Original Article

A Retrospective Study to Determine the Side Effects and Complications Associated with the Usage of Loop Diuretics in ADHF or Left Ventricular Heart Failure Patients

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ABSTRACT

Since the incidence of adverse events associated with the use of class of diuretics, named loop diuretics are increasing per subject, this study was found to be significant. The aim or hypothesis of the study was to monitor the associated complications like Arrhythmia, hyponatremia or Renal dysfunction and to study about the side effect profile of loop diuretics used in the treatment of ADHF/LVF patients; both adverse events and adverse drug effects. The study is a Single-Centered, Retrospective Observational Study and was designed in the Cardiology and Nephrology Departments of a tertiary care hospital. Data were collected from the medical records. Then those were analysed in detail as well as statistically for obtaining and intervening the results. Hypokalemia, Hyponatremia, Renal dysfunction, Cardiorenal dysregulation etc. were the major complications. About the adverse event, Arrhythmia occurred in 97 patients (38.04%), 115 patients (45.10%) resulted in Hyponatremia and acute Kidney Injury has occurred in 43(16.86%) of patients. Regarding adverse drug reactions as a result of diuretic use can be classified as allergic rashes, abdominal discomfort, edema, vomiting, diarrhoea, constipation, muscle spasm, restlessness. The most common adverse event observed was allergic rashes 24 (58.54%) followed by abdominal discomfort 5 (12.20%). The study reveals that states that non-potassium sparing diuretics have an increased risk of adverse event associated death in HF patients whereas, potassium supplementation improved the outcomes.

Keywords: Adverse events, Complications, ADHF/LVF patients, Hypokalemia, Loop diuretics.

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INTRODUCTION

Most HF patients have increased ventricular ectopy and about 50% exhibit non-sustained ventricular tachycardia. A total of 50% of cardiac deaths are sudden and unexpected, presumably due to arrhythmias. In victims of sudden cardiac death, the level of myocardial K+ is markedly lower than in controls, and survivors are often hypokalemic. The all-cause and cardiac mortality rates are higher in those taking non-K+-sparing diuretics for HF. The incidence of death due to arrhythmia are significantly and independently related to the use of non-K+-sparing diuretics. Moreover, hypokalemia predisposes a patient to digoxin toxicity by decreasing renal clearance and encouraging myocardial binding of the drug. This, in turn, produces increased automaticity and ventricular arrhythmias. K+ depletion exacerbates diastolic dysfunction in animal and human models.[1] Hypokalemia is associated with triggered arrhythmias such as Torsades-dePointes (TDP), polymorphic VT, ventricular fibrillation (VF), and ventricular ectopy. Hypokalemia has been shown to cause regional alterations in conduction and regional action potential duration

(APD) heterogeneity that establish functional re-entry circuits. Hypokalemia also promotes triggered arrhythmias by a reduction in cardiac repolarization reserve and increased intracellular Ca^{2+} in cardiomyocytes.[2]

Other adverse events associated with the use of loop diuretics are hyponatremia and it's prevalence in the acute hospital setting ranges from 4% to 45%.19% to 25% of patients with acute decompensated heart failure (ADHF) have hyponatremia, which is independently associated with increased short-term and long-term morbidity and mortality. Even mild hyponatremia among patients with ADHF, regardless of ventricular function, is associated with increased in-hospital and post discharge mortality, prolonged hospital length of stay, and frequent re-hospitalization.[3]

Renal Dysfunction is also a comorbid condition that occurs frequently in patients with ADHF. Also minor, transient increases in the creatinine in the setting of acute HF are not prognostically important, whereas persistent deterioration does indicate irreversible damage that portends a worse outcome. In addition, congestion plays an important role in the course of renal deterioration, and the combination of congestion and WRF is a significant clinical prognosticator in HF patients.[4] Cardiorenal dysregulation is manifested by acute decompensated heart failure, diuretic resistance and worsening renal function.[5]

The cardiorenal syndrome is subcategorized into the following types (Table 1).

The purpose/hypothesis of the study was to monitor the other associated complications like arrhythmia, hyponatremia or renal dysfunction and to study about the side effect profile of loop diuretics used in the treatment of ADHF/LVF.

Table 1: Shows the subcategories of cardiorenal syndrome.

