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Effect of Acetazolamide Additional Therapy on Loop Diuretic for Achieving an Effective Treatment in Acute Heart Failure Patients: A Systematic Review

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Abstract: Hospital readmissions are primarily caused by signs and symptoms of congestion of acute heart failure (AHF). Loop diuretics are commonly used to treat volume excess. It has been suggested by earlier studies in AHF patients that combination of loop diuretics with acetazolamide can increase the effectiveness of loop diuretics. This study aimed to obtain the impact of acetazolamide addition on loop diuretic therapy in AHF patients and assess the benefit of the combination. This was a systematic review using PubMed and ScienceDirect to retrieve data in 2013 and 2023, focusing on Randomized Controlled Trials (RCTs) involving AHF patients treated with both loop diuretics and acetazolamide. The results showed that 573 patients from a total of four RCTs were included in the study. Acetazolamide additional therapy helped loop diuretic to increase natriuresis (in all of the studies) and urine output (in two studies). The congestion symptoms also reduced in patients who received acetazolamide additional therapy on dose 500 mg intravenously within three days ($p<0.05$) in two studies. However, patients who received acetazolamide therapy also had an increase in serum creatinine levels in two studies. In conclusion, adding acetazolamide to loop diuretic therapy can increase the effectiveness of loop diuretics to achieve successful decongestion in AHF patients. Additionally, acetazolamide-treated individuals exhibit natriuresis and urin output higher than those in the control group, despite it also raises serum creatinin level.
Keywords: acetazolamide; loop diuretics; acute heart failure; decongestion

INTRODUCTION

Heart failure patients may have a range of symptoms as a result of fluid retention.[1] Diuretics are usually used to treat fluid retention in heart failure patients, yet there is no proof that this strategy reduces death rates. However, in both acute and chronic phases of overhydration, the European Society of Cardiology (ESC) recommends the use of diuretics to restore appropriate fluid balance in patients.[2] Acetazolamide is an inhibitor of carbonic anhydrase that prevents sodium from being absorbed through the proximal tubules. Since acetazolamide was discovered to be more effective and safe than sulfanilamide as a diuretic, it was initially utilised in humans as a novel diuretic with the potential to cure congestive heart failure.[3] Moreover, acetazolamide was used in a number of 1950s case studies involving heart failure patients, and the results showed promising decongestive features.[4]

Since the discovery of loop diuretics which are thought to be more powerful, the use of acetazolamide has been diminishing.[5] Dual use of acetazolamide and thiazide diuretics is a promising therapy for diuretic resistance, as new evidence indicates that the ceiling effect of acetazolamide is caused by a compensatory increase of distal tubular Na-Cl co-transporter mediated by decreased expression of pendrin.[3,4] A recent randomised control experiment on the impact of acetazolamide on heart failure by Imiela and Badaj[5] demonstrated a beneficial effect on diuretic augmentation. The effect of acetazolamide on the volume overload state is being particularly studied in ongoing clinical trials, albeit, the results are not yet available. As a result, in this clinical situation, a systematic review could offer a thorough background and comprehension of the available data.

However, an observational study in acute heart failure (AHF) found that adding acetazolamide increased the effectiveness of loop diuretics, excreting about 100 mmol sodium extra for every dose of 40 mg furosemide equivalent. Acetazolamide increases the sodium available to Henle's loop by inhibiting the reabsorption of sodium bicarbonate in the renal proximal tubules. This enhances the effect of loop diuretics, which may be particularly helpful in conditions where renal blood flow is compromised.[6] Moreover, acetazolamide has inherent renal vasodilatory properties that guard against ischaemia-reperfusion injury to the nephrons. Lastly, it inhibits the distal nephron's pendrin system, which may be a potential mechanism for diuretic resistance. Furthermore, the possible effects of acetazolamide on neurohumoral activation, renal function, and decongestion were examined.[7]

METHODS

The authors ensured that it complied with the requirements by adhering to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This was done to make sure the investigation's conclusions were accurate.

This systematic review aimed to obtain the effects of acetazolamide additional therapy to loop diuretic for achieving a more effective treatment in AHF patient, and to evaluate the overall benefit of the combination.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper were written in English; 2) The studied papers included several articles that were published between 2013 to 2023. Examples of studies that were not permitted included editorials, submissions that did not have DOIs, and review articles that had already been published.

