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Efficacy of furosemide in patients with chronic kidney disease with residual renal functions in hemodialysis and non-hemodialysis patients

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ABSTRACT

Introduction and aim. Chronic kidney disease (CKD) affects kidney function, characterized by albuminuria or reduced estimated glomerular filtration rate (eGFR), and is influenced by factors such as etiology, pathogenesis, intensity, and progression. According to data from the literature, the efficacy of furosemide has not been much researched much in CKD patients. The study evaluates the efficacy in chronic kidney disease patients, regardless of hemodialysis, and compares its diuretic effect based on the administration route.

Material and methods. A prospective observational study was conducted in a tertiary healthcare facility for 6 months (October 2021 to March 2022). 100 CKD patients who met the criteria were enrolled in the study. Data on study-relevant parameters, such as route of administration (ROA), hemodialysis frequency, hospital stay, blood urea, serum creatinine, sodium, and potassium, were collected. Pearson's chi-square test was used to evaluate the association between parameters. One-way ANOVA was applied to analyze the significant association between ROA and urine output.

Results. Of all the study samples, 72% received intravenous furosemide and 28% received furosemide orally. There was a significant difference in eGFR and urine output on admission and discharge days. There was an increase in urine output when the patient received furosemide and improvement in eGFR was found. A significant association was also observed between systolic blood pressure, sodium, and potassium.

Conclusion. The study found no significant differences in furosemide efficacy in CKD patients, regardless of ROA, hospital stay, or frequency of hemodialysis, indicating similar effectiveness.
Keywords. chronic kidney disease, efficacy, hemodialysis, route of administration

Introduction

Chronic kidney disease (CKD) refers to a variety of diseases that impact the structure and function of the kidneys. The diversity in the manifestation is influenced by factors such as etiology, pathogenesis, intensity, and pace of progress. CKD is characterized by albuminuria or a reduced glomerular filtration rate (GFR) [below 60 mL per min/1.73 m^2] for three months or more, regardless of clinical diagnosis.[1] CKD is characterized by initial phases of kidney damage, in which more than 50% of the kidney tissue is damaged, leading to elevated serum creatinine and reduced kidney function. This is the reason for the need for kidney transplantation and treatment focused on restoring the health of patients with kidney disease without risking the donor's health.[2] One of the most pressing global public health concerns is CKD. In general, the estimated frequency of CKD is 13.4% (11.7−15.1%), and the estimation of end-stage kidney disease (ESKD) that requires renal replacement therapy is between 4.902-7.083 million.[3] In 2017, globally, 1.2 million people died from CKD. The worldwide increase in the total age mortality rate from CKD was 41.5% between 1990 and 2017, although there was no remarkable difference in the age-related mortality rate.[4]

In India, the current estimated value of ESKD is 229 million people and annually, more than 100,000 new cases begin kidney replacement programs. The screening and early evaluation of kidney disease (SEEK) India cohort study found a 17.2% prevalence of CKD, with 6% having stage 3 or severe CKD. The prevalence of stages 1, 2, 3, 4, and 5 of CKD was 7%, 4.3%, 4.3%, and 0.8%respectively.[5] Diuretics play a key role in the management of CKD.[6] Although all drugs have their benefits and side effects, they commonly cause fluid, electrolyte abnormalities, and acid-base disturbances. Diuretics are used to modify interdialytic weight gain in patients with residual renal function. High-dose loop diuretics are recommended in patients who undergo hemodialysis on non-hemodialysis days. Furosemide in high doses has been found to be effective in high doses is efficient in both acute and chronic kidney disease. It is also helpful in correcting fluid overload.[7] Nearly 500 monogenetic causes of CKD have been recognized primarily in pediatric populations. A limited number of studies on monogenic causes in adults with CKD.[8] Most patients with CKD generally do not show any symptoms in the early stages. In the advanced stages of CKD, symptoms like weight loss, anorexia, pedal edema, shortness of breath, fatigue, hematuria, polyuria, insomnia, pruritus, headache, numbness, vomiting, and muscle cramps can be seen.[9] Hypertension: one of the leading causes of CKD.[10] Other risk factors: kidney stones, cirrhosis, atherosclerosis, bladder cancer, scleroderma, systemic lupus erythematosus, and kidney infection.[11] Diuretics play a crucial role in the management of CKD. However, all drugs have their benefits and side effects. In general, they cause fluid, electrolyte abnormalities, and acid-base disturbances.[6] Diuretics are used to modify interdialytic weight

