

Peer Review File

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Response to Reviewer's

Reviewer A:

Comment 1-Please add a short section on role of salt and fluid restriction prior to discussing diuretics.

Response: We thank the reviewer for their feedback. We have included a paragraph in our manuscript.

Changes in text-

“Salt and fluid restriction has been seen as a non-pharmacological way to prevent ADHF. Na restriction of less than 2 gm/day and fluid restriction <2 L/day are recommended to all patients with congestive heart failure and are endorsed by American heart association, Heart failure society of America as well as European society of cardiology. These guidelines are based on expert opinion.”

2- Briefly discuss the TORIC study (Eur J Heart Fail. 2002;4(4):507) and the article by Young et al (Torsemide: a pharmacoeconomic review of its use in chronic heart failure. Pharmacoeconomics 2001; 19:679)

Response: We thank the reviewer for their feedback. We have included a paragraph in our manuscript.

Changes in text-

“Torsemide in congestive heart failure (TORIC) study compared the efficacy, tolerability and safety of Torsemide in comparison to furosemide. This was a non-randomized, post market surveillance study which found not only torsemide was safe and well tolerated but it was also associated with 51.5% relative risk reduction of mortality and 59.5% reduction in cardiac mortality compared to furosemide or other diuretics. Functional improvement was observed more in torsemide group as well. Several post marketing studies have shown decreased hospitalization with torsemide use when compared to other diuretics. Considering which the overall cost of patients with ADHF who were treated with torsemide was significantly lower when compared with other diuretics. Even though the initial acquisition cost is higher for torsemide when compared to Lasix, the overall cost burden is lower.”

3-Also suggest referencing the NICE guidelines, Dworzynski K, Roberts E, Ludman A, Mant J; Guideline Development Group of the National Institute for Health and Care Excellence. Diagnosing and managing acute heart failure in adults: summary of NICE guidance. BMJ. 2014;349: g5695. Published 2014 Oct 8. doi:10.1136/bmj.g5695

Response: We appreciate reviewer’s feedback and have included reference to NICE guidelines in

our manuscript.

Reviewer B:

1- Abstract and manuscript should stand alone. If an acronym was used in the abstract needs to be spelled out in main manuscript again. I am assuming main manuscript starts with renal physiology on line 65?

Response- We appreciate reviews feedback and have adjusted the limitations that were mentioned above. The main manuscript starts with renal physiology.

2- The references need to be within the sentence and not after the period. For example, “elevation of filling pressures. (2)” should be “elevation of filling pressures (2).”

Response: We have adjusted the references to be within the sentences.

3- The abstracts focus too much on the physiopathology of ADHF, with diuretic management only briefly mentioned.

Response: We thank the Reviewer for highlighting this limitation. We have cut down on pathophysiology of ADHF and added more information on diuretic management.

Changes in text-

Added “Loop diuretics remain the mainstay of therapy for symptomatic management of heart failure with use of thiazide diuretics for synergistic effect in the setting of diuretic resistance. Poor diuretic efficacy has been linked with higher mortality and increased rehospitalizations.”

Removed -“ADHF further contributes to the disease progression through left ventricle remodeling,

multi organ failure including renal as well as liver dysfunction, pulmonary hypertension and right ventricular dysfunction”.

4- Since it is a commonly encountered problem, I would suggest to expand on the effects of metabolic alkalosis, as well as some insight on when to treat it (if needed at all).

For reference: Wongboonsin, J., Thongprayoon, C., Bathini, T., Ungprasert, P., Aeddula, N. R., Mao, M. A., & Cheungpasitporn, W. (2019). Acetazolamide Therapy in Patients with Heart Failure: A Meta-Analysis. *Journal of clinical medicine*, 8(3), 349.

<https://doi.org/10.3390/jcm8030349>

Response: - We appreciate reviewers feedback and have included below listed paragraph in the manuscript.

Changes in text-

Metabolic alkalosis is a common acid base disturbance associated with ADHF. It may occur due to volume overload, electrolyte disturbances, RAAS activation or as a consequence of diuresis. Acetazolamide acts on proximal tubule and lead to bicarbonaturia and may assist in reversing the alkalosis. But underlying reversible causes of alkalosis including electrolyte abnormalities, volume overload should be addressed first. Acetazolamide also induces natriuresis. The ongoing trial ADVOR will investigate effects of acetazolamide combined with loop diuretic therapy on improving diuresis and congestion in ADHF

5- Although small studies, I would suggest adding a comment of comparisons between thiazide diuretics and loop compared to thiazide diuretic , Moranville MP, Choi S, Hogg J,

Anderson AS, Rich JD. Comparison of metolazone versus chlorothiazide in acute decompensated heart failure with diuretic resistance

Response: We thank the reviewer for their input and have made these adjustments to the manuscript.

Changes in text-

Commonly used thiazide diuretics include metolazone, hydrochlorothiazide, and chlorothiazide. Addition of thiazide type diuretic, chlorthiazide and or metolazone as an add on therapy to loop diuretic was proven to be significant to augment diuresis in the setting of diuretic resistance and improved weight loss. No statistical significant difference was observed between oral metolazone vs IV chlorothiazide (comparison of metolazone vs chlorothiazide, feb 2015) as well as 3T trial (2019, jacc HF).

Combination diuretic therapy is associated various adverse effects including electrolyte abnormalities like hypokalemia, hyponatremia, hypomagnesemia, hypochloremia along with metabolic acidosis. They may also worsen renal dysfunction, cause hypotension and induce cardiac arrhythmias.

6-A conclusion or summary should be included at the end of the manuscript.

Response: We thank the reviewer for their comment and have included a conclusion.

HF is major cause of morbidity and mortality with consistently increasing prevalence around the world. Even though there is paucity of data for mortality benefits, loop diuretics do provide significant clinical benefit in ADHF and help Improve symptoms. They remain primary diuretic of choice for treatment. Intravenous form are more potent than oral formulation in ADHF.

Thiazide diuretics are used in synergy with loop diuretics for sequential nephron blockade to overcome diuretic resistance. Aldosterone antagonist though carry a weak diuretic effect, have been shown to have mortality benefit in patients with ADHF. Understanding the cause of diuretic resistance remains pivotal to help reverse it. When all else fails, UF may be considered to help with volume removal.