: patients with CHF NYHA II-III	Mean dose: 250 mg ALD + 90 mg LD[b] Follow-up period: 4 days Background therapy: ACE-I/ARB 80%; AS 50%; ST 80%; BB 90%; AB 50%; AM 70%; OAC/LMWH 70%; PPI 70%	Mean dose: 122 mg LD[b] Follow-up period: 4 days Background therapy: ACE-I/ARB 80%; AS 60%; ST 50%; BB 100%; AB 70%; AM 50%; OAC/LMWH 80%; PPI 90%	Natriuresis, diuresis, fluid balance
Verbrugge, *et al.*, 2019 [23]	RCT	Research Foundation – Flanders; foundation Limburg Sterk Merk	n=18 (exp); 16 (con) Age (years): 81±6 (exp); 78±7 (con) M/F: 11/7 (exp); 11/5 (con) EF <50%: patients with CHF NYHA II-IV	Mean dose: 250–500 mg ALD + 3–4 mg LD Follow-up period: 34 months Background therapy: ACE-1/ARB: 39%; BB: 89%; MRA: 56%	Mean dose: 6 mg LD Follow-up period: 34 months Background therapy: ACE-1/ARB: 44%; BB: 94%; MRA: 63%	Natriuresis, NTproBNP
Kataoka *et al.*, 2019 [22]	Cohort	Not declared	n=12 (exp); 18 (con) Age (years): 86.2±5.46 (exp); 83.6±8.99 (con) M/F: 2/10 (exp); 7/11 (con) N/A: patients with CHF NYHA II-IV	Mean dose: 250–500 mg ALD + LD Follow-up period: 60 days Background therapy: ACE-I/ARB: 33%; BB: 33%; CA: 42%; MRA: 50%; TD: 8%; LD: 75%; T: 17%	Mean dose: LD Follow-up period: 60 days Background therapy: ACE-I/ARB: 33%; BB: 33%; CA: 39%; MRA: 61%; TD: 33%; LD: 61%; T: 22%	Serum chloride
Mullens *et al.*, 2022 [25]	RCT	Belgian Health Care Knowledge Center	n=260 (exp); 259 (con) Age (years): 77.9±9 (exp); 78.5±8.8 (con) M/F: 155/105 (exp); 170/89 (con) EF <40% or >40%: patients with acute decompensated heart failure and clinical signs of volume overload	Mean dose: 500 mg ALDb + 40 mg LDb Follow-up period: 3 months Background therapy: ACE-I/ARB: 50.2%; BB: 79.9%; MRA: 43.6%	Mean dose: placebo + 40 mg LDb Follow-up period: 3 months Background therapy: ACE-I/ARB: 53.8% P; BB: 81.5% P; MRA: 39.6% P	Successful decongestion, Natriuresis, Diuresis

AB: antibiotics; ACE-I: angiotensin-converting enzyme inhibitor; ALD: acetazolamide with loop diuretic; AM: amiodarone; ARB: angiotensin receptor blockers; AS: aspirin; BB: b-blocker; CHF: chronic heart failure; con: control; EF: ejection fraction; exp: experimental; F: female; LMWH: low molecular weight heparin; LD: loop diuretic; M: male; MRA: mineralcorticoid receptor antagonist; NYHA: New York Heart Association functional class; OAC: oral anticoagulants; RCT: randomized controlled trials; ST: statin

