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Original Article

Tolvaptan add-on therapy and its effects on efficacy parameters and outcomes in patients hospitalized with heart failure

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ABSTRACT

Introduction: Even with the adequate use of diuretics and vasodilators, volume overload and congestion are the major causes of morbidity and mortality in patients hospitalized with acute heart failure (HF). We aim to evaluate the additive effect of tolvaptan on efficacy parameters as well as outcomes in hospitalized patients with HF.

Methods: We searched PubMed, EMBASE, Cochrane library, and Web of Science databases for randomized controlled trials that studied the effects of tolvaptan versus placebo in hospitalized patients with HF. Studies were included if they had any of the following endpoints: mortality, re-hospitalization, and in-hospital parameters like dyspnea relief, change in weight, sodium, and creatinine.

Results: The meta-analysis analyzed data from 14 studies involving 5945 patients. The follow up duration ranged from 30 days to 2 years. Between tolvaptan and placebo groups, there was no difference in mortality and rehospitalization. HF patients had a better dyspnea relief score (Likert score) in tolvaptan group and mean reduction in weight in the first 48 h (short-term). However, at 7 days (medium-term) the mean difference in weight was not significant. Serum sodium increased significantly in tolvaptan group. There was no difference in creatinine among the two groups.

Conclusions: Our meta-analysis shows that tolvaptan helps in short-term symptomatic dyspnea relief and weight reduction, but there are no long term benefits including reduction in mortality and rehospitalization.

1. Introduction

Volume overload and congestion of the lungs are the primary causes for hospitalization in a patient with acute congestive heart failure (HF). The use of diuretics and vasodilators, based on current guidelines for the treatment of acute HF, is effective in relieving congestive symptoms.[1] Despite the adequate use of diuretics and vasodilators, volume overload remains a major cause of morbidity and mortality in many patients with acute HF.[2] Hospitalized patients with acute HF are known to have an electrolyte imbalance, renal dysfunction, and poor response to diuretics and vasodilators despite dose escalation.[3,4]

Vasopressin receptor antagonists have been investigated as an adjunct to diuretics and other standard therapies in patients with acute HF. Tolvaptan, a selective V2 receptor antagonist, is the most studied medication in this regard. It produces a selective water diuresis without affecting sodium and potassium excretion.[5] The efficacy and safety of tolvaptan in addition to current standard

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therapy in the treatment of acute HF remains controversial. A recent meta-analysis by Wang et al compared short-term and long-term efficacy of tolvaptan in acute HF with standard HF care, which demonstrated tolvaptan as add-on therapy can help reduce body weight, increase serum sodium concentration and helps improving dyspnea score.[6] However, this study included randomized clinical trials and observational studies as well as combined studies with short term (up to 48 h), medium term (up to 7 days) and long term (up to 18 months) follow up while analyzing clinical outcomes. We performed an updated meta-analysis of randomized double-blinded trials comparing add on tolvaptan compared with standard diuretic therapy in patients hospitalized with acute HF and provided the outcomes on short term, medium term, and long-term follow-ups.

2. Methods

2.1. Literature search

The PubMed, EMBASE, Cochrane library and Web of science databases were systematically searched for randomized controlled trials (RCTs) involving add on tolvaptan compared with standard care in the treatment of acute HF up to December 2020. Two independent reviewers (TK and HG) worked on literature selection, extraction of data, and performing a quality assessment of the included studies. We searched the database using search keywords "Tolvaptan", "Loop diuretics'', "Heart failure", and "Randomized clinical trial". We also reviewed relevant papers looking for reference lists to identify additional studies that may contain pertinent data. Any disagreements were resolved by consensus (Fig. 1).

2.2. Inclusion and exclusion criteria

The inclusion criteria in this meta-analysis were a) randomized trial of hospitalized patients with acute HF, where tolvaptan was an add-on to the traditional diuretics in the treatment group and compared with placebo. b) Studies reported any of the following outcomes: all-cause mortality, changes in electrolytes, fluid loss, dyspnea relief, length of stay and data regarding short term and long-term side effects such as thirst, dry mouth, arrhythmia, mortality, and rehospitalization. Studies such as review articles, medical reports, observational studies case reports, or any editorials were excluded.