Type	Denomination	Description	Example
1	Acute Cardiorenal Syndrome	HF Leading to AKI	ACS Leading to AHF and ARF
2	Chronic Cardiorenal Syndrome	CHF Leading to Kidney Failure	CHF
3	Acute Nephrocardiac	AKI Leading to AHF	Uremic Cardiomyopathy, AKI Related
4	Chronic Nephrocardiac	CKD Leading to HF	LVH and Diastolic HF due to RF
5	Secondary	Systemic Disease Leading to Heart and Kidney Failure	DM, Vasculitis and Sepsis

MATERIALS AND METHODS

Study Design

A Single-Centered, Retrospective Observational Study.

Study Site

The study was carried out in the Cardiology and Nephrology Departments of one of the Tertiary Health-Care Centre in South-India, CARITAS HOSPITAL, located in Thellakom, Kottayam. It is a multi-specialty hospital with modern technology, automated equipments and the first quaternary care hospital in Kerala to achieve the coveted JCI (Joint Commission International). Caritas has also won the NABH accreditation. The hospital has an in-patient capacity of 670 beds and has 24-hr emergency and accident trauma care facilities.

Study Period

The study was carried out for a period of 36 months (3 years), starting from November 2017 to November 2020.

Sample Size

The adequate sample size required to support the study was calculated by using the ready-made table. The table was used to calculate the sample size by taking relative precision ($\in$ = 10% / 0.10) and 95% confidence interval.

Sample size Determination = 100(1- et)%

Relative precision = 10%

Confidence level = 95%

Equation n = (1- α/2) ÷ $\in$

[RP = 0.10 and a confidence level of 95% a sample size of 385.]

Study Population

The data of all in-patients who visited the hospital in the time period (November 2017-November 2020, respectively) regardless of age and sex in Cardiology ICU and who satisfied the inclusion and exclusion criteria were included in the study.

The inclusion criteria for the study were:

- Patients administered with loop diuretics.
- Patients with an age group greater than 20 years.

The exclusion criteria for the study were as follows:

- Patients administered with the drugs that affect the baseline K+ like ARBs, ACE Inhibitors.

- Patients with malignancy, chronic liver disease, cardiogenic blocks.
- Patients whose follow-up details were missing.

MATERIALS AND METHODS

The patient's demographic details including age, gender, comorbidities, social history and number of days in the hospital, past medical history, vitals, clinical laboratory parameters like Blood urea, serum creatinine, electrolyte levels of potassium and sodium before and after treatment with diuretics were also recorded. The occurrence of other adverse events like hyponatremia, cardiac conduction changes like arrhythmia, worsening renal function were noted using electrolyte panel, ECG report, renal function test correspondingly, analyzed and interpreted.

RESULTS

Monitoring the Other Associated Complications in ADHF/LVF Patients

During the study, it was observed that complications like Arrhythmia, Hyponatremia and Acute Kidney Injury (AKI) in patients with ADHF/LVF (Table 2). Diuretic-induced electrolyte disturbances may result in fatal Arrhythmias in patients with ADHF/LVF. Hyponatremia is an occasional, but serious, and potentially fatal complication of diuretic therapy. AKI is a sudden decline in kidney function, associated with a range of adverse outcomes, particularly an increase in subsequent admission with heart failure. In a total of 170 patients, apart from hypokalemia complications like arrhythmia occurred in 97 patients (38.04%), 115 patients (45.10%) resulted in hyponatremia, and acute kidney injury has occurred in 43(16.86%) of patients and it was depicted in Figure 1.

Evaluation of Hyponatremia

Severity of Hyponatremia

Based on the findings, Hyponatremia also occurred in patients administered with loop diuretics in addition to hypokalemia. Out of 170 patients who had hypokalemia, 55 (32.35%) patients had a normal serum sodium level. Upon analyzing the severity, the majority of patients

Table 2: Shows the Determination of other Complications along with Hypokalemia.