[a]Otherwise stated, the administration via oral route

[b]Intravenous

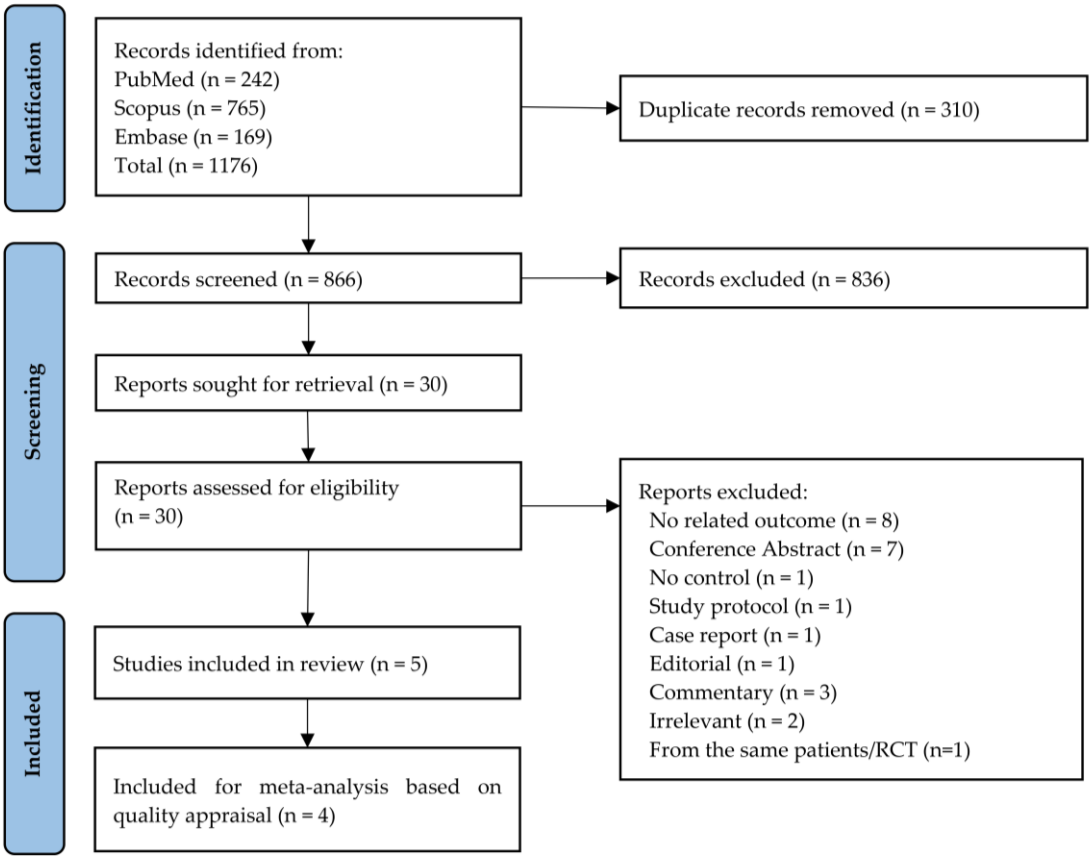

Figure 1. PRISMA flow-chart of the included studies that reported the efficacy of acetazolamide in ameliorating congestion among heart failure patients.

All studies recruited chronic or acute heart failure patients with left ventricular ejection fraction (EF) <50%, had at least one clinical sign of volume overload (i.e., edema, pleural effusion, or ascites), and plasma N-terminal pro-B-type natriuretic peptide (NTproBNP) levels >1000 ng/L. Most of the studies administered acetazolamide as an adjunct therapy orally [14,22-24] (14,23-25), except for one study that was administered intravenously [25]. The follow-up duration across different studies ranged from four to 1020 days. Studies assessed several outcomes including diuresis, natriuresis, fluid balance, N-terminal pro-B-type natriuretic peptide (NTproBNP), serum chloride concentration, and successful decongestion.

Quality of the included studies

The summary risk of bias analysis for the RCTs design has been presented in **Figure 2**. Overall, all included studies performed randomized sequence generation, concealed the allocation process, reported all of the outcomes, and were not selective when reporting the data [14,22-25]. However, a study suffered performance bias and detection bias [25]. Additionally, for the observational study, the results have been presented in **Table 3**. The mean Newcastle Ottawa Scale obtained herein is eight, categorized as high quality.

Effect on successful decongestion

The effect on successful decongestion was only reported in one study [25]. Successful decongestion was measured by several parameters, *viz* no more than trace edema, no residual ascites, and no residual pleural effusion. The result revealed that successful decongestion occurred in 108 of 256 patients (42.2%) in the acetazolamide group and in 79 of 259 (30.5%) in the placebo group (risk ratio, 1.46; 95%CI: 1.17–1.82; $p<0.001$).