2.3. Data extraction

We analyzed and compared the study characteristics and outcomes of the included RCTs, including patient demographics, comorbidities, medications, laboratory parameters, clinical outcomes, length of the study, and side effects. The outcomes were categorized into three groups: short term (less than 48 h), medium term (up to 7 days) and long term (30 days and beyond).

2.4. Statistical analysis

RevMan 5.4.1 was used to analyze data. A meta-analysis was performed if at least 3 studies provided the same outcome. The Mantel-Haenszel method was used to analyze the dichotomous data with a random effect model. Relative risk (RR), mean difference (MD) and 95% confidence interval (CI) were used as effect measures. The I^2 test was used to determine the test of heterogeneity. The difference was considered statistically significant at $p < 0.05$.

3. Results

3.1. Study characteristics

We included 14 RCTs in our meta-analysis involving a total of 5945 patients with hospitalizations for HF [2920 (49.11%) patients in the tolvaptan group and 3025 (50.89%) in the control group]. The study characteristics are shown in *Supplemental File 1.*

3.2. Clinical outcomes

Dyspnea was the main reason for hospitalizations in patients with HF. Three studies reported changes in dyspnea within the short term (up to 48 h) with a Likert psychometric scale. Our meta-analysis showed a significant improvement in dyspnea in the tolvaptan group [RR 1.19 (1.06, 1.33) $p = 0.003$, I^2 0%). There was a significant reduction in weight at short term (within 48 h) with tolvaptan compared to placebo [mean difference, MD -2.19 (-3.52, -0.86) $p = 0.001$, I^2 91%] but not at medium-term (up to 7 days) [MD -0.67 (-1.45, -0.11) $p = 0.09$, I^2 63%]. Some studies also reported side effects like thirst, urinary frequency, dry mouth, HF exacerbation, arrhythmia, cough, and dehydration. As there was limited data available, they could not be compared.

3.3. Laboratory outcomes

Studies reported changes in serum sodium, potassium, creatinine, and BNP. Among the 5 studies showing the change in serum sodium, there was a significant rise in serum sodium in patients treated with tolvaptan in short term [MD 3.75 (2.92, 4.58) $p < 0.001$, I^2 77%]. Based on the reported change in serum creatinine among 5 studies, there was no difference between serum creatinine in patients treated with tolvaptan versus placebo [MD 0.00 (-0.08, 0.08) $p = 0.98$, I^2 66%].

3.4. Length of stay, rehospitalization and mortality

4 studies documented length of stay. There was no difference in length of stay in patients taking tolvaptan versus placebo [MD -0.65 (-3.38, 2.07) $p = 0.64$, I^2 64%]. A total of 7 studies reported mortality as an outcome of follow-up. It was found that there was no difference in mortality [RR 0.73 (0.46, 1.18) $p = 0.20$, I^2 0%] or rehospitalizations [RR 0.79 (0.51, 1.22) $p = 0.28$, I^2 73%] in patients treated with tolvaptan compared with placebo.

The results are shown in Fig. 2.

3.5. Publication bias

Publication bias was visualized using a funnel plot diagram. By performing a regression test for funnel plot asymmetry, we found that there was no significant publication bias in summarizing the effect of add-on tolvaptan in providing dyspnea relief and in assessing mortality benefit *(Supplemental File 2 – 9).*

4. Discussion

In this study, we included 14 RCTs to estimate the effects of tolvaptan as an add-on therapy to conventional HF treatment on clinical outcomes, length of stay, rehospitalization, and mortality in patients hospitalized with HF. Our study concluded that add-on tolvaptan therapy had significant dyspnea relief by reducing volume overload within 48 h. We also found that the tolvaptan group had a significant weight loss over the short term within 48 h. This

