



## Original Article

# Efficacy of Combination of Metolazone and Torsemide in Type 2 and 4 Cardiorenal Syndrome

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## Abstract

**Background:** *There is paucity of literature on use of combination of metolazone and torsemide in patients of type 2 and type 4 cardiorenal syndrome. These patients develop resistance to loop diuretics and fluid overload one of the most important issue. Therefore optimization of diuretic use is crucial for successful management of such patients. We undertook this study to look for efficacy and safety of using metolazone on top of torsemide in patients of type 2 and type 4 cardiorenal syndrome.*

**Methods:** *We did retrospective analysis of our patients with type 2 and type 4 cardiorenal syndrome. All of them were started on torsemide 100 mg intravenous bolus and 5 mg metolazone was added later. There hourly urine output, weight loss and BP was recorded. Their demographic data and laboratory parameters were recorded. Appropriate statistics was applied.*

**Results:** *We had cohort of 37 patients. They had man age of 56.4±8.5 years. Study population included 22 males and 15 females. There were 54% patients with CRS type 2 and 46% patients with type 4 CRS. 33 patients responded to addition of metolazone. Four patients needed dialysis. Patients had mean weight loss of 2.3± 1.3 kg after 3 days. Hypokalemia was seen in seven patients. Hypotension was also observed in n=2 patients. There was significant increase in urine output. NYHA class also improved in 33 patients.*

**Conclusion:** *Combination of metolazone and torsemide was effective and safe in majority of our patients as reflected by increase in urine output and improvement in dyspnea.*

## Introduction

Cardiorenal syndrome (CRS) has been used to include clinical conditions where cardiac and renal dysfunction overlap.<sup>(1)</sup> There are various studies to suggest that presence of renal dysfunction is a risk factor for cardiovascular

disease. Epidemiological studies provide evidence for cardiovascular disease (CVD) as leading cause of death in chronic kidney disease (CKD).<sup>(2,3)</sup> Acute Dialysis Quality Initiative (ADQI) consensus group proposed a classification of Cardiorenal Syndrome into 5 categories.<sup>(4)</sup>

Different categories reflect likely primary and secondary pathology and time frame to define each. Depending on the type of Cardiorenal Syndrome and setting, incidence ranges from 5 to 50%. CRS has been found to be an independent risk factor of mortality.<sup>(5,6)</sup> Cardiac (heart failure) and/or renal dysfunction (manifested by oliguria and azotemia) is the endpoint of this syndrome. This leads to fluid retention and subsequently volume overload.<sup>(7)</sup> Management of volume overload is one of the immediate goals to relieve symptoms. It also reduces associated morbidity and mortality.<sup>(8,9)</sup> Both Heart failure and CKD are associated with loop diuretic resistance. Various factors have been implicated for loop diuretic resistance like Braking phenomenon, increased activity of renin angiotensin system, reduced renal blood flow, increased absorption of sodium in proximal tubule and reduced number of surviving nephrons.<sup>(10)</sup> Metolazone has been found to be useful in increasing output in various edematous conditions like heart failure, nephrotic syndrome, CKD and liver cirrhosis.<sup>(11,12)</sup> It is the only drug in thiazide group which acts on both the cortical thick ascending limb at the Loop of Henle and the distal convoluted tubule. This makes sodium excretion more efficient.<sup>(13)</sup>

We undertook this study to assess and efficacy of coadministration of torsemide and metolazone in patients with type 2 and type 4 cardiorenal syndrome. This is the first study of metolazone with torsemide as earlier studies has been done with combination of furosemide with metolazone.

### Material and Methods

This study is retrospective analysis of patients admitted in our hospital with diagnosis of cardiorenal syndrome type 2 or type 4 from 31 July 2018 to 1 July 2019. All patients with age  $\geq 18$  years were included. Type 2 Cardiorenal syndrome was diagnosed by chronic abnormalities in cardiac function leading to kidney injury or dysfunction. Type-4 CRS was diagnosed as chronic reno-cardiac disease, is characterized by cardiovascular involvement in patients affected by

CKD. Patients were excluded if they were on dialysis or had renal transplant. If patient was already on another thiazide diuretic then they were excluded. Basic demographic data age, gender, cardiac, renal diagnosis and comorbidities were recorded. Data of other drugs and interventions were collected. Initial (on admission or prior to administration of Metolazone) serum creatinine, sodium, potassium and urine output and weight were also noted. All of the subjects were initially started on injection torsemide 100 mg IV bolus. All patients were started on Metolazone 5 mg daily subsequently. Urine output was noted for the first 24 hours after Metolazone was given. Urea, s. creatinine. S. sodium and Potassium was repeated afterwards daily. Clinical course was observed till final outcome.