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gain in patients with residual renal function. High-dose loop diuretics are recommended in patients undergoing hemodialysis on nonhemodialysis days.[12] Furosemide is often preferred in the treatment of CKD due to its potent diuretic effects, which help manage fluid overload and hypertension commonly associated with CKD. Key reasons include its potent diuresis, which effectively promotes sodium and water excretion, relieving symptoms of volume overload.[13] Additionally, it helps lower blood pressure, which is crucial for managing CKD management to slow disease progression.[14] Furosemide remains vital for managing fluid overload in the early to moderate CKD stages. However, in patients with severe CKD and dialysis, clinicians may need to consider other approaches to fluid management.[15]

Aim

The study assesses the efficacy of furosemide in the treatment of patients with chronic kidney disease, regardless of hemodialysis, and compares its diuretic effect based on the administration route.

Material and methods

Study design and study settings

An observational cross-sectional study of all eligible patients with chronic kidney disease was conducted in the nephrology department of a South Indian hospital and research center from October 2021 to March 2022. The institution's research ethics committee approved the study. The demographics and parameters relevant to the study were collected, such as age, sex, hospital stay, hemodialysis frequency, route of hemodialysis, furosemide administration route, blood pressure, urine output, blood urea, serum creatinine, sodium, and potassium. The selection of furosemide dosage was mainly based on the patient's body weight of the patient and kidney function. The study has been approved by the Human Ethics Committee of Mahavir Hospital and Research Center, with reference no. ECR01/450/Inst/AP/11/03/22.

Inclusion criteria

Patients over 18 years old, Individuals belonging to any class, caste, or sex, Patients diagnosed with CKD receiving furosemide, and both hemodialysis and nonhemodialysis patients were included.

Exclusion criteria

The patients were prescribed diuretics other than furosemide. Patients who had undergone a kidney transplant and pregnant women were excluded from the study, and patients who were not ready to give their consent to participate in the survey.

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Sample size

A total of 130 patients diagnosed with CKD, regardless of hemodialysis, were assessed, of which 30 patients were excluded according to exclusion criteria. In our study, around 70% of the participants had hypertension as a comorbidity and around 48% to 59% of the participants had diabetes and cardiac abnormalities as a comorbidity. The baseline characteristics were obtained for each patient.

Statistical analysis

Data were analyzed using SPSS (version 28.0, IBM, Armonk, NY, USA). In this statistical analysis, the dependent variables were route of administration (ROA) of furosemide, hemodialysis, estimated glomerular filtration rate (eGFR), sodium, potassium, blood pressure (BP), and urine output. The independent variables were demographics, hospital stay, comorbidities, serum creatinine, and blood urea. Pearson's chi-square test evaluated the association between ROA, hemodialysis (HD) frequency, and hospital stay. To analyze the significant association between the parameters taken on the day of admission and discharge, a one-way analysis of variance (ANOVA) was used.

Results

The present study compared the relevant admission parameters with the discharge parameters. As shown in the table, there was a significant difference in eGFR and fluid output (Tables 1 and 2).

Table 1. Association among parameters on admission and discharge

		n	Correlation	p
Pair 1	Systolic BP on admission and systolic BP discharge	100	0.105	0.296
Pair 2	Diastolic BP on admission and diastolic BP on discharge	100	0.006	0.956
Pair 3	EGFR at admission and EGFR mL/min/1.73 m^2 on discharge	100	0.646	<0.001
Pair 4	Serum creatinine at admission and serum creatinine on discharge	100	0.155	0.123
Pair 5	Blood urea on admission and blood urea on discharge	100	-0.099	0.325
Pair 6	Sodium on admission and sodium on discharge	100	-0.041	0.688
Pair 7	Potassium on admission and potassium on discharge	100	-0.078	0.443

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Pair 8	Fluid output (mL) on admission and fluid output (mL) on discharge	100	0.390	<0.001

Table 2. Mean, standard deviation, and associations of parameters using one-way analysis of variance (ANOVA).