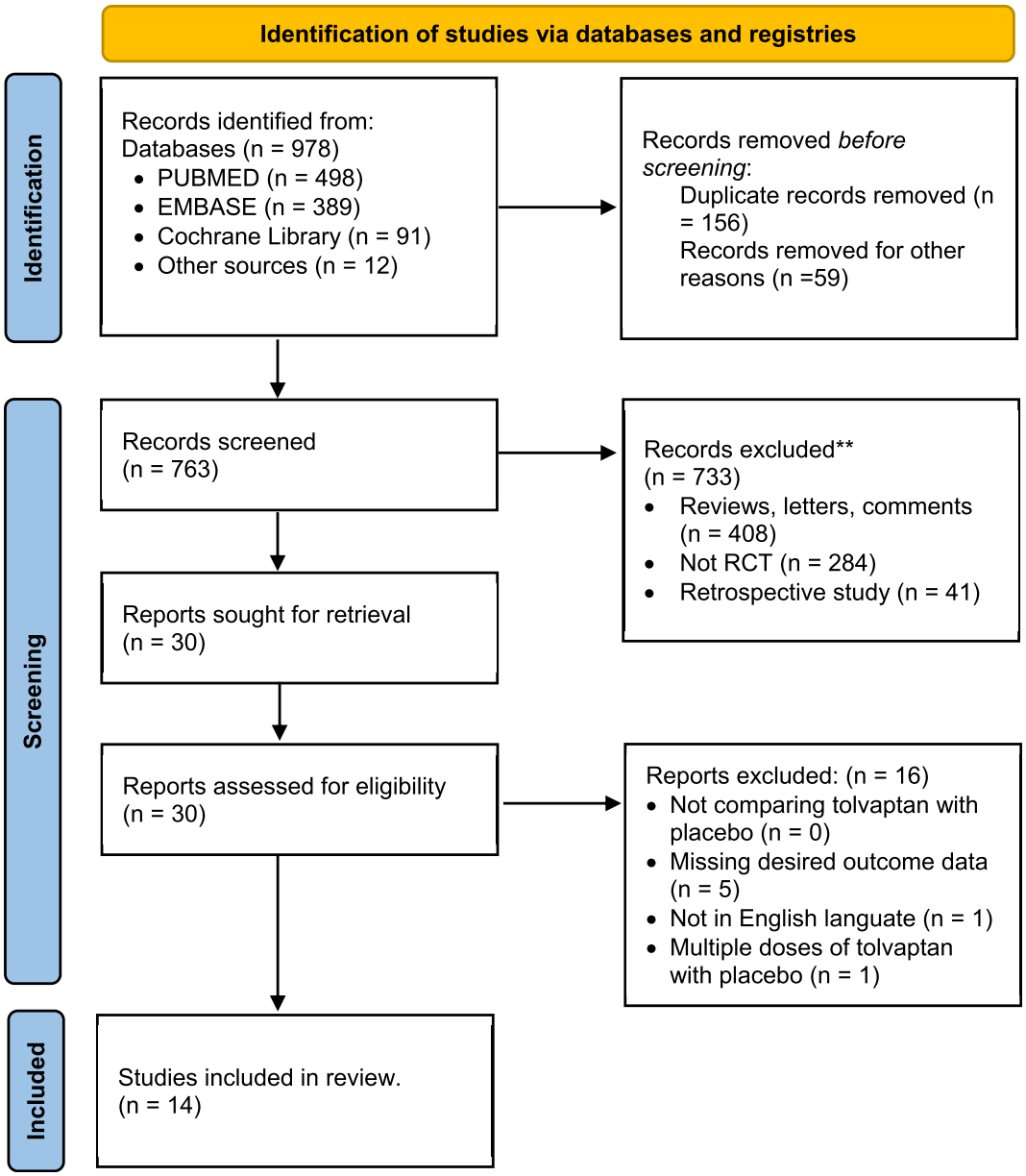

Fig. 1. PRISMA flowchart showing eligibility of studies for inclusion in the meta-analysis.

change in weight was short-lived with no significant changes in weight observed over the medium term (up to 7 days). We saw an increase in serum sodium concentration in the tolvaptan group during hospitalization. There was no change in the re-hospitalization rates, length of stay and mortality between the two groups of interest.