Complications	*n* = 255	Percentage (%)
Hyponatremia	115	45.10%
Arrhythmia	97	38.04%
Acute Kidney Injury	43	16.86%

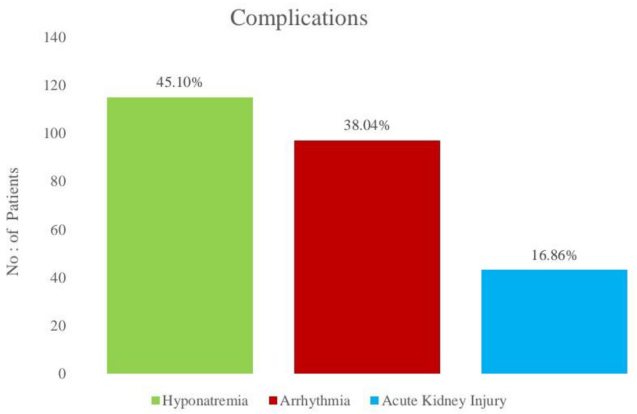

Figure 1: The Figure below shows the other associated complications along with hypokalemia.

Table 3: Depicts the Details of Hyponatremia Occurred in Patients.

Classifications	*n*=170	Percentage (%)
Normal	55	32.35%
Mild	65	38.23%
Moderate	43	25.29%
Severe	7	4.11%

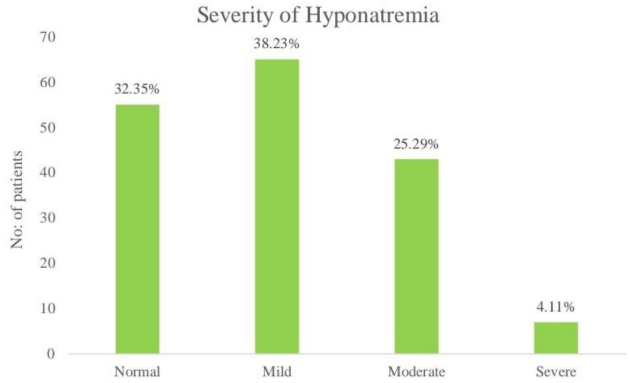

Figure 2: Depicts the Details of Hyponatremia Occurred in Patients.

65 (38.23%) resulted in mild hyponatremia along with 43(25.29%) patients moderate, and 7(4.11%) had severe Hyponatremia (Table 3, Figure 2).

Management of Hyponatremia

Out of a total of 115 patients (45.10%) with Hyponatremia, 44 patients (38.26%) patients were managed with various therapeutic interventions, and 71 patients (61.67%) were not managed which is depicited in Table 4.

Various Treatment Strategies for the Management of Hyponatremia

Out of 115 patients with Hyponatremia, 44 patients were managed with therapeutic interventions. Various

Table 4: Describes the Management of Hyponatremia.

Interventions	*n*= 115	Percentage (%)
Not Treated	71	61.67%
Treated	44	38.26%

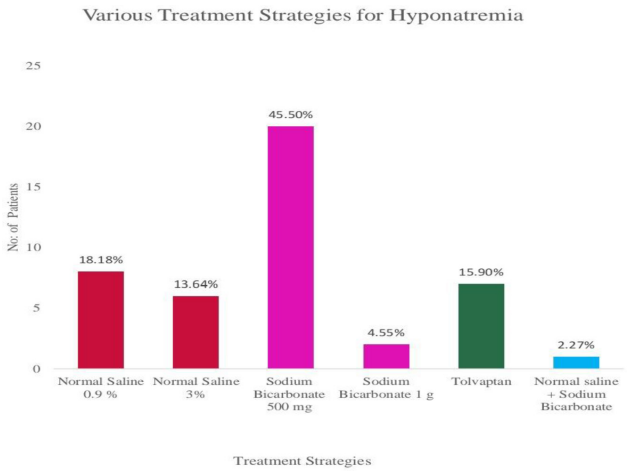

Figure 3: Shows the Various Treatment Strategies Provided for the Management of Hyponatremia.

treatment strategies provided were Normal Saline (NS), Sodium bicarbonate, Tolvaptan, a combination of Normal Saline and Sodium Bicarbonate. From a total of 44 (38.26%) patients with Hyponatremia, Sodium Bicarbonate was given to 22 patients as 500mg (20, 45.45%) patients, and 1g (2, 4.55%) patients respectively and it was clear from Figure 3.