	Paired differences					t	df	p
	Mean	Std. deviation	Std. error mean	95% confidence interval of the difference				
				Lower	Upper			
Systolic BP on admission – systolic bp discharge	14.29	46.145	4.614	5.133	23.446	3.097	99	0.003
Diastolic BP on admission diastolic BP on discharge	2.69	67.738	6.774	-10.751	16.13	0.397	99	0.692
EGFR at admission EGFR ml/min/1.73 m^2 on discharge	-2.51	21.703	2.17	-6.816	1.796	-1.157	99	0.250
Serum creatinine at admission – serum creatinine on discharge	1.072	5.291	0.529	0.022	2.121	2.026	99	0.045
Blood urea on admission – blood urea on discharge	-4.14	67.476	6.748	-17.529	9.249	-0.614	99	0.541
Sodium at admission – sodium on discharge	4.942	17.104	1.71	1.548	8.336	2.889	99	0.005
Potassium on admission – potassium on discharge	0.429	1.37	0.137	0.158	0.701	3.134	99	0.002
Fluid output (mL) at admission – fluid output (mL) on discharge	-236.03	916.53	91.653	-417.89	-54.17	-2.575	99	0.011

There was a significant association between systolic BP, sodium, and potassium on admission day and discharge day, as indicated by a one-way ANOVA test of significance ($p \leq 0.05$, Table 3).

Table 3. Analysis of variance (ANOVA) for urine output of IV furosemide in HD and non-HD

	Paired differences					T	df	p
	Mean	Std. deviation	Std. error mean	95% confidence interval of the difference				
				Lower	Upper			

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Urine output of IV furosemide in HD urine output of iv furosemide in non-HD	-871.657	1086.169	183.596	-1244.769	-498.545	-4.748	34	<0.001

There was a significant association between the urine output of participants on HD receiving IV furosemide and the urine output of participants not on HD receiving oral furosemide, as indicated by a one-way ANOVA test of significance ($p<0.05$, Table 4).

Table 4. ANOVA for oral furosemide urine output in HD and non-HD Patients in the study*

	Paired differences					**t**	**df**	**p**
	Mean	**Std. deviation**	**Std. error mean**	**95% confidence interval of the difference**				
				Lower	**Upper**			
Urine output of oral furosemide in HD urine output of oral furosemide in non-HD	-1050.769	520.359	144.322	-1365.219	-736.319	-7.281	12	<0.001

* HD hemodialysis, Non-HD – non-hemodialysis patients

There was a significant association between the urine output of participants on HD who received oral furosemide and those not on hemodialysis who received oral furosemide, as indicated by a one-way ANOVA test of significance ($p<0.05$, Table 4).

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Table 5. Correlation of oral dose furosemide with frequency of HD patients

		Frequency of HD						Total
		No	Once a week	Twice a week	Thrice a week	Daily	SOS	
Oral dosage	No	37	3	7	18	6	1	72
	20 mg	3	0	1	1	0	0	5
	40 mg	9	3	4	6	1	0	23
Total		49	6	12	25	7	1	100
χ^2=5.6, df=10, p=0.8								

The frequency of HD was higher in participants who received 40 mg of oral furosemide than in participants who received 20 mg of oral furosemide. There was no significant association between oral dose and frequency of HD at p=0.8 (Table 5).

Table 6. Oral dose frequency correlated with HD frequency of HD

		Frequency of HD						Total
		No	Once a week	Twice a week	Thrice a week	Daily	SOS	
Oral dose frequency	No	37	3	6	18	6	1	71
	OD	1	0	1	2	0	0	4
	BD	11	3	4	4	1	0	23
	TID	0	0	1	1	0	0	2
Total		49	6	12	25	7	1	100
χ^2=11.81, df=15, p=0.63								

* OD once daily, BD – twice daily, TID – thrice daily

The frequency of HD was found to be higher in participants who received oral furosemide twice a day, followed by once a day and three times a day. There was no significant association between oral dose frequency and frequency of HD at p=0.63 (Table 6).

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Table 7. Dose of IV bolus correlated with frequency of HD

		Frequency of HD						Total
		No	Once a week	Twice a week	Thrice a week	Daily	SOS	
IV bolus dose	No	12	3	5	7	1	0	28
	20 mg	7	1	2	2	2	1	15
	40 mg	16	2	3	11	3	0	35
	60 mg	14	0	2	5	1	0	22
Total		49	6	12	25	7	1	100
χ^2=13.71, df=15, p=0.54								

The frequency of HD was found to be higher in participants receiving 40 mg of IV furosemide, followed by participants receiving 60 mg of IV furosemide and 20 mg IV furosemide. There was no significant association between oral dose and frequency of HD at p=0.54 (Table 7).

