Original Article

Nepalese Heart Journal 2022; Vol 19(2), 19-22

# Treatment of Acute Decompensated Chronic Heart Failure: Furosemide vs Furosemide and Metolazone: A Cross-Sectional Comparative Study

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***Cite this article as:*** Risal UP, Karki P, Shah P. Treatment of Acute Decompensated Chronic Heart Failure: Furosemide vs Furosemide and Metolazone: A Cross-Sectional Comparative Study. Nepalese Heart Journal 2022; 19(2), 19-22

***Submission date:*** 31st January, 2022
***Accepted date:*** 5th July, 2022

## Abstract

**Background:** Heart failure is a leading cause of hospital admissions each year. In Nepal also the incidence of heart failure is increasing. Acute decompensated heart failure carries a poor prognosis. Most patients respond to intravenous loop diuretics but a substantial proportion of patients are resistant to them and may need additional diuretic agents like metolazone by the principle of "sequential nephron blockade".

**Methods:** In a hospital-based cross-sectional comparative study, we assigned 68 patients with acute decompensated chronic heart failure patients to receive furosemide at 1 mg/kg twice daily or furosemide at 1 mg/kg twice daily plus metolazone 5mg/day. The primary end-points were daily weight loss, negative water balance (difference between urine output and fluid intake) and symptomatic improvement on NYHA grading.

**Results:** There were 55% males and 45% females in total. There was a significant difference (p-value =0.003) in mean weight loss observed between the two groups on day three, i.e., 0.971±0.6 kg and 1.5±0.78 kg in furosemide group and furosemide plus metolazone group respectively. Mean negative water balance was significantly more in the combination group on day two (750.59±416.92 ml vs 450±230.94 ml) with p-value <0.001 and day three (780.88±352.48 ml vs 504.38±292.46 ml) with p-value 0.001. There was no significant change in symptoms on the basis of NYHA grading between the two groups, duration of hospital stay and adverse events like hypotension, acute kidney injury and dyselectrolytemia.

**Conclusion:** Among patients with acute decompensated chronic heart failure, treatment with combination of furosemide and metolazone was found to be more effective than furosemide alone without significant increase in adverse effects.

**Keywords:** Heart Failure, furosemide, metolazone

**DOI:** https://doi.org/10.3126/njh.v20i2.48870

## Introduction

Heart failure (HF) is a leading cause of hospital admissions each year. Overall, more than 37.7 million people are affected from heart failure worldwide.[1] In Nepal, the prevalence of heart failure is increasing but exact data are lacking. The epidemiology of HF is becoming similar to that of Western countries because of increasing adaptation of Western life-style. In one hospital-based study from Nepal, coronary artery disease (CAD) was the most important cause of HF.[2]

Acute Decompensated HF is the most common cause of hospital admissions among patients older than 65 years.[3] High doses of loop diuretics are most commonly used to treat these patients. However, studies have shown the associations between high doses of diuretics and adverse clinical outcomes, including renal failure, progression of heart failure and death.[4-6] Also in a few patients with severe congestive HF, even chronic therapy with high-dose furosemide fails to reduce the volume of extracellular compartment to the desired level. A combination of diuretics acting on different segments of the nephron may then be a possible approach to overcome this diuretic resistance. Metolazone is a thiazide-like diuretic which is commonly used for this purpose. The basis for combination diuretic therapy is the principle of sequential nephron blockade: i.e., the proximal and more primary distal site of action of metolazone bolstering the effect of furosemide within the loop of Henle.[7,8]

This study is the first of its kind from Nepal which aims to compare the benefits and risks of combination of furosemide and metolazone to furosemide in patients with acute decompensated chronic heart failure (ADCHF).

## Methods

It was a cross-sectional comparative study which was done in the emergency, ward and coronary care unit (CCU) of the department of Internal medicine of B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal. The duration of this study was one year (September 2015 to August 2016). Ethical clearance was obtained from the Institutional Review Committee (IRC) of BPKIHS, Dharan. The inclusion criteria included a diagnosis of heart failure as defined by the presence of at least one symptom [New York Heart Association (NYHA) grade III or IV dyspnea, orthopnea, or edema] and one sign (bilateral basal crepitations on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography) with diagnosed cardiac illness along with the anticipated need for