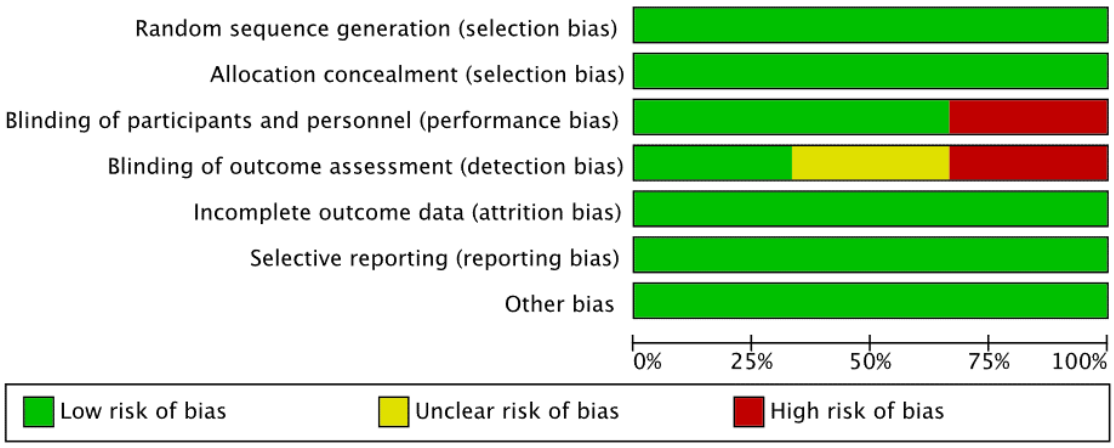

Figure 2. Summarized results of the quality appraisal based on Cochrane 5.2.0. risk of bias tool.

Table 3. Results from the quality assessment on observational studies using Newcastle Ottawa Scale

Author, years	Study design	Selection	Comparability	Outcome	Total score	Remark
Kataoka *et al.*, 2019	Cohort	★★★	★★	★★★	8	Good
Verbrugge *et al.*, 2015	Cohort	★★★	★★	★★★	8	Good

Effect on diuresis and natriuresis

The results of the random effect meta-analysis of the effect on diuresis and natriuresis have been presented in **Figure 3**. The effect of acetazolamide on natriuresis was assessed in four studies [14, 23-25]. The effect of acetazolamide therapy on natriuresis was statistically significant and favored the experimental group (n=4, SMD: 0.65, 95%CI: 0.07–1.24, p=0.03). The I^2 of this analysis exceeded the 50% threshold (71%).

The effect on diuresis was measured in two studies [24,25]. The effect of acetazolamide therapy on diuresis favored the experimental group with statistically insignificant (n=2, SMD: 0.29, 95%CI: 0.12–0.46, p=0.0009) (**Figure 3**). There is no heterogeneity in the analysis (I^2=0%).

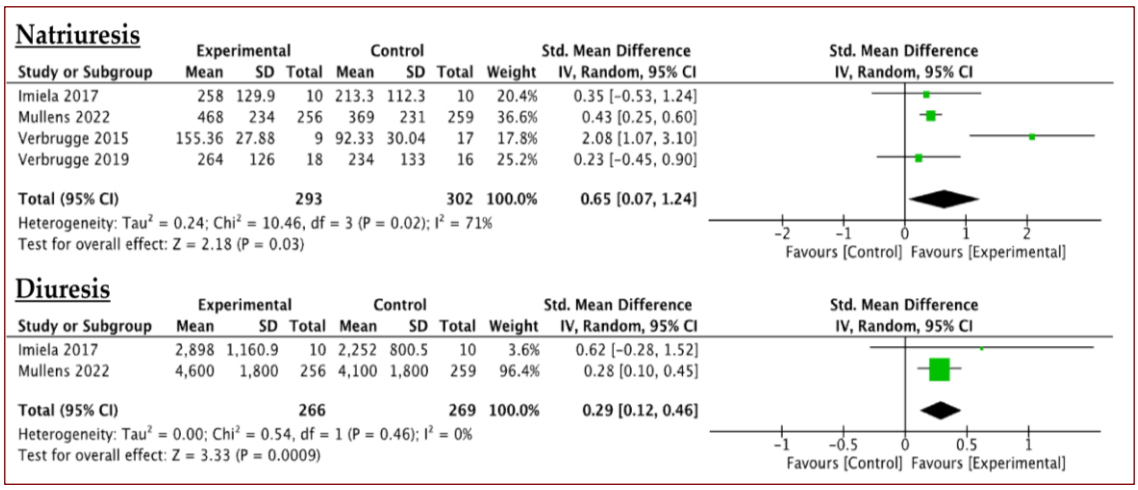

Figure 3. Forest plots for the efficacy of acetazolamide against diuresis and natriuresis in heart failure patients with congestion.

