

# Sequential Combination Diuretic-Therapy for Massive Fluid Overload in Furosemide-Refractory Patients with Diabetic Kidney Disease

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## Abstract

Patients with renal disease are at risk of fluid overload which escalates as the disease progresses. In the present study, we evaluated the efficacy of sequential combination diuretic-therapy (SCDT) in management of massive fluid overload in Furosemide-refractory renal patients. The added diuretics were Spironolactone 25 mg daily for 3 days, to those without risk of hyperkalemia, followed by Hydrochlorothiazide 25 mg/Metolazone 5 mg daily for 3 more days. Excluded patients were those with 1) acute renal disease, 2) echocardiographic evidence of: a) left ventricular ejection fraction < 40%, b) significant stenotic or incompetent valvular disease, c) ASD or VSD, d) significant pericardial disease, and 3) significant limb venous disease or on drugs likely to cause limb-oedema. To assess the extent of fluid overload; clinical examination was complemented with radiological imaging as well as echocardiographic measurement of systolic pulmonary arterial pressure (sPAP). SCDT led to significant symptomatic, clinical, and radiological improvement of fluid overload without significant side effects. The latter were limited to hyperkalemia and hyponatremia which improved with dietary compliance. Moreover, hyperkalemia improved after subsequent addition of Thiazide/Metolazone. SCDT led to significant ( $p < 0.001$ ) increase in fractional excretion of sodium and decrease in body weight and sPAP. In conclusion; SCDT is a safe and efficacious measure to control fluid overload in patients with renal diseases.

## Keywords

Aldactone, Diabetes Mellitus, Echocardiography, Fluid Overload, Furosemide, Hydrochlorothiazide, Kidney Disease, Metolazone, Spironolactone

## 1. Introduction

In critically ill patients; positive fluid balance is associated with increased morbidity and mortality [1]. Salt and water retention inherent in acute kidney injury and/or chronic kidney disease; renders such patients at high risk for such complications independent of coincident sepsis and cardiac disease [2]. Fluid overload is defined by a cut-off value of 10% fluid accumulation above baseline body weight [3]. Slow ultrafiltration by extracorporeal machines is indicated in critically ill patients yet it is invasive, expensive and requires intensive care setting [4]. On the other hand; blocking the 25% of the reabsorbed sodium from the thick ascending limb of Henle, by loop diuretics, has been the most potent conservative therapy [5]. However, since 90% of loop diuretics are protein bound; their secretion into the proximal convoluted tubules, through organic anion transports (OAT-1, OAT-2 and ABCC4) is reduced in renal failure. Moreover, after an initial diuretic period, subsequent diuretic resistance (DR) is encountered, in some patients, due to activation of renin-angiotensin system by reduced extracellular volume leading to: 1) reduction of sodium transport into macula densa leading to activation of renin-angiotensin system and sodium retention via aldosterone release, 2) distal nephron remodeling (increase in distal convoluted cells, principle cells, and intercalated cells) leading to sodium retention by sodium-chloride symporters [6]. In this study we evaluated the role of sequential combination diuretic-therapy (SCDT) *i.e.* addition of Spironolactone then Hydrochlorothiazide/Metolazone (HT/M) to patients refractory to high-dose IV Furosemide to prevent distal sodium reabsorption and overcome such DR.

## 2. Patients and Methods

The study was conducted between 1 January 2018 and 31 December 2020 to evaluate the efficacy of SCDT in management of DR patients with massive fluid due to chronic renal disease. The sequentially added diuretics were Spironolactone 25 mg to those without risk of hyperkalemia followed by Hydrochlorothiazide 25 mg/Metolazone 5 mg.

Selection criteria:

Patients with chronic renal disease who presented with DR-fluid overload.

Exclusion criteria:

Patients with 1) acute renal disease, 2) morbid obesity, 3) intrinsic lung disease (COPD and fibrosis), 4) significant left ventricular (LV) dysfunction with echocardiographic evidence of: a) LV ejection fraction < 40%, b) significant stenotic or incompetent valvular disease, c) ASD or VSD, d) significant pericardial disease, and 5) significant limb venous disease or on drugs likely to cause limb-oedema. Exclusion was to avoid spontaneous recovery in those with acute renal insult, positive impact of vasodilator therapy in those with LV dysfunction and lastly difficulties in assessment of those with primary venous limb diseases.

Dietary restrictions:

It was prepared as precooked deep frozen meals with a standard sodium con-

tent of 150 mmol/day and avoidance of high-potassium items viz. fruits, juices, dates and concentrated tomatoes. In addition, patients were instructed to keep daily intake of fluids  $\leq$  500 ml/day.