IV diuretics for at least 48 hours.[9] Patients were excluded if they had systolic blood pressure less than 90 mmHg, hemodynamically significant arrhythmias, NYHA grade I or II heart failure, serum creatinine more than 3 mg/dl at baseline or patient under renal replacement therapy. All patients gave written informed consent for participation. Sample size was estimated based on the study by TPJ Dormans et.al. which had shown a mean weight reduction of 0.6± 1.2 Kg who had received high dose furosemide.[10] With power of 90% and level of significance 5%, the estimated sample size was 68(34 in each arm). Patients were given either intravenous furosemide alone at the dose of 1 mg/kg body weight twice daily or combination of intravenous furosemide at 1 mg/kg body weight twice daily and oral metolazone 5 mg once daily. Patients were followed up throughout the hospital stay. Weight loss and negative fluid balance were judged to indicate diuresis and the efficacy of the diuretics. After taking baseline weights, daily weight measurement and strict input/output chartings were done for three consecutive days. Patients' subjective improvement was measured on the basis of NYHA grading. Serum sodium/potassium, and urea/creatinine were sent after 72 hours of treatment or as needed.

**Endpoints and Analyses:** The primary endpoints were weight loss measured at 24, 48, 72 hours, negative fluid balance as calculated by subtracting urine output from input which was done daily for three consecutive days and resolution of dyspnea on the basis of NYHA grading. The secondary endpoint was duration of hospital stay.

The safety outcome measures were development of dyselectrolytemia defined as hypokalemia (<2.5 mmol/L) or hyponatremia (<125 mmol/L) 72 hours after treatment that required either withdrawal of treatment or decrease in dose, development of acute kidney injury (AKI) defined as an increase in serum creatinine from baseline by more than 0.3 mg/dl after 72 hours of treatment, development of hypotension defined as a fall in mean arterial pressure(MAP) by more than 10 mmHg from baseline after the treatment, development of hypotension requiring inotropes, need for ICU/CCU stay, need for mechanical ventilation, and death after initiation of treatment.

**Statistical Analysis:** Collected data were entered in Microsoft Excel 2010 and uploaded into Statistical Package for Social Science (SPSS) version 11.5 for statistical analysis. Descriptive statistics measures such as mean, standard deviation, percentage, median, inter-quartile range were calculated for quantitative variables along with graphical and tabular presentations. Pearson's chi-square test was used for comparison of categorical variables, Student's t-test was used to compare parametric continuous variables and Mann-Whitney test was used to compare non-parametric continuous variables. A p-value of <0.05 was considered the level of significance.

## Results

Among the 68 patients included in the study, the mean age of patients in the furosemide group was 67.44±13.71 years whereas that in the combination diuretic group was 62.74±13.50 years. The baseline characteristics were similar in both the groups as shown in table 1. Ischemic cardiomyopathy was the most common cause of heart failure (38%) followed by valvular heart disease (VHD [32%] and dilated cardiomyopathy (DCM) [21%] in the furosemide and metolazone group compared to furosemide group in which DCM was the most common cause (38%) followed equally by ischemic cardiomyopathy and VHD (26%).

Mean weight in furosemide group was 53.15±11.07 kg and that in the combination diuretic group was 51.32±11.81 kg (table 1). There was a significantly greater mean weight loss on day three (p-value 0.003) in the combination diuretic group than the furosemide group, i.e., 1.5±0.78 kg vs 0.971±0.6 kg (table 2). Mean negative fluid balance with treatment on day one was not significant between the two groups but was significantly more in the combination group on day two (750.59±416.92 ml vs 450±230.94 ml) with p-value <0.001 and day three (780.88±352.48 ml vs 504.38±292.46 ml) with p-value 0.001 (table 3). There was no significant difference between the two groups in terms of symptom resolution on NYHA grading. On the third day, two (6%) patients were in NYHA class I in the furosemide group in comparison to one (3%) in the combination group (p-value =0.201). 27(80%) and 30(88%) patients were in NYHA II in the furosemide and combination diuretic group respectively (p-value 0.112). Five (14%) patients in the furosemide group and three (9%) in the combination group were in NYHA class III (p-value= 0.204). Mean duration of hospital stay was 5.53±3.04 days in the furosemide group and 5.26±2.30 days in the combination group and there was no statistically significant difference between the two groups (p-value= 0.687).

