Effect of Different Drugs on Diuretic Resistance Indices in Patients with Renal Impairment Using Intravenous Furosemide

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Abstract

Chronic kidney disease is a medical condition defined as a reduction in kidney function, made known by glomerular filtration rate of a less than 60 mL/min per 1·73 m², or signs of kidney impairment (albuminuria), or both for at least three months period, nevertheless of the original cause.

Diuretic resistance in the edematous patient is defined as a clinical state in which diuretic response is diminished or lost before the therapeutic goal of relief from edema has been reached.

This study aims to find the effect of different drugs on kidney functionindices and the relationship of using these drugs with the development or improvement of diuretic resistance.

The study is a cross-sectional observational study. It was carried out at Al-Hussein-Teaching Hospital in Thi-Qar. Nasiriya. Data from 104 patients were collected and analyzed using different statistical methods.

The results showed that there was a different odd of effects of the drugs commonly used to patients with CKD due to other comorbidities on diuretic resistance indices. There was a significant increase in the body weight and decline in serum urea in patients already with edema when they used calcium ampoule. Serum urea was not affected by any of the other studied drugs. There were two drugs affected positively on serum creatinine, which are clopidogrel and heparin. Albuminuria was highly improved in patients receiving aspirin and atorvastatin. Clopidogrel significantly increased GFR in these patients.

Key words: *Aspirin, Atorvastatin, Calcium ampule, Clopidogrel, CKD, Heparin, Hydrocortisone, serum urea.*

Introduction

Chronic kidney disease is a medical condition characterized by a reduction in kidney function, made known by rate of glomerular filtration of a lesser amount of than 60 mL/min per 1·73 m², or signs of kidney impairment (albuminuria), or both, for at least three months period, nevertheless of the original cause **(1)**.

The main causes of CKD globally are Diabetes (DM) and hypertension in all high, middle-income nations and in many low-income countries **(2)** Rate, occurrence, and advance of CKD also differ within countries by ethnicity and social causes of health, possibly through epigenetic influence **(3)**.

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Diuretic resistance is a clinical condition when diuretic effect is lessened or disappeared before the helpful objective of edema has been overtaken [4].The most demanding problems that the cardio nephrologist must mark in daily clinical practice is diuretic resistance, because of considerable burden on health care costs and hospital admissions [5].

loop diuretics are agents used in CKD to decrease blood pressure and treat edema [6, 7] ,such as Furosemide, bumetanide, and torsemide , they bind to the extracellular surface of sodium-potassium-chloride symporters (NKCCs) of thick ascending limb cells along the loop of Henle by translocation pocket at the blocking ion transport directly. Hence, they increase the excretion of sodium, potassium, magnesium, and hydrogen [89].

loop diuretics are used for medical conditions like in Oedematose disorders include (congestive heart failure (CHF), hepatic cirrhosis, nephrotic syndrome), renal insufficiency, hypertension in kidney disease, hypercalcemia, hypernatremia, syndrome of inappropriate antidiuretic hormone (SIADH) and renal tubular acidosis [10, 11].

The comorbid diseases which associated with CKD should be treated, like hyperlipidemia, diabetes mellitus and hypertension, in order to decrease the cardio vascular events and improve the kidney function so that the quality of life. These drugs like aspirin that is used for its antiplatelet action. It is well known to use in secondary prevention of stroke and myocardial infarction [12]. Clopidogrel, which is a thienopyridine drug that, by blocking the adenosine diphosphate P2Y12 receptor, inhibits platelet aggregation. Clopidogrel is used more commonly to avoid potentially lethal thrombosis of newly inserted coronary stents [13].

Meanwhile in CKD, both thrombotic events and bleeding are at greater risk. The initial stages of CKD are predominantly associated with prothrombotic risk, while platelets can become unstable due to uremic-related toxin toxicity in their advanced stages, besides the prothrombotic condition, leading to an increased predisposition to bleed. For the treatment or prevention of thromboembolic diseases, CKD patients typically need anticoagulation therapy like heparin [14].

In (CKD), hyperparathyroidism occurs in a reduced parathyroid hormone calcemic response (PTH). Ca ampule helps to establish hyperparathyroidism and is presumed to be due to decreased bone efflux of calcium, so prevent osteoporosis [15, 16].

Atorvastatin is used in patients at CKD due to risk of or with cardiovascular disease. It had renal protective effects and given for dyslipidemia atorvastatin improved kidney function over time in a dose dependent manner [17,18,19]. The patients also take corticosteroid as hydrocortisone and dexamethasone which are used for breathing problems to asthmatic patients or for skin or drug allergy [20].