Criteria for diagnosis of fluid overload:

The latter were established based on; 1) clinical examination showing dyspnea on excursion (DOE), LL and sacral edema as well as bilateral basal crepitations (BBC) on chest auscultation, 2) pulmonary congestion in chest x-rays, 3) high systolic pulmonary arterial pressure (sPAP) on echocardiography.

Assessment and grading of fluid overload:

Grading was defined as 1) euvolumic or grade 0: when DOE, LL and sacral edema and BBC disappears, pulmonary congestion clears from chest x-ray, and sPAP decrease to  $<30$  mm Hg by Doppler 2D echocardiography, 2) mild or grade 1 when DOE, trace oedema and BBC are encountered and were associated with mild pulmonary congestion in chest x-ray and sPAP is 30 - 49 mm HG, 3) Moderate or grade 2: when DOE, oedema and BBC were evident with congested lungs and sPAP is 50 - 75 mm Hg, 4) severe or grade 3 when DOE, edema BBC are is excessive and are associated with pulmonary edema in chest x-ray and sPAP  $> 75$  mm Hg [7].

Criteria for diagnosis of DR-fluid overload:

Failure to remove fluid after 3 days of intravenous Furosemide up to 250 mg every 6 hours.

Study design:

All patients had prepared diet as precooked deep frozen meals with a standard Na content of 150 umol/day with avoidance of high K-containing foods viz. fruits, juices, dates and concentrated tomato's. In addition, patients were instructed to limit their oral fluid intake to  $>500$  ml/day. After establishment of DR-fluid overload; Spironolactone was added for 3 days followed by HT/M on day 7.

Periodic assessment during the study:

1) Daily BP, pulse, weight and urine output, 2) serum urea, creatinine and electrolytes (Na, K, Ca, Mag) and eGFR, 3) urinary fractional excretion of Na (FE Na%). In addition; echocardiography was done at start then on day 3 and day 6 to assess sPAP.

Statistical analysis:

SPSS statistical package version 25 was used for data entry and processing. The p-value  $\leq 0.05$  was used as the cut-off level for significance. All continuous variables (age, serum creatinine, e-GFR, FE Na%, weight and sPAP) were not normally distributed. Hence; they were presented as median (interquartile range). Moreover, comparison between the age of males and females was done using Mann-Whitney test. Furthermore, comparison between variables of (age, serum creatinine, e-GFR, FE Na%, weight and sPAP) prior to combination diuretics, after addition of Spironolactone and later after addition of HT/M was done using Wilcoxon Signed rank test.

### 3. Results

After 3 days of high-dose IV Lasix, a total of 47 patients satisfied the criteria of severe fluid overload and DR. Females were 25 (53.2%). The median (IQ) age of females and males were 50 (7) and 49.5 (7) years, respectively. The gender distribution and their respected age were not statistically different.

Course of response:

As shown in **Table 1**; after establishment of DR to high-dose Lasix; addition of Spironolactone resulted in significant increase of FE Na% from 1.2 (0.2) to 1.6 (0.2) with fluid removal leading to weight reduction from 98 (11) kg to 95 (12) three days later ( $p < 0.001$ ). Moreover; subsequent addition of HT/M to Lasix and Spironolactone resulted in further increase in FE Na% to 1.9 (0.1) and more fluid removal leading to weight reduction to 90 (11) kg three days later ( $p < 0.001$ ). At start, sPAP was high at 75 (5) mm Hg and decreased to 59 (7) after addition of Spironolactone and to 27 (4) after HT/M with  $p < 0.001$ . As expected; such therapy has resulted in increase in serum creatinine from 210 (40) to 240 (3)  $\mu\text{mol/L}$  and decrease e-GFR from 25 (10) to 22 (8) ( $\text{ml/min}/1.73\text{m}^2$ ). The response to SCDT was statistically similar in both genders.