Effect on fluid balance

The effect on fluid balance was only reported in one study [24]. The study showed that acetazolamide effectively ameliorates the fluid balance among people with heart failure. The difference was statistically significant on day 4 (-666.0±1194.4 mL) and mean days 3 and 4 (-541.0±774.3 mL) between the acetazolamide and control groups.

Effect on serum chloride concentration

Serum chloride concentration increased in the short-term and the long-term observation periods compared to the baseline (paired t-test). Its effect to enhance the serum chloride concentration appears promptly within 10 days and persists for at least ~60 days [22].

Effect on plasma NTproBNP

The effect on fluid balance was only reported in one study [23]. Plasma NTproBNP levels decreased from 8165 ng/L (4242–20719 ng/L) to 6341 ng/L (3377–14034 ng/L) after 72 h in the combinational treatment arm (p=0.001). However, the relative change in NTproBNP levels was similar among treatment arms at -12±38% vs -9±40% (p=0.829).

Safety

Among 515 patients who received acetazolamide or placebo did not experience severe metabolic acidosis in the treatment phase. Moreover, the incidence of hypokalemia, hypotension, and combined renal safety endpoint was not different between groups and did not associate with the acetazolamide or placebo [25].

Publication bias

Unfortunately, our data were not sufficient for constructing the funnel plot which was aimed to identify publication bias since only five studies were included in the total. According to previous studies, funnel plot would not be able to generate reliable results if the studies were less than 10 [20,21].

Discussion

From the systematic review, it was found that a study reported a significantly higher number of successful decongestions in acetazolamide add-on group [25]. Since many patients were discharged without residual congestion, it can be considered as a significant achievement [26]. Residual discharges have been linked to poor outcomes, which further stresses the importance of acetazolamide in diuretic therapy [27]. Furthermore, significantly higher success rates were achieved for fluid balance [24], replenished chloride concentration [22], and NTproBNP [23] which were reported by a single study each. From a meta-analysis of pooled SMDs from four studies, groups receiving acetazolamide add-on had higher natriuresis (Z=2.18; p=0.03). Based on the meta-analysis of two studies, diuresis was achieved significantly higher in the treatment group (Z=3.33; p=0.0009). Large effect size and p-value suggest that combinatorial therapy of acetazolamide and loop diuretics is more efficacious in improving congestion as compared to loop diuretics alone.

Acetazolamide works by inhibiting carbonic anhydrase that is responsible in catalyzing the production of CO_2 and water from carbonic acid that occurs in proximal convoluted tubules [28]. In this part of nephron, a large portion of total tubular sodium reabsorption takes place, around 65% in normal conditions or 85% in cases of acute heart failure [13,29]. Moreover, it is worth noting that acetazolamide has a “non-reabsorbable anion-like effect”, which prompts the elimination of bicarbonate (HCO_3^-) through the urinary tubules while allowing the absorption of filtered chloride into the bloodstream [30,31]. This simultaneously leads to higher potassium excretion through urine. Inhibiting carbonic anhydrase in proximal convoluted tubules consequently causes increased concentration of sodium in subsequent tubular segments (such as Henle’s loop and distal tubules) which are affected by sodium reabsorption promoter – renin–angiotensin–aldosterone system [32,33]. This consequence of acetazolamide effect is actually beneficial for loop diuretics that work in more distal tubules by inhibiting $Na^+/2Cl^-/K^+$ cotransporter [33, 34]. The mechanisms of actions of acetazolamide and loop diuretics have been presented in **Figure 4**.

Other advantages of acetazolamide include its effect in improving sleep apnea [35], which is a common complication in the case of heart failure [36,37]. Further, acetazolamide might improve acid-base disorders (such as metabolic alkalosis) that prevalently occur during heart failure [38,39]. Moreover, heart failure patients developing blood alkalosis and urine acidosis have been associated with increased diuretic resistance [40]. These conditions could be mitigated

by acetazolamide since it acts in promoting tubular bicarbonate excretion and absorption of chloride ions into blood stream [41].