All these drugs may affect positively or negatively on diuretic resistance indices, which are body mass index (BMI), serum urea, serum creatinine, estimated glomerular filtration rate (eGFR) and albuminuria or they may have no any significant effect.

The goal of this study is to find the effect of different drugs on kidney function indices in patients with CKD treated acutely by furosemide, as a method of detecting diuretic resistance and factors affecting it.

Patients and Methods

This research was conducted at (Al-Hussein-teaching hospital) in Thi-Qar, Nasiriya. Data were collected from patients after getting approval from the Ethical and Scientific Committees of the Faculty of Pharmacy/ Basra University in addition to the Scientific Committee of Researches of Thi-Qar Health Directorate.

This study is a cross-sectional observational study, carried out from October 2019 to June 2020.

The Inclusion criteria were patients age of 18 years and older of either gender, patients or relative should be able to communicate and willing to participate in this study, patients that take loop diuretic (intravenous furosemide) only. Also, patients with chronic kidney

disease (GFR ≤ 60), diabetes mellitus, asthma, Chronic obstructive pulmonary disease (COPD), hypertension (HT), cancer and had no contraindication to diuretics or other standard medications for heart failure and kidney diseases. Excluded patients were those with acute infectious diseases like pneumonia, complicated urinary tract infection (UTI), human immunodeficiency virus (HIV), Children or Patients who were <18 years. Patients excluded if they refused to participate, Patients who had cognitive deficits (physical or mental state), females who were pregnant or breastfeeding, Patients taking oral diuretics or other diuretics than loop diuretic and patients with Acute Surgery. Patients with recent myocardial infection (MI) within 3 weeks also were excluded, in addition to patients who already on anticoagulant therapy for other indications. Patients with nephrotic syndrome, urinary tract malformation, urolithiasis, kidney transplant, Hemodialysis also were added to the exclusion list.

In the present study, (104) patients were recruited. They were all agreed with the data collection formats used. The data collected from patients by their specific file and the laboratory analysis.

Statistical analysis used in this study included the use of SPSS version 2017 and Excel Soft Ware 2019, the p value of (<0.05) is considered as statistically significant. Statistical programs were Chi Square for analysis of frequency, T- test used for analysis for continuous variables defined as Mean ± Standard deviation (SD), Pearson correlation was performed to find correlation among different variables.

Estimation of GFR is done by modification of diet in renal disease (MDRD) equation[21] and BMI (kg/m²) calculated as BMI= $weight/height^2$[22].

Albuminuria is known as an indicator for renal dysfunction, the method used to detect albuminuria is Albumin-to-creatinine ratio (ACR). This method detects albuminuria by a spot urine sample. By dividing concentration of albumin in (mg) to concentration of creatinine in (gm), we can calculate ACR [23].

Results

One hundred and four patients were included in this study, number of females was 54 (51.9%) and that of male was 50(48.1%). Mean age of patients was (67±13.5). Other data regarding patients in the study considering BMI, laboratory data, age distribution are involved in table (1).

General characteristics of patientsenrolled in the study and the drugs used are detailed in table (2).

Table (1) General characteristics of patients enrolled in the study, N=104

Parameters	N (%)	P value
Gender		
Male	50 (48.1%)	0.7686
Female	54 (51.9%)	
Data of patients		
Age (years)	67 ± 13.5	
BMI (kg/m2)	25.3 ± 2.8	
S. creatinine (mg/dl)	3.2 ± 1.7	

Cont... **Table (1) General characteristics of patients enrolled in the study, N=104**

S. urea (mg/dl)	117.6 ± 56.5	
Hb (g/dl)	10.4 ± 2.2	
Age Distribution (years)		
<=40	5 (4.8%)	< 0.0001
41 – 50	6 (5.8%)	
51- 60	18 (17.3%)	
>60	75 (72.1%)	
BMI (kg/m2)		
<18.5	2 (1.9%)	< 0.0001
18.5-25	42 (40.4%)	
25-30	55 (52.9%)	
>=30	5 (4.8%)	
P value < 0.05 considered significant.		

Table (2) General characteristics of patients enrolled in the study, N=104.

Parameters	N (%)	P value
Occupation		
Helpless	72 (69.2%)	< 0.0001
Student	2 (1.9%)	
Housewife	17 (16.3%)	
Retired	8 (7.7%)	
Officer	2 (1.9%)	
Worker	3 (2.9%)	
Drugs Used		
Aspirin 100mg	53 (51%)	< 0.0001
Hydrocortisone	8 (7.7%)	
Atorvastatin	38 (36.5%)	
Clopidogrel	27 (26%)	
Heparin	20 (19.2%)	
Calcium ampule	33 (31.7%)	
P value < 0.05 considered significant.		