In terms of safety outcomes, only two patients (5.8%) developed dysectrolytemia in terms of hypokalemia and hyponatremia in the combination diuretic group but none in the furosemide group (p-value= 0.246) [table 4]. There was no significant difference between the two groups in terms of development of hypotension (p-value=0.246). Two (5.8%) patients in the combination group developed hypotension whereas no patient developed hypotension in the furosemide group. Similarly, there was no significant difference between the two groups in terms of development of AKI (p-value=0.246). Two (5.8%) patients in the combination group developed AKI whereas no patient developed AKI in the furosemide group. No patient in either group developed hypotension requiring inotropic agents nor did they develop complications that required mechanical ventilation or need for ICU stay. There was no mortality in either group with the treatment.

**Table 1:** Baseline characteristics of the study population

| | Furosemide group Mean± SD | Furosemide + Metolazone group Mean ± SD | p -value |
|---|---|---|---|
| Male(number) | 21 (62%) | 18 (53%) | 0.624 |
| Female(number) | 13 (38%) | 16 (47%) | - |
| Duration of heart failure in months (median) | 30 (22.5-51) | 36 (12-60) | 0.746 |
| Baseline weight (kg) | 53.15 ± 11.07 | 51.32 ± 11.81 | 0.514 |
| Systolic Blood pressure (mmHg) | 124.71 ± 13.63 | 117.06 ±1 8.78 | 0.059 |
| Hemoglobin(gm/dl) | 11.68 ± 1.68 | 11.22 ± 1.31 | 0.207 |
| Serum creatinine (mg/dl) | 0.98 ± 0.43 | 1.15±0.68 | 0.232 |
| Serum Sodium (mmol/L) | 133.79 ± 5.44 | 134.06 ± 5.18 | 0.838 |
| Serum Potassium (mmol/L) | 4.24 ± 0.93 | 4.30 ± 3.80 | 0.792 |

**Table 2:** Weight Loss with Treatment

| Day | Furosemide group Mean weight loss in Kg± SD | Furosemide+ Metolazone group Mean Weight loss in Kg± SD | p -value |
|---|---|---|---|
| Day 1 | 1.147±0.41 | 1.235±0.64 | 0.504 |
| Day 2 | 1.235±0.73 | 1.059±0.36 | 0.212 |
| Day 3 | 0.971±0.0.60 | 1.5±0.78 | 0.003 |

**Table 3:** Negative Water Balance with Treatment

| Day | Furosemide group Mean Negative water balance in ml ±SD | Furosemide+ Metolazone group Mean Negative water balance in ml ±SD | p-value |
|---|---|---|---|
| Day1 | 525.59±416.46 | 571.76±326.34 | 0.613 |
| Day2 | 450±230.94 | 750.59±416.92 | <0.001 |
| Day3 | 504.38±292.46 | 780.88±352.48 | 0.001 |

**Table 4:** Safety outcomes with Treatment

| Variable | Furosemide (n=34) | Furosemide + Metolazone (n=34) | p-value |
|---|---|---|---|
| Hypotension | 0 | 2(6%) | 0.246 |
| Dyselectrolytemia | 0 | 2(6%) | 0.246 |
| Acute Kidney Injury | 0 | 2(6%) | 0.246 |
| Need for ICU/CCU | 0 | 0 | - |
| Hypotension requiring inotropic agents | 0 | 0 | - |
| Need For mechanical ventilation | 0 | 0 | - |
| Mortality | 0 | 0 | - |

## Discussion

In previous studies, the addition of metolazone was compared to patients already taking furosemide with resistant edema, our study is the first of its kind that directly compares the addition of metolazone in patients who may or may not have been taking loop diuretics. There have been few studies comparing the efficacy of furosemide and metolazone. One of the largest studies in this regard was a retrospective study done on 1438 heart failure patients.[11]Another large retrospective study compared the efficacy of furosemide and bumetanide to combination of metolazone and furosemide.[12] A randomized controlled trial involving 33 consecutive patients of heart failure done by Channer et.al was a landmark study in comparing the efficacy of these regimens.[4]