### 4. Discussion

Studies in patients with heart failure have shown that; approximately 25% - 30% develop DR [7]. Sodium and water loss due to diuretic administration triggers RAAS activation [8], leading to increase sodium absorption along the distal nephron [9]. Moreover, experimental studies have shown 3 added ultrastructural mechanisms; 1) upregulation of proteins involved in renal sodium absorption [9], 2) activation of the sympathetic nervous system leading to increase expression and activity of sodium transporters, including the sodium-hydrogen exchanger NHE3 [10], and 3) upregulation of all  $\alpha$ -,  $\beta$ -, and  $\gamma$ -subunits of the epithelial sodium channel (ENaC), along the collecting duct (CD) [11]. The coexistence of chronic kidney disease (CKD) leads to 1) renal hypoperfusion, 2) low glomerular filtration, 3) low active tubular secretion in the proximal convoluted

**Table 1.** Changes in kidney function (SCr and eGFR), FE Na%, weight and sPAP after sequential addition of diuretics.

Parameter	At start	After combination diuretics	
	(After high-dose Lasix)	3 days after addition of Aldactone	3 days after further addition of Thiazides/Metalazone
Serum creatinine ( $\mu\text{mol/L}$ )	210 (40)	230 (30)	240 (30)
estimated GFR ( $\text{ml/min}/1.73\text{m}^2$ )	25 (10)	23 (8)	22 (8)
FE Na%	1.2 (0.2)	1.6 (0.2)	1.9 (0.1)
Body weight (Kg)	98 (11)	95 (12)	90 (11)
sPAP (mm Hg)	75 (5)	59 (7)	27 (4)

Abbreviations: SCr: serum creatinine; eGFR: estimated GFR; FE Na%: fractional excretion of sodium; sPAP: systolic pulmonary arterial pressure. Comparison between prior to combination diuretics (after high-dose Lasix), 3 days after addition of Aldactone and 3 days after addition of Thiazides/Metalazone was done using Wilcoxon Signed rank test showed significance at ( $p < 0.001$ ).

tubules. The latter is mediated by organic anion transporters (OAT) which are competitively decreased by accumulation of organic acids in RF and inhibited by depolarization of tubular cell membrane with metabolic acidosis [12]. Hence, the proposed strategies to overcome diuretic resistance should include; 1) low dietary sodium intake, 2) reduction of drug-free intervals, and 3) combined diuretic therapy (CDT) with sequential blockade of the sodium absorption along the nephron, in order to escape rebound sodium retention [13]. A landmark study, in 1994, evaluated the effectiveness of the combination of a thiazide (bendrofluzide or metolazone) with furosemide in HF patients with symptomatic fluid congestion compared to LD monotherapy [14]. The American Heart Association recommends the use of CDT in HF patients with considerable fluid overload refractory to optimized doses of LDs in monotherapy (at least 160 - 320 mg/day of intravenous furosemide in bolus or as a continuous infusion) [15] though it did not improve mortality [16]. However, the use of aldosterone to block RAS axis improved mortality both in HF and CKD [17]. Resistance to diuretics is mostly demonstrated to be linked to an upregulation of sodium reabsorption in distal tubules. Chloride seems to play a major role in renal salt sensing mechanisms triggering neuro-hormonal sodium recovery. Despite conflicting evidence of the role of hypertonic saline improving dose-response curve of LD in HF such a phenomenon was not seen in patients with severe renal failure in a randomized double-blind controlled study [18]. Several antidiuretic hormone (ADH) receptor antagonists, globally known as “vaptans,” have been developed. Tolvaptan is an oral competitive V2 receptor (V2R) antagonist approved by the US Food and Drug Administration to correct euvolumic and hypervolumic hyponatremia in patients with HF, cirrhosis, and syndrome of inappropriate ADH (SIADH) [19]. However, several studies did not show its efficiency in HF and CKD except for cases of hyponatremia [20]. A new therapeutic option to diuretic resistance is the selective blockers of the renal sodium-glucose transporter (SGLT2), which induce osmotic diuresis and exert protective effects on the cardiovascular system. The selective SGT2 inhibitors inhibit glucose transport in the proximal tubule, thus inducing glycosuria, blood pressure lowering, natriuresis, and osmotic diuresis [21]. However, their diuretic effect is transient, limited to the initial treatment phase, without intrarenal RAAS activation [22].

It should be noted that management of fluid overload in patients with heart failure is different from that in chronic renal disease. In the former; vasodilator therapy may unload the heart and improve DR and even morbidity and mortality [23]. Patients with renal disease; do not benefit from vasodilator therapy and induce hypotension that limits renal perfusion. The only available measure is CDT. In the present study; we have shown clearly that such therapy has improved their morbidity and avoided ultrafiltration therapy. In conclusion; it was safe, efficacious and cost-effective.

1) Statement of ethics:

The case was reported according to World Medical Association Declaration of Helsinki.

There was no new or investigational drug added to the patient's maintenance therapy and they were not subjected to any harmful or injurious investigation.

2) Conflict of interest statement:

The authors declare no conflicts of interest regarding the publication of this paper.

3) Funding Sources:

The authors did not have any funding sources for this article.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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