Acetazolamide as an adjunct for volume overload To pee, or not to pee

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INTRODUCTION

In Canada, more than 100,000 people are diagnosed with congestive heart failure each year. In this population, symptoms associated with volume overload are the main reason for emergency department presentations. Due to factors like burden of cost and hospital bed shortages, only 38% of overload patients presenting to emergency departments are admitted to hospital.

In accordance with recent guidelines from the European Society of Cardiology, the cornerstone therapy for treating the symptoms of volume overload from acute decompensated heart failure is the use of intravenous loop diuretics. Despite its championed use, studies suggest that patients are still discharged with findings of volume overload. This, in turn, has led to poorer outcomes and recurrent presentations to emergency departments.

As a result of the increasing prevalence of loop diuretic resistance, insufficient diuresis while in hospital, and recurrent emergency department presentations for volume overload, should Manitoba emergency physicians consider adopting a new practice to better treat our affected population?

AIM

Background

The use of carbonic anhydrase inhibitors for diuresis in congestive heart failure was first studied in the 1950s. With the advent of more potent loop diuretics in the 1960s, this practice fell out of fashion. However, with loop diuretic resistance found to be a major cause of insufficient resolution of volume overload and associated recurrent hospital presentations, the use of acetazolamide as an adjunct therapy to loop diuretics has been revisited in the last decade.

Clinical Question

In adults presenting to the emergency department with acute decompensated heart failure, does the addition of acetazolamide to loop diuretics result in a shorter emergency department length of stay when compared to management using loop diuretic therapy alone?

REFERENCES

- Decompensated Heart Failure with Volume Overload. N Engl J Med. 2022 Sep 29;387(13):1185-1195. doi: 10.1056/NEJMoa2203094. Epub 2022 Aug 27. PMID: 36027559.



METHODS

- To allow for a comprehensive search, a concept map was first created expanding on the components of the PICO question (Figure 1).
- These terms were then applied to PubMed and EMBASSE to yield relevant literature. 91 articles were retrieved, of which 84 were excluded as they were either duplicates or conducted on patients aged < 18 years.
- The 7 remaining articles were assessed for eligibility. 1 study was excluded as it took place in an ICU setting, and 2 other studies were excluded for lack of clinical relevance to the question at hand.
- 1 prospective cohort study, and 3 randomized control studies were eligible for the narrative review



Figure 1. Concept map to facilitate a comprehensive literature search.

(1) Verbrugge FH, Dupont M, Bertrand PB, Nijst P, Penders J, Dens J, Verhaert D, Vandervoort P, Tang WH, Mullens W. Determinants and impact of the natriuretic response to diuretic therapy in heart failure with reduced ejection fraction and volume overload. Acta Cardiol. 2015 Jun;70(3):265-73. doi: 10.1080/ac.70.3.3080630. PMID: 26226699 (2) Imiela T, Budaj A. Acetazolamide as Add-on Diuretic Therapy in Exacerbations of Chronic Heart Failure: a Pilot Study. Clin Drug Investig. 2017 Dec;37(12):1175-1181. doi: 10.1007/s40261-017-0577-1. PMID: 28965280; PMCID: PMC5684277. (3) Verbrugge FH, Martens P, Ameloot K, Haemels V, Penders J, Dupont M, Tang WHW, Droogné W, Mullens W. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. Eur J Heart Fail. 2019 Nov;21(11):1415-1422. doi: 10.1002/ejhf.1478. Epub 2019 May 9. PMID: 31074184. (4) Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, Tartaglia K, Chenot F, Moubayed S, Dierckx R, Blouard P, Troisfontaines P, Derthoo D, Smolders W, Ter Maaten JM, Damman K, Lassus J, Mebazaa A, Filippatos G, Ruschitzka F, Dupont M; ADVOR Study Group. Acetazolamide in Acute

RESULTS

Verbrugge¹

n = 54, prospective cohort study

AIM: Examined the relationships between neurohumoral activation, NT-proBNP and volume overload in patients receiving loop-diuretic therapy.

METHODS: Daily doses of loop-diuretic were administered to patients. For three days the three variables were clinically and biochemically analyzed. To limit resistance, acetazolamide was added to loop diuretics depending on kidney function.

RESULTS: One unexpected finding was that the combination of acetazolamide to the bumetanide significantly increased natriuresis by more than 100 mmol/mg of bumetanide.

LIMITATIONS: Acetazolamide administration was not randomized, with a small sample population that received this intervention (n=9). Sicker patients were deliberately selected for this study, most of which were male.

Imiela et al ²

n = 20, randomized control trial

AIM: Compared the efficacy of acetazolamide when added to a variety of other diuretics.

METHODS: Different diuretic combinations were examined. some of which included loop diuretics. Acetazolamide was added to these background diuretics on the second and third day of the study.

RESULTS: A more negative fluid balance was observed in the interventional arms, where dyspnea was less pronounced. An increase in diuresis and natriuresis were observed in the acetazolamide group, although not statistically significant.

LIMITATIONS: The sample size was too small for generalizability. There was no standardization of the background diuretic regimens, and there was a high probability of chance findings given the wide standard deviations.

Verbrugge et al³

n = 34, randomized control trial

AIM: First study to directly examine the effect of acetazolamide on loop-diuretic efficiency.

RESULTS: There was no significant difference in natriuresis between both groups. When corrected for loop diuretic dosing, the combination therapy increased loop diuretic efficiency by 62%. This benefit might come at the cost of exacerbating an acute kidney injury.

LIMITATIONS: The sample size was too small to meet the pre-determined threshold for statistical power. Sicker patients were recruited, with a predicted 62% chance of all-cause mortality risk within 34 months.

Mullens et al (The ADVOR Trial)⁴

AIM: Looked at whether the addition of acetazolamide to loop-diuretics resulted in a faster and more pronounced resolution of volume overload.

METHODS: Home doses of hospitalized patients' furosemide were doubled and administered IV for three days. The intervention group received a daily dose of IV acetazolamide. A standardized score was used to assess for overload.

RESULTS: Successful decongestion occurred in 42.2% of patients in the treatment group, and 30.5% of patients in the placebo. Patients receiving acetazolamide had shorter hospitals stays and were more likely to be discharged from hospital without residual signs of fluid overload.

LIMITATIONS: There was a lack of external validity, as this study occurred in 27 sites in Belgium. Like the other studies, this did not take place in an ED setting.

RECOMMENDATIONS

Acetazolamide shows promise to help efficiently and safely diurese patients with overload. However, there is no evidence to suggest its efficacy in an emergency department setting. Some instances to consider concomitant treatment with acetazolamide include: When higher doses of lasix are needed to mitigate associated risks (like ototoxicity), when a lasix infusion is anticipated- consider this approach for its added benefit of being less labour intensive on nursing staff, and in very lasix resistant patients in attempt to achieve more effective diuresis synergistically





METHODS: Randomization of either a daily combination therapy of acetazolamide with low-dose bumetanide, or single therapy with high-dose bumetanide.

n = 519, randomized control trial