Table 8. IV bolus dose frequency correlated with HD cross-tabulation

		Frequency of HD						Total
		No	Once a week	Twice a week	Thrice a week	Daily	SOS	
IV bolus dose frequency	No	12	3	5	7	1	0	28
	OD	0	1	0	1	0	0	2
	BD	26	2	3	11	3	1	46
	TID	8	0	3	2	1	0	14
	SOS	3	0	1	4	2	0	10
Total		49	6	12	25	7	1	100

The frequency of HD was found to be higher in participants who received an IV bolus twice a day, followed by three times a day, when necessary, and once a day. There was no significant association between the frequency of IV bolus and frequency of HD at p=0.037 (Table 8).

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Discussion

CKD is a prominent contributor to global mortality. CKD ranks among the top five leading causes of death in multiple nations. CKD was ranked as the eighth leading cause of death in India, according to global burden of disease. The main purpose of our study was to evaluate the efficacy of furosemide in improving renal function in patients with chronic kidney disease. Our study consists of 130 patients diagnosed with CKD irrespective of hemodialysis, of which 30 patients were excluded based on exclusion criteria, making the participation rate 80%. Our study includes 41% (41) females and 59% (59) males, compared to the study conducted by Sanjay et al., where the percentage of males was predominant (55%).[16] In this present study, half of the participants (50%) were in between the 30−60 year age group, 45%were above 60 years, and 5% were below30 years, concluding that the highest number of people suffering from CKD belonged to the middle age group (30–60 years). In the current study, half of the participants (51%) were undergoing maintenance HD and the other half (49%) were not on hemodialysis. The percentage of participants who undergo hemodialysis is 6% once a week, 12% twice a week 25% three times a week, and 1% as required. In our study, the sum of participants staying in the hospital for 1-10 days was 70%, while the sum of participants staying there for 10-20 days was 30%. All participants were prescribed furosemide; most (72%) received intravenous furosemide and 28% received furosemide orally. Among participants receiving oral furosemide, 5% were prescribed a dose of 20 mg and 23% were prescribed a dose of 40 mg; The frequency percentage of BD (23%) was higher than OD (3%) and TID (2%). As mentioned above, most participants have been prescribed IV furosemide; of these, a higher number of patients received a 40 mg dose (35%), followed by a 60 mg dose (22%), and a 20mg dose (15%), the frequency percentage of participants taking BD (46%) was higher than OD (2%), TID (14%), and as needed (10%). In our current study, the main comorbidities were found to be hypertension (74%), diabetes (59%), heart disease (48%), and edema (25%). Parameters relevant to the study at admission were compared with those at discharge; There was a significant difference in eGFR and urine output; Similar results were seen in other studies.[17] We found that the mean systolic and diastolic blood pressure, serum creatinine, sodium concentration and potassium concentration decreased slightly, and estimated glomerular count, blood urea nitrogen, and fluid output were increased; similar results were seen compared to other studies.[18] There was a significant association between systolic bp, sodium and potassium on admission day and day of discharge, indicated by a one-way ANOVA test of significance ($p<0.05$), compared to the study conducted by Bunyoung et al., where there was a significant increase in BP, sodium, and potassium.[19] In our present study, mean urine output was lower in participants receiving IV furosemide in HD patients compared with non-hemodialysis; we also found no significant difference in urine output among participants receiving IV furosemide undergoing HD compared to those who did not undergo HD. There was a significant association between the urine output of participants on HD receiving IV furosemide and those not on HD receiving oral furosemide, as indicated by a one-way ANOVA test of significance ($p<0.05$). In this study, the average urine output of the