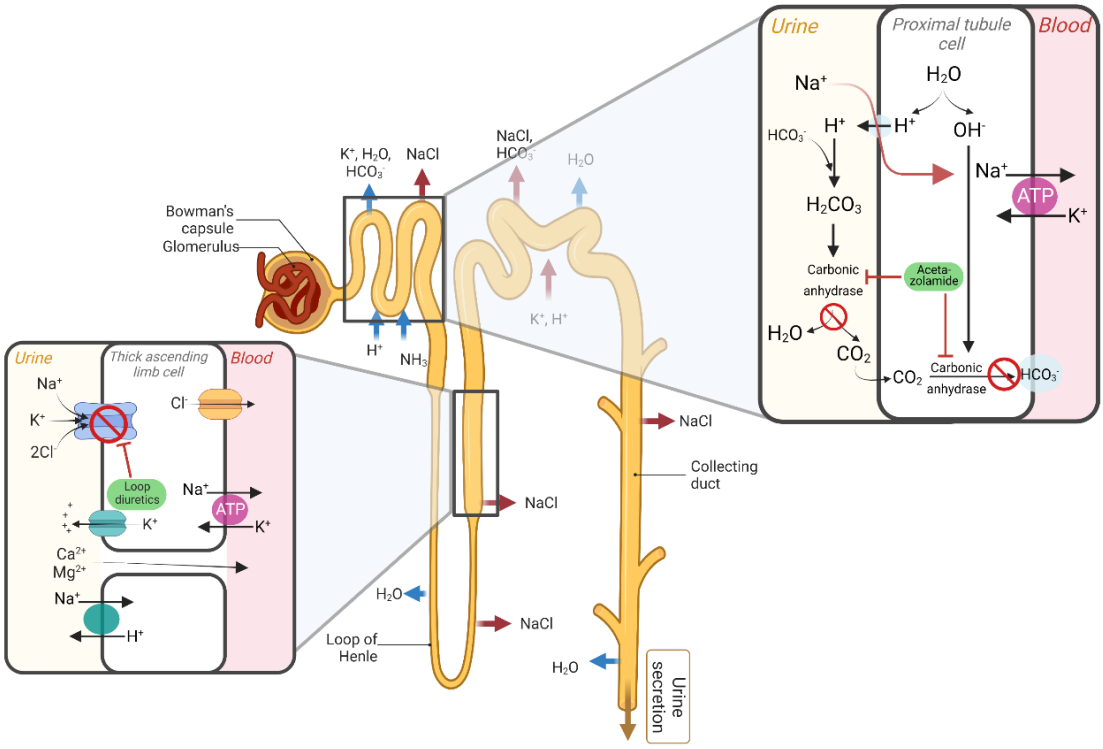

Figure 4. Mechanisms of actions of acetazolamide and loop diuretics in the proximal and distal tubules, respectively. Acetazolamide works by inhibiting the carbonic anhydrase that produces protons which are later exchanged with the tubular sodium ions and causes their reabsorption to the blood. Loop diuretics work by inhibiting $Na^+/2Cl^-/K^+$ co-transporter that effectively stops the reabsorption of tubular sodium ions. Combination of acetazolamide in the proximal tubules and loop diuretics in the end of the loop of Henle or distal tubules results in successful decongestion.

Congestion treatment with acetazolamide should be carried out by careful monitoring on the serum potassium concentration for possible fast appearance of hypokalemia (≤10 days) [22]. The level of serum potassium can be returned to normal by introducing or adding more dose of mineralocorticoid receptor antagonists and/or a potassium supplement for the possibility of malignant ventricular arrhythmias [42,43].

The interpretation of findings in this study is constrained by several factors including the limited number of studies available. Five studies were retrieved from the databases, only four of which were included in the meta-analysis. Nonetheless, with such limited evidence, this study was able to pool natriuresis data from 302 patients. Additionally, the heterogeneity was high which is ascribed to different subjects' characteristics, level of heart disease, dose of acetazolamide, and type of loop diuretics used. The heterogeneity in the present study was resolved by employing random effect model. Nonetheless, the review authors were not able to identify the source of the heterogeneity.