Our findings are consistent with the previous meta-analysis studies.[6,7] Like the prior studies including the EVEREST trial, our study concluded that add-on tolvaptan therapy significantly increased serum sodium levels compared to the standard diuretic therapy.[8–11] We found no significant difference in change in creatinine between the two groups. Our results in conjunction with a recent meta-analysis by Wang, et al which concluded that add-on tolvaptan significantly reduced the risk of worsening renal failure[6] suggests that tolvaptan has no significant detrimental effect on renal function. Further, tolvaptan can be used in patients with creatinine clearance of up to 10 ml/min. Based on this principle, tolvaptan could be a promising agent to manage congestion symptoms in HF patients with chronic kidney disease.

Our meta-analysis indicated that there was no mortality benefit with add-on tolvaptan therapy, which is consistent with the previous meta-analysis findings[6,7] as well as the EVEREST clinical trial outcome.[11]

Previous meta-analysis studies[6,7] demonstrated a significant effect on weight loss with tolvaptan. Our study concluded that tolvaptan provides significant weight loss benefit over the short-term (within 48 h), with no benefit observed over the medium-term (7 days) follow-up. There are a few reasons for such disparities. The study by Want *et al.*[6] included both observational studies and RCTs. Further, this meta-analysis combined studies in weight loss which had follow up of 48 h, 7 days and one year. Similarly, the meta-analysis by Luo *et al.*[7] combined the studies with 48 h and 30 days follow-up while analyzing the weight loss. Our meta-analysis calculated the weight difference by duration which we consider is

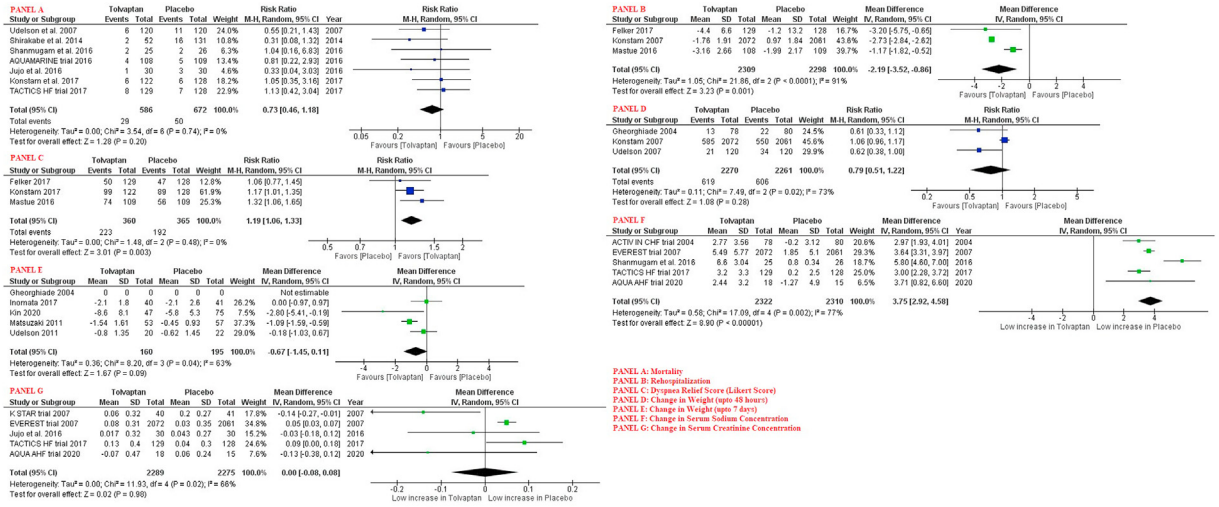

Fig. 2. Figure showing forest plots for outcomes in heart failure patients treated with tolvaptan versus placebo.

more justified with weight loss. The reason for weight loss not being sustained is the lack of antagonism of the V1a receptor which is equally important than pure V2 antagonism provided by tolvaptan, for the overall cardiovascular benefits and effect on weight loss. In support of this hypothesis, it has been studied that treatment with a combined V1A/V2-receptor (e.g., conivaptan) antagonist has been shown to improve hemodynamics in patients with severe HF.[12] It has also been studied that initial aquaretic response to tolvaptan is positively correlated with baseline urine osmolality and baseline GFR,[13] which may be contributing to higher initial aquaresis and weight loss after tolvaptan therapy. Like the prior clinical trials and meta-analysis, we concluded that there was no difference in overall length of stay observed between the two groups. Our study also demonstrated no difference in the rehospitalization rate for HF between the two groups.