1. Effect of aspirin on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity).

Aspirin administration showed non-significant ($p<0.05$) effects on BMI, serum urea, serum creatinine, eGFR. However, it had significantly ($p<0.05$) lowered the severity of albuminuria (1.5 ± 1.2 with aspirin vs. 2.1 ± 1 without aspirin, p=0.0052). See table (3)

2. Effect of Hydrocortisone and dexamethasone on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity).

Hydrocortisone or dexamethasone administration showed non-significant ($p<0.05$) effects on BMI, serum urea, serum creatinine, eGFRand albuminuria severity. See table (3)

3. Effect of Atorvastatin on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity).

Atorvastatin administration showed non-significant ($p<0.05$) effects on BMI, serum urea, serum creatinine, eGFR.Nevertheless, it had significantly ($p<0.05$) lowered the severity of albuminuria (1.4 ± 1.2 with atorvastatin vs. 2 ± 1 without atorvastatin, p=0.0367). See table (3).

Table (3) Effects of drugs used on BMI, serum urea, Serum creatinine, eGFR and albuminuria severity.

Parameters	With	Without	P value
Aspirin			
BMI (kg/m2)	25.5 ± 2.7	25.1 ± 3	0.4531
S. Creatinine (mg/dl)	2.8 ± 1.6	3.5 ± 1.7	0.0764
eGFR (ml/min)	31.6 ± 28.6	23.8 ± 18.6	0.1253
Albuminuria severity	1.5 ± 1.2	2.1 ± 1	0.0052
S. Urea (mg/dl)	115.6 ± 60.8	119.7 ± 52.1	0.5163
Hydrocortisone & dexamethasone			
BMI (kg/m2)	25.9 ± 2.1	25.3 ± 2.9	0.3319
S. Creatinine (mg/dl)	3.1 ± 2.1	3.2 ± 1.7	0.5436
eGFR (ml/min)	38.1 ± 45	26.9 ± 22	0.4138
Albuminuria severity	1.1 ± 1.4	1.8 ± 1.1	0.6491
S. Urea (mg/dl)	87.1 ± 69.5	120.5 ± 54.7	0.2957
Atorvastatin			
BMI (kg/m2)	25.8 ± 2.4	25 ± 3.1	0.2229
S. Creatinine (mg/dl)	3.1 ± 1.8	3.2 ± 1.6	0.4032
eGFR (ml/min)	31.9 ± 32.6	25.4 ± 17.9	0.0997
Albuminuria severity	1.4 ± 1.2	2 ± 1	0.0367
S. Urea (mg/dl)	114.4 ± 65.9	119.6 ± 49.9	0.8707

P value < 0.05 considered significant.

4. Effect of Clopidogrel on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity).

Clopidogrel administration showed non-significant ($p<0.05$) effects on BMI, serum urea, and Severity of albuminuria. However, patients using clopidogrel showed significantly ($p<0.05$) lowered serum creatinine as compared with those non using it, (2.8 ± 1.7 with clopidogrel vs. 3.3 ± 1.7 without clopidogrel, p=0.0356). In addition, eGFR was significantly ($p<0.05$) higher with clopidogrel as compared with clopidogrel free group (33.8 ± 29 with clopidogrel vs. 25.5 ± 22.7 without clopidogrel, p=0.0276). See table (4).

5. Effect of Heparin on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity.)

Heparin administration showed non-significant ($p<0.05$) effects on BMI, serum urea, eGFR and severity of albuminuria. Patients using Heparin showed significantly ($p<0.05$) lower serum creatinine levels as compared with those non using it, (2.8 ± 1.3 with Heparin vs. 3.2 ± 1.8 without Heparin, p=0.0146). See table (4).

6. Effect of Calcium ampoule on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity.)

Calcium ampoule administration showed non-significant ($p<0.05$) effects on Serum creatinine, eGFR, and Severity of albuminuria. However, patients using Calcium ampoule showed significantly ($p<0.05$) lowered serum urea as compared with those not using it, (103.3 ± 47.9 with Calcium ampoule vs. 142.7 ± 62.1 without Calcium ampoule, p=0.0242). In addition, BMI was significantly ($p<0.05$) higher with Calcium ampoule as compared with non (25.8 ± 2.7 with calcium ampoule vs. 24.4 ± 2.9 without calcium ampoule, p=0.0243). See table (4)

Table (4)Effects of drugs used on BMI, serum urea, Serum creatinine, eGFR and albuminuria severity.