Primary outcome measure was hourly urine output measurement before and after metolazone. Secondary outcome measures include comparison of serum sodium, potassium, creatinine, symptomatic relief, need for dialysis and adverse events such as hypotension, hypokalemia. Symptomatic relief was defined as discontinuation of oxygen or disappearance of dyspnea in 48 hours. Weight loss after 72 hours was also recorded. Descriptive statistics was recorded with computation of frequency percentage or mean  $\pm$  standard deviation. Laboratory values were compared with analysis of variance (ANOVA) computed at 95% Confidence Interval.

### Results

There were thirty seven patients in the study. They had man age of  $56.4 \pm 8.5$  years. Study population included 22 males and 15 females. There were 54% patients (n=20) with CRS type 2 and 46% patients (n=17) with type 4 CRS. All patients presented with edema and dyspnea. Majority of the patients had hypertension, coronary artery disease, dyslipidemia. Table 1 shows various comorbidities present in the study group.

Patients had baseline GFR of  $28.9 \pm 5.3$  ml/minute. Anemia was present in 15 (40.5%) patients. Table 2 shows baseline characteristics of the patients.<sup>33</sup>

patients (89.5%) responded to addition of metolazone. Four patients needed dialysis. Patients had mean weight loss of  $2.3 \pm 1.3$  kg after 3 days. They also had significant reduction of blood pressure after metolazone administration. Both systolic and diastolic BP was reduced. Hypokalemia was seen in seven (18.9%) patients. Hypotension was also observed in 5.4% (n=2) patients. There was significant increase in urine output. NYHA class also improved in 33 patients. Twenty three patients (62.16%) patients NYHA class improved from class 4 to class 2 and ten patients improved from class 3 to class 2. Table 3 shows comparison of different parameters before and after addition of metolazone.

**Table 1** showing various comorbidities

comorbidity	No of patients	percentage
Diabetes mellitus	18	48.6
CAD	17	45.9
Dyslipidemia	15	40.54
Cerebrovascular disease	5	13.5
COAD	5	13.5
Pneumonia	3	8.1

**Table 2** showing baseline characteristics

Parameter	Value
S.Creatinine	$3.3 \pm 2.2$ mg%
BUN	$48.3 \pm 8.2$ mg%
S.albumin	$3.1 \pm$ gm%
Hemoglobin	$11.2 \pm 2.4$ gm%

**Table 3:** comparison of parameters before and after metolazone

Parameter	Torseamide use	After metolazone	p
Hourly urine output	$31.2 \pm 7.5$ ml	$55.4 \pm 8.7$ ml	<.05
S.sodium	$137.2 \pm 8.7$ meq/L	$135.8 \pm 7.9$ meq/L	.31
S. potassium	$4.3 \pm .52$ meq/L	$3.9 \pm .45$ meq/L	.06
S.creatinine	$3.3 \pm 1.7$ mg%	$3.7 \pm 2.5$ mg%	.12
Systolic BP	$158 \pm 10.9$ mm Hg	$151 \pm 9.8$ mm Hg	<.01
Diastolic BP	$96.3 \pm 4.3$ mm Hg	$93.5 \pm 5.1$ mm Hg	<.05

**Discussion**

This study is the first study to evaluate effect of combination of torsemide and metolazone in patients with type 2 and type 4 CRS. Significant

diuresis was achieved in most of the patients. 89% patients responded in our study. Bataclan et al found response in 78% patients.<sup>(14)</sup> But their population was heterogeneous having all types of CRS acute as well as chronic. Desai et also showed efficacy of adding metolazone on top of loop diuretic. They showed significant increase in urine volume in 90% patients. Ng et also showed that furosemide infusion and metolazone combination was significantly superior to furosemide only.<sup>(16)</sup> Our study also showed that significant weight loss was achieved in majority of patients. But another study did not mention about this. Mean weight loss of 1 Kg per day has been reported by authors. There have been reports of weight loss of 2-3 Kg per day also but in different patient setting.<sup>(17)</sup> We found hypokalemia was seen in 18.9 % patients while another study found almost same incidence of 13%.Hypokalemia has been described by different authors.<sup>(14,18)</sup> We observed hypotension in 5.4 % patients but Bataclan et al found in 13% patients.<sup>(18)</sup> We have patients with type 2 or type 4 CRS. This may be a cause for lesser number of hypotension.

Dialysis was needed in 11.5 % patients but it was needed in 22% in another study. We could discharge all patients but 6.5% died in study by Bataclan et al. This difference may be due to heterogeneous population in their study. There has been significant improvement in NYHA class in our most of the patients. Other study also showed similar observations.<sup>(7)</sup>

**Conclusion**

Present study showed that addition of metolazone to torsemide in patients with type 2 or type 4 cardio renal syndrome resulted in significant increase in urine output. Patients also lost 2.5 kg weight in 72 hours. Hypokalemia and hypotension were the complications seen in 18.9% and 5.4% patients. Combination of torsemide and metolazone appears safe and effective in patients with type 2 and type 4 CRS.

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