Based on the theoretical possibility of sequential diuresis and past literature, addition of metolazone to furosemide was expected to produce more diuresis than furosemide alone. The efficacy outcomes were based on weight loss, negative water balance and improvement of symptoms on the basis of NYHA which was consistent with previous studies. This study showed that there was significant diuresis in the furosemide plus metolazone arm on the second and third day in comparison to furosemide alone (p value <0.001 and 0.002 respectively). Similarly, the combination of furosemide and metolazone caused significantly more weight loss on the third day than furosemide alone. (p value=0.003). This finding is consistent with previous study conducted by Oleson et. al. done among 24 CHF patients in which addition of quinethazone 50-100 mg/day was compared to daily furosemide 40-80 mg/day. The combination of quinethazone and furosemide was found to be superior to doubling the dose of furosemide alone.[13] Gunstone et al. in 1971 enrolled 13 patients of CHF in which metolazone 2.5-10mg/day was given in addition to furosemide 120-400 mg/day in which it was found that the above treatment resulted in ≥2 kg weight loss over four days in over two-thirds of the patients. 14Similarly, K S Channer et. al in 1994 involved 33 patients with severe CHF and found that median weight loss was 5.05 kg with the addition of bendroflumethiazide and 5.6 kg with the addition of metolazone with clinical response in 92.5% with symptomatic improvement allowing hospital discharge in 90% in patients with severe CHF resistant to loop diuretics.[4] In 1996 TPJ Dormans et. al. found that there was a significant increase in urine volume with the combination diuretic treatment (p value<0.001). In the same study the urine volume increased from 1899±958 ml to 3065±925 ml.[10] The above findings reflect the fact that the combination of different diuretics with different mechanisms of action are definitely more beneficial than high dose loop diuretics alone in the treatment of ADHF. In our study there was statistically significant diuresis with combination diuretics in comparison to furosemide alone on the second and third day but weight loss was significant only on the third day. The reason behind this discrepancy could be because of subjective difference in weight measurement and the fact that weights were not taken at the same time of the day with patients in the same clothes.

The efficacy of the diuretics was compared on the basis of resolution of symptoms and NYHA grading. All the patients had presented with NYHA class IV dyspnea. Patients responded to the treatment as none of the patients were in NYHA IV after treatment but there was no significant difference in symptom resolution on the basis of NYHA grading between the two groups. The reason for the above discrepancy could be because NYHA grading is subjective and most of our patients were elderly with poor educational background which could have influenced the result.

The beneficial effect of combination diuretics comes at the cost of various adverse effects. In our study also two patients in the furosemide plus metolazone group developed dyselectrolytemia in the form of hyponatremia and hypokalemia that required the reduction in dose of the drug. The same two patients also developed acute kidney injury after treatment, neither of which was statistically significant. Other studies done until now have shown hypokalemia as a major dose-limiting side effect of this combination. Olesen et al. in 1970 found that hypokalemia of 0.5 mEq/L and bigeminy were the most common adverse effects.[13] Grosskopf et al. in 1986 found hypokalemia of 0.4 mEq/L as the most common side effect with this regimen.[14] Likewise, Channer et. al.in 1994 found hypokalemia <3.5mEq/L in 65% of the patients who had received this combination.[4] In the study by Rosenberg et. al in 2005, it was found that serum potassium had decreased by 0.8 mEq/L and creatinine had increased by 27%.[15] Although many studies cited

above have shown dyselectrolytemia as a major cause for concern, our study showed that there was no statistically significant change in serum electrolytes with the combination therapy. The reason for this could be because of the small sample size.

In this study, two patients developed hypotension after treatment which was again not statistically significant (p-value= 0.246) but none of the patients developed hypotension requiring inotropic agents. In a study done by Rosenberg et.al in 2005 it was seen that there was a reduction in blood pressure by 10/8 mmHg from baseline after adding metolazone.[15] Also, none of the patients in either group developed the need for ICU/CCU stay or mechanical ventilation. There was no mortality with treatment in either of the groups. This study compared the efficacy of two groups in terms of duration of hospital stay as well. There was no significant difference between the two groups in terms of duration of hospital stay.

The strength of the study was it was the first of its kind from Nepal that evaluated the benefit of combination diuretic therapy. The study has also looked at various efficacy and safety parameters at the same time making an in-depth comparison between the two regimens.

However, this study had several limitations. We could not use the same weighing machines in the patients. Therefore, weights could not be taken with precision and that could have influenced the results. The input/output charting of some patients was not precise because of various technical reasons (nursing error, patient error). The other factors that could influence diuretic resistance such as serum albumin were not taken into account.

## Conclusion

The combination of furosemide and metolazone in the treatment of acute decompensated chronic heart failure shows more efficacy than furosemide alone in producing diuresis without any additional risks of electrolyte imbalances, hypotension or other serious adverse events. Randomized controlled trials with a large sample size are needed to study the further benefits and adverse effects of this combination therapy.

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