Parameters	With	Without	P value
Clopidogrel (Plavix)®			
BMI (kg/m2)	26 ± 2.4	25.1 ± 2.9	0.5418
S. Creatinine (mg/dl)	2.8 ± 1.7	3.3 ± 1.7	0.0356
eGFR (ml/min)	33.8 ± 29	25.5 ± 22.7	0.0276
Albuminuria severity	1.4 ± 1.1	1.9 ± 1.1	0.5253
S. Urea (mg/dl)	101.4 ± 52.9	125.6 ± 57.5	0.0572
Heparin			
BMI (kg/m2)	26 ± 2.8	25.2 ± 2.9	0.2098
S. Creatinine (mg/dl)	2.8 ± 1.3	3.2 ± 1.8	0.0146
eGFR (ml/min)	34.7 ± 37.4	26.1 ± 20.1	0.0786
Albuminuria severity	1.4 ± 1.1	1.9 ± 1.1	0.2341
S. Urea (mg/dl)	91.8 ± 52.3	124.4 ± 55.9	0.0518
Calcium ampoule			
BMI (kg/m2)	25.8 ± 2.7	24.4 ± 2.9	0.0243
S. Creatinine (mg/dl)	2.9 ± 1.6	3.6 ± 1.8	0.1940
eGFR (ml/min)	27.9 ± 20.6	27.5 ± 31.4	0.4849
Albuminuria severity	1.7 ± 1.1	1.8 ± 1.1	0.0670
S. Urea (mg/dl)	103.3 ± 47.9	142.7 ± 62.1	0.0242
P value < 0.05 considered significant			

Discussion

1. Effects of Aspirin on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity).

The results of this study were not consistent with a study of Okada et.al 2016 concerning albuminuria. He found that there is non-significant effect of low-dose aspirin on albuminuria severity in patients with DM2 who had renal dysfunction [24] but the study done on patients not using intravenous furosemide . However, this study was consistent with a study of Pastori .et.al, 2016 who found that the low dose of aspirin had no effect on the eGFR in patient with CKD and hypertension ,who was taking intravenous furosemide [25].

Aspirin is an active inhibitor of cyclooxygenase enzyme, at low dose (75mg-160mg) it acts as an antiplatelet agent, which demonstrates its action by inhibiting irreversibly platelet COX-1 enzyme, thereby stopping the development of thromboxane A2 (TXA2). It has been used in the Prevention of vascular thromboembolic event[2627].

Aspirin may positively interfere with the severity of albuminuria, through interference in thromboxane A2 synthesis that affects the albuminuria severity according to studies [28].

TXA2 is a potent vasoconstrictor and platelet aggregator, its production increases in renal dysfunction, HF and hypertension; when aspirin inhibits cyclooxygenase, it will inhibit the production of TXA2, which may reduce deteriorating the renal function, and reduce of albuminuria [29].

2. Effect of Hydrocortisone and dexamethasone on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity).

Corticosteroids are potent anti-inflammatory drugs and immuno-suppressants used in many conditions like asthma [30]. Patients that use hydrocortisone and dexamethasone in low doses through injection in the present study as a combination with furosemide, showed non-significant ($p<0.05$) effect on kidney function and their use were to avoid allergic reaction and not intended to treat any possible adrenal or endocrine problems or any autoimmune problem.

Since all corticosteroid-treated diseases have inflammatory components at least, so that exacerbation of this inflammation is treated with a systemic corticosteroid, the impact on renal function was attributed to diseases themselves [31].

3. Effects of Atorvastatin on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity).

In this study, the results regarding atorvastatin effects were consistent with result of Stefano Bianchi et.al 2003 who found that using atorvastatin would decrease the albuminuria severity [32], however, his study was done on patients using diuretics but intravenous furosemide was not specified.

Atorvastatin is a class of HMG-CO reductase inhibitor drugs, which decreases the glomerular damage and preserves the renal function by decreasing the deposition of lipid in the kidney [33].

Therefore, Atorvastatin had a role in reducing the renal injury that comes from elevation in oxidative stress levels, procoagulant and inflammatory biochemical levels in renal insufficiency[32]resulted in improvement of intra renal endothelial functions [34].

4. Effects of Clopidogrel on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity).

The study of Tonelli et.al. 2007 found that patients who had CKD and HF would benefit from the addition of clopidogrel, as antiplatelet with or without aspirin, and this was consistent with our study that clopidogrel will reserve the eGFR [35] .However, the study was done on patients using diuretics, the intravenous furosemide was not specified.

It was also consistent with finding of study of Gremmel et.al., 2013 who found that using clopidogrel had significant effect on serum creatinine and eGFR but the study was done on patients not using intravenous furosemide[36].