Loop diuretic therapy continues to be the first line of treatment for volume overload in patients with acute HF exacerbation. However, there are a significant number of patients refractory to treatment with diuretics who require additional therapy for volume overload and symptomatic relief. For example, in nephrotic syndrome, hypoalbuminemia reduces the delivery of furosemide to the distal tubules.[14] The secretion of diuretics is also inhibited by the presence of several organic anions, uric acid, and acidosis.[15] Patients with acute HF who require higher doses of diuretic therapy are at increased risk of electrolyte derangement.[16] Compared to loop diuretic therapy, tolvaptan promotes sustained renal blood flow and glomerular filtration rate without affecting sodium and/or potassium excretion.[17] Tolvaptan can be used to increase diuresis and reduce body weight in such patients.

Based on the above results, we feel that although tolvaptan does not provide any mortality benefit or any potentially favorable outcomes over the long term compared to the loop diuretic therapy alone for acute HF patients, tolvaptan has a good potential for use in acute symptom relief for patients hospitalized with HF requiring higher doses of diuretics. The significant benefits on dyspnea, body weight, and serum sodium, coupled with the neutral survival effect, preservation of renal function, and the overall safety profile, could justify tolvaptan as a potentially useful agent for treating patients with acute HF exacerbation.

5. Limitations

Our study has several limitations: 1) Upon examinations of different outcomes including side effects, only a small fraction of the included studies provided extractable data, limiting meta-analysis data for side effects comparison between the tolvaptan and the control group which could potentially reduce the use in clinical setup. 2) Studies have used different doses of tolvaptan to compare with traditional diuretic therapy which could alter the results. For example, studies in North America used a higher dose while those from Japan used a lower dose of tolvaptan. 3) The hospitalizations for HF were not differentiated based on the severity of HF. This could have an unforeseen effect on the outcomes. 4) The EVEREST trial had almost 69.5% of patients, so the results were biased towards EVEREST trial results. 5) While analyzing the change in weight, serum sodium concentration and rehospitalization, it was found that the studies had a very high heterogenicity, and subgroup analysis with ejection fraction or other parameter could not be done due to lack of data.

6. Conclusion

During hospitalization of HF patients, tolvaptan can be helpful in short–term symptomatic dyspnea relief and initial reduction in weight due to its additive diuretic effect. However, this benefit is short-lived and there is no advantage in reducing rehospitalization rates, mortality, or as a means of sustained weight loss.

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None.

Author contributions

Tikal Kansara: Concepts, Design, Definition of intellectual content, Literature search, Clinical & query backup, Data acquisition, Manuscript preparation, Manuscript review, Guarantor. Haresh Gandhi: Design, Definition of intellectual content, Literature search, Clinical & query backup, Data acquisition. Monil Majmundar:

Literature search, Clinical & query backup, Data acquisition, Data analysis, Statistical analysis. Jignesh Patel: Concepts, Design, Statistical analysis, Manuscript editing, Manuscript review, Guarantor. Aravind Kokkirala: Design, Manuscript preparation, Manuscript editing, Manuscript review. Norbert Moskovits: Definition of intellectual content, Data analysis, Statistical analysis, Manuscript editing, Manuscript review, Guarantor. Savi Mushiyev: Concepts, Manuscript preparation, Manuscript editing, Guarantor. Craig Basman: Concepts, Definition of intellectual content, Manuscript preparation, Manuscript review, Guarantor.

Declaration of competing interest

The authors declare they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2021.12.003.

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