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participants receiving oral furosemide in HD patients was lower than that in non-HD. We found a significant difference in the performance of participants who received oral furosemide in HD patients compared to non-HD patients. Improvement in diuresis was observed in patients not on HD. The result showed a significant association between the urine output of participants on HD receiving oral furosemide and those not on HD, as indicated by a one-way ANOVA test of significance ($p<0.05$). The frequency of HD was higher in participants who received 40 mg of furosemide orally, followed by participants who received 20 mg of furosemide orally. There was no significant association between oral dose and frequency of HD at $p=0.8$. Hemodialysis was found to be more frequent in participants who received oral furosemide twice a day, followed by once a day and three times a day. At $p=0.63$, there was no significant association between oral dose and HD frequency. The frequency of HD was higher in participants who received 40 mg of IV furosemide, followed by 60 mg and 20 mg. There was no significant association between the IV dose and the frequency of HD at $p=0.54$. The frequency of HD was found to be highest in participants given intravenous furosemide twice daily, followed by three times daily, as needed, and once daily. There was no significant association between the frequency of IV furosemide and the frequency of HD at p=0. 037. The sum of hospital stays for patients receiving oral furosemide was 18 for 1–10 days and 10 for 10–20 days. For participants who received IV furosemide, the percentage of hospital stay was 52% for 10 days and 20% for 10-20 days. There was no significant association between the route of administration and hospital stay at $p=0.43$. The sum of hospital stay for participants who received 20 mg of oral furosemide was 3 for 1-10 days, 2 for 10–20 days, and for participants who received 40 mg of oral furosemide, it was 15 for 1–10 days and 8 for 10–20 days. There was no significant association between oral dose and hospital stay at $p=0.72$. The sum of hospital stays for participants receiving oral furosemide once a day was 3 for 1–10 days and 1 for 10–20 days; twice a day, it was 14 for 1–10 days and 9 for 10–20 days, thrice a day it was 1 for 1–10 days and 1 for 10–20 days. There was no significant association between the frequency of oral dose and hospital stay at $p=0.63$. The total hospital stay days of patients receiving 20 mg IV furosemide was 9 for 1–10 days and 6 for 10–20 days; for 40 mg, it was 26 for 1–10 days and 9 for 10–20 days, 60 mg it was 17 for 1–10 days 5 for 10–20 days. There was no significant association between IV dose and frequency of hospital stay days. The total hospital stay days of participants receiving IV furosemide once a day for 1–10 days was 2, and for 10–20 days was 0; twice a day, it was 30 for 1–10 days and 16 for 10–20 days, and for thrice a day it was 10 for 1–10 days and 0 for 10–20. There was no significant association between IV dose frequency and the sum of hospital stays at $p=0.19$. In our study, the evaluation of side effects was not included as an objective. The KDIGO guidelines emphasize personalized treatment plans, recommending diuretics for volume overload while closely monitoring renal function and electrolytes.[20] Optimization strategies are dosing adjustment, monitoring protocols, and combination therapies such as the use of thiazide diuretics in conjunction with loop diuretics.[21]

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Study limitations

The main limitation of the study was the small sample size. The study was limited by a limited sample size, which may affect the generalizability of the findings. Resource limitations: insufficient resources impacted the scope of the investigation, potentially limiting the depth of the analysis. Adverse effects: the study did not adequately address the adverse effects associated with the intervention, which is crucial for a comprehensive understanding of its safety profile. Supportive therapy information: there was a lack of detailed information on supportive therapies, which could influence treatment outcomes and recommendations.

Conclusion

CKD refers to a variety of diseases that impact both the structure and function of the kidney. The variability in the manifestation of the illness is influenced by factors such as etiology, pathogenesis, severity, and pace of development. It is one of the leading causes of death. It is prevalent in both men and females; higher testosterone levels in men can cause a loss in kidney function, thereby leading to a higher risk of CKD. The result did not show a significant association between ROA correlated with hospital stay and the Route of administration route correlated with hemodialysis frequency. In our study, we do not have sufficient data to conclude any significant difference in the outcome caused by changes in the dose of furosemide. It were found that there was not many differences and the efficacy of furosemide was similar in CKD patients regardless of ROA. It does not show much significance in improving renal function. The results of this study conclude that the administration of furosemide to patients with chronic kidney disease with residual dieresis could improve urinary volume, sodium and potassium regardless of hemodialysis.

Declarations

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Author contributions

Conceptualization, P.A.K, S. and M.B.; Methodology, S.N.F and N.F.; Software, S.N.F and N.F.; Validation, P.A.K., A.F.F. and S.T.; Formal Analysis, P.A.K., A.F.F. and S.T.; Investigation, S., S.T. and M.B.; Resources, S., S.T. and M.B.; Data Curation, S., S.T. and M.B.; Writing – Original Draft Preparation, P.A.K, S., S.T., M.B., A.F.F., S.N.F. and N.F.; Writing – Review & Editing, P.A.K, S., S.T., M.B., A.F.F., S.N.F. and N.F.

Conflicts of interest

There are no conflict of interest involved in the study.

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Data availability

Due to privacy concerns, the data are not publicly available, but can be accessed upon reasonable request from the corresponding author with a signed data access agreement.

Ethics approval

The study has been approved by the Human Ethics Committee of Mahavir Hospital and Research Center, with reference no. ECR01/450/Inst/AP/11/03/22.

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