Using ADP receptor antagonist like clopidogrel may have beneficial effects on eGFR and creatinine. This indicate implicated role of platelets in deterioration of kidney function [37] may be through interference with renin and kidney perfusion pressure and hence eGFR [38].

5. Effects of Heparin on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity.)

The clearance of heparin occurred by renal excretion, the unfractionated heparin doesn't accumulate in the kidney like LMW heparin [39]Nagge, et.al.,2002. Heparins have many physiological effects beyond their anticoagulant property; Nagge study was done on patients not using intravenous furosemide [40].

Heparin, in animal model, was associated with reduction levels of parameters that indicate renal problems like urea, creatinine, reduce renal damage induced by ischemia and albuminuria and it may improve eGFR [40].

In this study, these finding came in agreement to those mentioned by previous studies. Blood urea was lower for patients using heparin (91.8 ± 52.3 with heparin vs. 124.4 ± 55.9, p=0.0518) but was non-significant for eGFR; there was improvement but again it was nonsignificant (34.7 ± 37.4 with heparin Vs. 26.1 ± 20.1, p=0.0786). However, serum creatinine was significantly ($p<0.05$) lowered in patients with heparin as compared with those not using it.

Histones might be implicated in the damage of kidney infrastructures, through inducing inflammation and the apoptosis [41]. Heparin may attenuate these effects by neutralizing these histones and may help in reserving kidney function [41]. In addition to that, heparin injection may affect level of midkine, a heparin-binding growth factor. Recently it was found to be implicated in many inflammatory processes and its expression was elevated in renal tubules [42].In acute and chronic kidney diseases, Pulsated elevation of midkine, after injection of heparin may has a beneficial effect on renal tubules and other endothelial cells by reducing apoptosis, and it enhances tubular cells regeneration. The effect of heparin and midkine on kidney function may be more complicated and not fully elucidated [43].

6. Effects of Calcium ampoule on diuretic resistance parameters (BMI, serum urea, serum creatinine, eGFR and albuminuria severity.)

In this study, High percentage of Patients had CKD, where its complications are hyperparathyroidism and alteration in the absorption of calcium and phosphate. This causes osteoporosis. Therefore, calcium ampule has a tendency to decrease the release of calcium from bone to blood in order to prevent osteoporosis and to replace calcium lost in urine by using of furosemide, which may increases calcium resorption and degradation of bone by action of parathyroid hormone [44].

One of complications of renal failure is the uremic encephalopathy where serum urea level increased significantly. It was found that PTH, one of hormones that had a direct effect on serum urea by regulating the calcium in the cerebral area. Calcium will decrease the uremic encephalopathy caused by elevation of serum urea [45]. It was found also that any increase in PTH hormone would increase renin release [46]. Addition of calcium may reduce renin release and study of Davies, et. al 2000 found that calcium intake decreases BMI and that was not consistent with our findings [47] and the study was done on patients not using intravenous furosemide.

Conclusion

Concomitant use of drugs with furosemide injection that is used to overcome edema associated with CKD has had different odd of effects on the activity of the diuretic on renal function itself. It was found in this study that drugs frequently used to treat comorbidities associated

with CKD were most likely helpful in potentiating the effect of furosemide on renal function and we may be able to say that they decreased likelihood of diuretic resistance that usually associated with the diuretic in CKD patients due to different causes.

From this study, we can get issue that no drug affected positively on BMI. In case of calcium ampule, the effect was negatively by increasing the body weight in patients already with edema. The only drug that affected positively on Serum urea was calcium ampule; however, all other drugs had no significant effect on serum urea.

Clopidogrel and heparin reduced significantly Serum creatinine levels, meanwhile, they did not reduce albuminuria severity, the effect that was positive from two drugs, Aspirin and Atorvastatin only. The only drug that affects the eGFR was clopidogrel. It affected positively by increasing eGFR in these patients.

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Limitations:

The limited number of patients where only 104 patients were involved, it was only one group and there was no control group to compare the effect on kidney function. In addition, lack of follow up for these patients;all data collected were in the time of patient's admission only. In addition, the study was a single center study.

Recommendations: We recommend by increasing the number of patients and using more lab tests that indicate diuretic resistance like urinary Na – K ratio, Fractional Na excretion (FeNa) □, Spot urinary Na and more marker for kidney to see the effect of drugs on this organ.

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Ethical Clearances: Approval from the Ethical and Scientific Committee of the Faculty of Pharmacy/ Basra University in addition to the Scientific Committee of Researches of Thi-Qar Health Directorate.

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