The search for studies to be included in the systematic review was carried out using the PubMed and ScienceDirect databases in 2013 and 2023. MeSH headings for ((("acetazolamide"[All Fields]) AND ("diuretics"[All Fields]) AND ("heart failure "[All Fields])) were included in the search keywords. A systematic review of the published studies was conducted, focusing on Randomized Controlled Trials (RCTs) involving AHF patients treated with both loop diuretics and acetazolamide.

The criteria for analyzing studies in this research synthesis were randomized controlled

trials (Jadad score >3) with statistical value, full text, and was relevant to discuss the effects of acetazolamide to loop diuretics for increasing an effective treatment in AHF patients.

After reading the abstract and the title of each study, we performed an examination to determine whether or not the study met the inclusion criteria, and decided which previous research to utilize as sources for their articles and selected studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions needed to be written in English.

The papers included in the systematic review were limited to those that met all of the inclusion criteria. As a result, only relevant results remained after the reduction in the number of results. Any study whose conclusions did not meet our standards were not taken into consideration. Following this, a thorough analysis of the research findings would be conducted.

The subsequent phase involved assessing every article that met the review's inclusion criteria and was thus appropriate for inclusion. The articles that should be included in the review would then be chosen based on the conclusions that we found. The selection of papers for additional evaluation was done using this criterion. in an effort to choose the papers for evaluation as simply as possible. We would discuss which previous studies were conducted and what aspects of those investigations warranted inclusion in the review.

RESULTS

A total of 140 eligible studies were identified through initial database searching. After removing duplicates, 139 records were assessed using the title and abstract. The full text of 72 articles was obtained, and a detailed assessment of the studies was conducted, and then 68 out of the final 72 records were excluded from the full-length review. As a result, the final analysis included studies consisting of four randomized control trials (RCTs) with a total of 573 heart failure patients. Figure 1 shows the process of literature retrieval, review, and selection and Table 1 displays the characteristics of the included studies. The studies were published between 2013 and 2023.

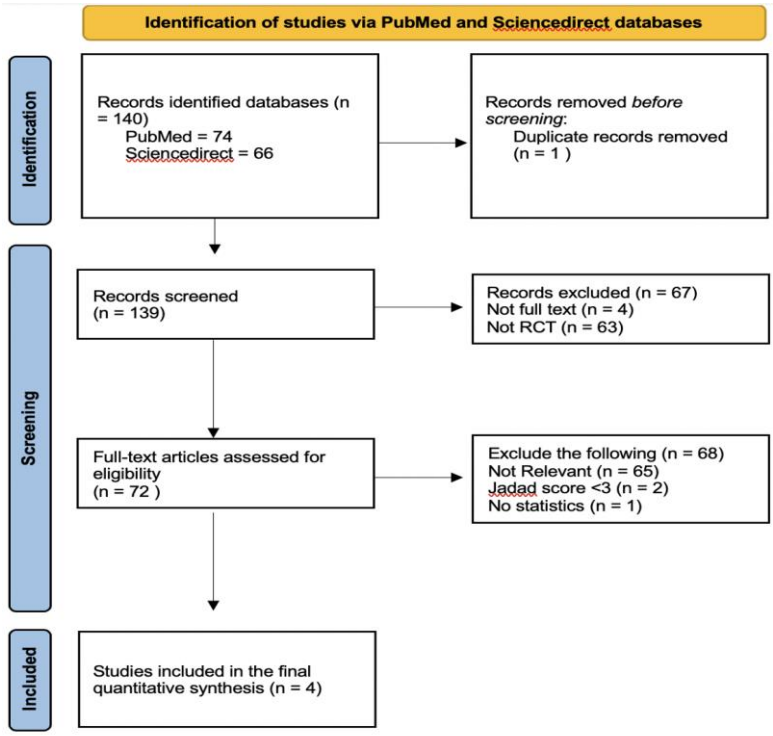

Figure 1. PRISMA flowchart of selection studies

A number of 573 patients from a total of four RCTs were included in this study. In all of the studies, acetazolamide additional therapy helped loop diuretic to increase natriuresis. Verbrugge et al (2023)[8] showed that the total natriuresis of acetazolamide was 476±229 mmol compared to of placebo 375±229 mmol during the first two days ($p<0.001$). Two studies examined the number of patients who achieved decongestion within 72 hours of beginning the treatment ($p<0.001$). The congestion symptoms reduced in patients who received acetazolamide additional therapy on dose 500 mg intravenously compared to placebo plus standardized intravenous loop diuretics (dose = 2x's oral maintenance).