Conclusion

Acetazolamide could be used as adjunct therapy to loop diuretics to treat congestive heart failure. The combination between acetazolamide and loop diuretics is effective in increasing natriuresis and diuresis. By inhibiting the reabsorption of sodium reabsorption in the proximal tubules of nephron, acetazolamide increases the efficacy of diuretics working on more distal tubules. We recommend the use of acetazolamide to achieve natriuresis and diuresis among congestive heart failure patients, but the serum sodium level should be closely monitored for possible hypokalemia. More evidence, especially from RCTs, is required to conclude the efficacy of acetazolamide to achieve successful decongestion.

Ethics approval

Not applicable.

Acknowledgments

None.

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

No new data was generated in this research.

How to cite

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References

1. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. J Am Coll Cardiol 2008;52(6):428-434.
2. Bueno H, Ross JS, Wang Y, *et al*. Trends in length of stay and short-term outcomes among medicare patients hospitalized for heart failure, 1993-2006. J Am Med Assoc 2010;303(21):2141-2147.
3. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail 2020;22(8):1342-1356.
4. Conrad N, Judge A, Tran J, *et al*. Temporal trends and patterns in heart failure incidence: A population-based study of 4 million individuals. The Lancet 2018;391(10120):572-580.
5. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev 2017;3(1):7-11.
6. Adams KF, Fonarow GC, Emerman CL, *et al*. Characteristics and outcomes of patients hospitalized for heart failure in the United States: Rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149(2):209-216.
7. Chioncel O, Mebazaa A, Maggioni AP, *et al*. Acute heart failure congestion and perfusion status – impact of the clinical classification on in-hospital and long-term outcomes; Insights from the ESC-EORP-HFA heart failure long-term registry. Eur J Heart Fail 2019;21(11):1338-1352.
8. Ambrosy AP, Pang PS, Khan S, *et al*. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: Findings from the EVEREST trial. Eur Heart J 2013;34(11):835-843.
9. Greger R. Loop diuretics. In: Greger RF, Knauf H, Mutschler E, editors. Diuretics. Berlin: Springer; 1995.
10. Ellison DH. The physiologic basis of diuretic synergism: Its role in treating diuretic resistance. Ann Intern Med 1991;114(10):886-894.
11. Felker GM. Loop diuretics in heart failure. Heart Fail Rev 2012;17(2):305-311.
12. Heidenreich PA, Bozkurt B, Aguilar D, *et al*. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of cardiology/American heart association joint committee on clinical practice guidelines. Circulation 2022;145(18):e895-e1032.
13. Verbrugge FH, Dupont M, Steels P, *et al*. The kidney in congestive heart failure: 'Are natriuresis, sodium, and diuretics really the good, the bad and the ugly?'. Eur J Heart Fail 2014;16(2):133-142.
14. Verbrugge F, Dupont M, B. Bertrand P, *et al*. Determinants and impact of the natriuretic response to diuretic therapy in heart failure with reduced ejection fraction and volume overload. Acta Cardiol 2015;70(3):265-273.