Two studies evaluated urine output in a total of 519 patients. Compared to those in the control group, the acetazolamide group had total urine output 4,689±1,667, and the control group 4,166±1,789 mL on the second morning ($p=0.001$). However, it is worth noting that patients who received acetazolamide therapy also had an increase in serum creatinine (sCr) levels in two studies. Verbrugge et al (2019)[12] showed that 5 out of 18 patients with acetazolamide 500 mg plus low dose loop diuretic (bumetanid 2 mg) demonstrated worsening renal function (WRF), defined as more than 0.3 mg/dL rise in serum creatinine within 72 h ($p=0.046$).

DISCUSSION

About 90% of AHF patients are treated with loop diuretics, and in more than half of those cases, this is the only course of treatment. Since the loop diuretics are protein-bound (>90%), the glomeruli are unable to filter them. In order for them to function on the Na+/K+/2Cl- symporter at the luminal side of the thick ascending limb of Henle's loop, they must be secreted in the proximal tubules by the multidrug resistance-associated protein 4.26 and organic anion transporters. Loop diuretics are the most effective diuretics because they encourage the excretion of sodium, potassium, and chloride since 25% of sodium is reabsorbed at this level in the nephrons. By encouraging compensatory distal tubular salt reabsorption, chronic loop diuretic treatment helps to avoid excessive natriuresis.[8] Additional factors contributing to loop diuretic resistance include low absorption in cases of abdominal congestion, decreased proximal tubule secretion of loop diuretic drugs due to anions competing with them in chronic kidney disease, or metabolic acidosis.[9]

In the ADVOR trial, 519 participants were randomised to either acetazolamide (259 patients) or a placebo (260 patients). On the third day, acetazolamide-treated patients experienced successful decongestion in 108 out of 256 and placebo-treated patients in 79 out of 259 cases. Over the course of many days, the majority of patients who had been given acetazolamide showed a more noticeable decrease in their congestion score than those who had been given a placebo.[10] Acetazolamide may be used in conjunction with loop diuretics to treat refractory congestive conditions that exhibit fluid overload. This drug inhibits carbonic anhydrase which reduces the reabsorption of water, salt, bicarbonate, and chloride in the proximal convoluted tubules. Moreover, acetazolamide raises blood acidity and urine pH by encouraging the excretion of bicarbonate in the urine.[11]

Loop diuretics can excrete more water and salt because they increase the availability of both in the loop of Henle when proximal sodium reabsorption is inhibited.[6] Acetazolamide also promotes renal vasodilation and inhibits pendrin, both of which aid in diuresis. Pendrin is a Cl/HCO3 exchanger that may be involved in the diuretic resistance mechanism. Comparing 250–500 mg of acetazolamide with a low-dose loop diuretic produced equivalent natriuresis but higher loop diuretic efficiency when compared to using a high-dose loop diuretic alone in a recent trial including 34 patients with congestive heart failure with reduced EF.[12,13]

Based on increased diuresis and natriuresis, this systematic review verifies that loop diuretics are more effective in patients receiving acetazolamide treatment. It is significant to remember that, while the causality of this relationship has not been established, the efficacy of loop diuretics has been demonstrated to be a robust and independent predictor of clinical outcomes in acute heart failure.[14] It functions similarly to sodium-glucose co-transporter 2

(SGLT2) inhibitors in stimulating tubuloglomerular feedback.[15] During decongestive treatment in AHF, acetazolamide use was linked to a trend towards greater worsening renal function (WRF). One of the biggest challenges faced by clinicians managing volume overload is WRF. Generally speaking, WRF determinations are made using either a drop in estimated glomerular filtration rate (eGFR) or an increase in basal serum creatinine level (sCr). There is no universally accepted definition of acute renal dysfunction in worldwide heart failure treatment guidelines. However, most publications define it as an increase in sCr of 0.3 mg/dl or more, which is the same threshold that the Kidney Diseases Improving Global Outcomes (KDIGO) AKI guidelines use to define acute kidney injury (AKI).[16]

Patients with AHF have a complex and multiple mechanism of renal impairment. Historically, it was believed that the primary mechanism was renal hypoperfusion brought on by decreased cardiac output. Because this combination could exacerbate intravascular volume depletion, physicians were apprehensive about the use of strong diuretics.[17] Even though it is now well established that WRF during decongestive treatment in AHF does not accurately predict persistent renal impairment and may even be linked to better outcomes when reflecting better decongestion, the clinical implications of this finding remain uncertain.[18] The current study provides comfort in the lack of any indication of elevated mortality associated with acetazolamide.[19]

Randomised clinical trials with sufficient power should be conducted to further investigate this. Furthermore, it has been suggested by Verbrugge et al (2019)[12] that acetazolamide is especially useful in promoting natriuresis in patients who already have WRF. Significantly, compared to glomerular filtration rate changes, achieving a net negative sodium balance is more reliably linked to a favourable outcome in AHF.[20] Although acetazolamide is protective over the long term, its vasodilatory effects, particularly at the level of the efferent arteriole, may account for a temporary decrease in intraglomerular pressure and, consequently, glomerular filtration rate. Similar observations have already been observed with SGLT2 inhibitors that decrease intraglomerular pressure through afferent arteriolar vasoconstriction in cases of glomerular hyperfiltration.[21-23] Eventually, more mechanistic and long-term studies are needed to fully comprehend the effects of acetazolamide on kidney function.

CONCLUSION

The addition of acetazolamide to loop diuretic may benefit heart failure patients by increasing the number of successful decongestion. Compared to patients in the control group, acetazolamide-treated patients exhibited significantly higher natriuresis and urine output. nevertheless, in comparison to a placebo, it also increases serum creatinin levels. Worsening renal function during decongestive treatment in AHF does not accurately predict persistent renal impairment and may even be linked to better outcomes when reflecting better decongestion. It would be imperative to carry out further research to examine the mechanisms, safety, and possible advantages of combining acetazolamide with other diuretics prior to its widespread implementation in clinical practise.

Conflict of Interest

The authors declare that there is no conflict of interest in this study.

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Table 1. Summary of the effects of acetazolamide additional therapy to loop diuretic

Authors, years	Design	N	Inclusion criteria	Reduce congestion	Natriuresis	Urine output	Increase serum creatinin
Verbrugge et al, 2023[8]	Multicenter, randomized, parallel-arm, double-blind, placebo-controlled trial	462	Patients from the ADVOR trial with complete data on urine output and urine sodium concentration (UNa) (urine sample >500 mL over 24 hours)	-	Acetazolamide (231 of 462 patients) = 476 ± 229 mmol Placebo (231 of 462 patients) = 375 ± 229 mmol p<0.001	Acetazolamide (231 of 462 patients) = 4,689 ± 1,667 Placebo (231 of 462 patients) = 4,166 ± 1,789 mL p = 0.001	-
Imiela and Budaj, 2017[5]	Prospective, randomized, unblinded, single-center	20	1.Clinical sign of volume overload 2. EF <50 % 3. Stable dose of diuretics over the next 4 days 4. Age ≥18 years	-	Acetazolamide (10 of 20 patients) = 253.1 ± 72.6 mmol Control (10 of 20 patients) = 240.70± 131.5 mmol p = 0.81	-	-
Verbrugg et al, 2019[12]	Prospective, two-centre study, randomised study	34	1. ≥2 clinical signs of congestion 2. EF <50% 3. NT-pro-BNP levels > 1000 ng/L. 4. Maintenance therapy with oral loop diuretics at a ≥ 1 mg equivalent dose of bumetanide for ≥1 month prior to enrolment.	Acetazolamide = 5 out of 18 patients Control = 6 out of 16 patients p = 1.000	Acetazolamide = 264 ± 126 mmol Control = 234 ± 133 mmol p = 0.515	-	Acetazolamide = 5 out of 18 patients Control = 0 out of 16 patients p = 0.046
Mullens et al, 2022[10]	Multicenter, double blind, randomized, placebo controlled parallel-group	519	1. ADHF 2. ≥1 clinical sign of volume overload 3. NT-pro-BNP level >1000 pg/mL or BNP level > 250 pg/mL	Acetazolamide = 108 out of 256 patients Placebo = 79 out of 259 P <0.001	Acetazolamide 468±234 mmol Placebo 369±231 mmol	Acetazolamide 4.6±1.7 L Placebo 4.1±1.8 L	Acetazolamide = 2 out of 256 patients Placebo = 0 out of 259 p = 0.24