15. Zahedi K, Barone S, Xu J, Soleimani M. Potentiation of the effect of thiazide derivatives by carbonic anhydrase inhibitors: Molecular mechanisms and potential clinical implications. PLOS One 2013;8(11):e79327.
16. Amir-Behghadami M, Janati A. Population, intervention, comparison, outcomes and study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. Emerg Med J 2020;37(6):387.
17. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
18. Sharma D, Ulaganathan SP, Sharma V, *et al*. Deep meta tool: GUI tool to obtain mean and standard deviation (SD) from median and interquartile range (IQR). Res Square 2021.
19. Thorlund K, Imberger G, Johnston BC, *et al*. Evolution of heterogeneity (I2) estimates and their 95% confidence intervals in large meta-analyses. PLoS One 2012;7(7):e39471.
20. Thornton A, Lee P. Publication bias in meta-analysis: Its causes and consequences. J Clin Epidemiol 2000;53(2):207-216.
21. Terrin N, Schmid CH, Lau J, Olkin I. Adjusting for publication bias in the presence of heterogeneity. Stat Med 2003;22(13):2113-2126.
22. Kataoka H. Acetazolamide as a potent chloride-regaining diuretic: Short- and long-term effects, and its pharmacologic role under the 'chloride theory' for heart failure pathophysiology. Heart Vessels 2019;34(12):1952-1960.
23. Verbrugge FH, Martens P, Ameloot K, *et al*. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. Eur J Heart Fail 2019;21(11):1415-1422.
24. Imiela T, Budaj A. Acetazolamide as add-on diuretic therapy in exacerbations of chronic heart failure: A pilot study. Clin Drug Investig 2017;37(12):1175-1181.
25. Mullens W, Dauw J, Martens P, *et al*. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med 2022;387(13):1185-1195.
26. Girerd N, Seronde M-F, Coiro S, *et al*. Integrative assessment of congestion in heart failure throughout the patient journey. JACC: Heart Fail 2018;6(4):273-285.
27. Rubio-Gracia J, Demissei BG, Ter Maaten JM, *et al*. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. Int J Cardiol 2018;258:185-191.
28. Shukralla AA, Dolan E, Delanty N. Acetazolamide: Old drug, new evidence?. Epilepsia Open 2022;7(3):378-392.
29. Gibson D, Marshall J, Lockey E. Assessment of proximal tubular sodium reabsorption during water diuresis in patients with heart disease. Heart 1970;32(3):399-405.
30. Kataoka H. Treatment of hypochloremia with acetazolamide in an advanced heart failure patient and importance of monitoring urinary electrolytes. J Cardiol Cases 2018;17(3):80-84.
31. Caramelo C, Albalate M, Baldoví S, *et al*. Actuality of the use of acetazolamide as a diuretic: Usefulness in refractory edema and in aldosteroneantagonist-related hyperkalemia. Nefrología 2008;28(2):234-238.
32. Eiskjaer H, Bagger J, Danielsen H, *et al*. Mechanisms of sodium retention in heart failure: Relation to the renin-angiotensin-aldosterone system. Am J Physiol Renal Physiol 1991;260(6):F883-F889.
33. Hall J, Guyton A, Mizelle H. Role of the renin-angiotensin system in control of sodium excretion and arterial pressure. Acta Physiol Scand 1990;591:48-62.
34. Ellison DH, Velazquez H, Wright FS. Thiazide-sensitive sodium chloride cotransport in early distal tubule. Am J Physiol Renal Physiol 1987;253(3):F546-F554.
35. Wongboonsin J, Thongprayoon C, Bathini T, *et al*. Acetazolamide therapy in patients with heart failure: A meta-analysis. J Clin Med 2019;8(3):349.
36. Yeghiazarians Y, Jneid H, Tietjens JR, *et al*. Obstructive sleep apnea and cardiovascular disease: A scientific statement from the American Heart Association. Circulation 2021;144(3):e56-e67.
37. Azarbarzin A, Sands SA, Taranto-Montemurro L, *et al*. The sleep apnea-specific hypoxic burden predicts incident heart failure. Chest 2020;158(2):739-750.
38. Wilcox CS, Testani JM, Pitt B. Pathophysiology of diuretic resistance and its implications for the management of chronic heart failure. Hypertension 2020;76(4):1045-1054.
39. Cuthbert JJ, Bhandari S, Clark AL. Hypochloraemia in patients with heart failure: causes and consequences. Cardiol Ther 2020;9(2):333-347.
40. Imiela T, Imiela AM, Karczmarewicz G, Budaj A. Acidic urine as a novel risk factor for diuretic resistance and worse in-hospital prognosis in patients with acute heart failure. Pol Arch Intern Med 2021;131:16054.

41. Cimolai N. The neurological spectrum for acetazolamide pharmacotherapy: From basic science to clinical applications. SN Compr Clin Med 2021;3:2576-2592.
42. Grodin JL. Pharmacologic approaches to electrolyte abnormalities in heart failure. Curr Heart Fail Rep 2016;13:181-189.
43. Urso C, Brucculeri S, Caimi G. Acid–base and electrolyte abnormalities in heart failure: Pathophysiology and implications. Heart Fail Rev 2015;20:493-503.