Classifications of Arrhythmic Events

From Table 5 and Figure 4, it was evident that among the various Arrhythmic Events, Sinus Tachycardia is the major Arrhythmic event observed in 38 patients (39.17%). Heart block was present in 19 patients (19.59%). Atrial Fibrillation was occurred in 15 patients (15.46%). Apart from these arrhythmic events, Sinus bradycardia was present in 11 patients (11.34%). Ventricular fiibrillation occurred in 8 patients (8.25%). Ventricular Tachycardia was present in 6 patients (6.19%).

Side Effect Profile of Loop Diuretics used in the Treatment of ADHF/LVF

Adverse Drug Reaction Profile of Loop Diuretics

Based on the understanding, the adverse events occurred in 41 (24.11%) patients (Table 6, Figure 5).

Details of ADR

Based on the findings, the adverse drug reactions as a result of diuretic use can be classified as allergic rashes,

Table 5: Demonstrates the Incidence of various Arrhythmic Events.

Arrhythmic Events	*n*= 97	Percentage (%)
Atrial Fibrillation	15	15.46%
Heart Block	19	19.59%
Sinus Bradycardia	11	11.34%
Sinus Tachycardia	38	39.17%
Ventricular Fibrillation	8	8.25%
Ventricular Tachycardia	6	6.19%

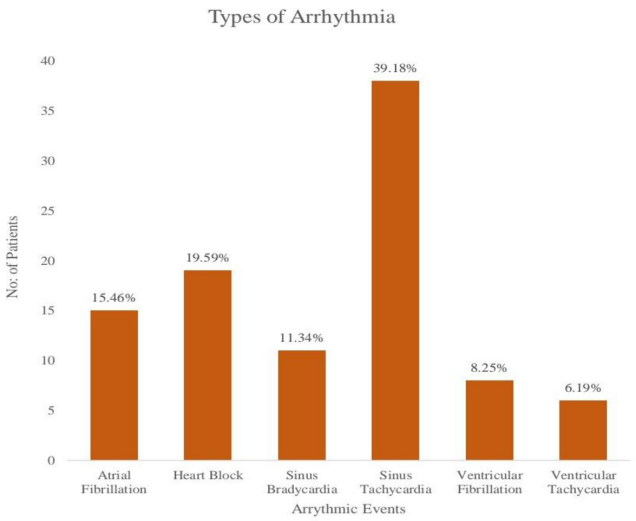

Figure 4: Demonstrates the Incidence of Various Arrhythmic Events.

Table 6: Illustrates the Adverse Drug Reaction Profile of Loop Diuretics.

No. of Patients	*n*= 170	Percentage (%)
With ADR	41	24.11%
Without ADR	129	75.88%

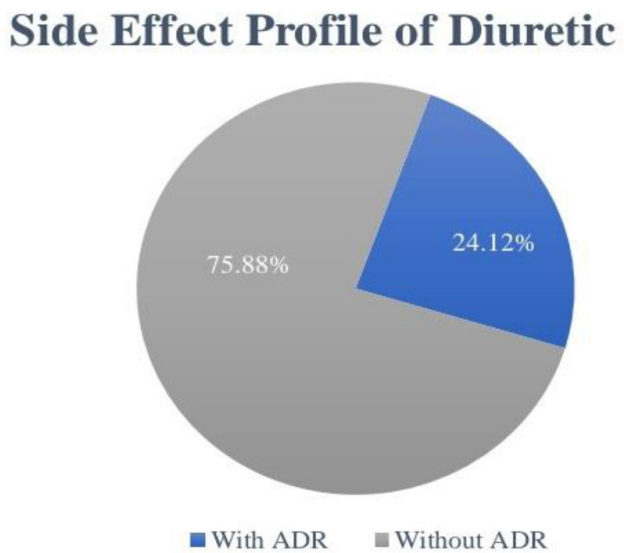

Figure 5: Illustrates the Adverse Drug Reaction Profile of Loop Diuretics.

Table 7: Describes the Details of Different ADRs.

Details of ADR	*n* = 41	Percentage (%)
Allergic Rashes	24	58.54%
Abdominal Discomfort	5	12.20%
Edema	4	9.76%
Vomiting	3	7.32%
Diarrhoea	2	4.88%
Constipation	1	2.44%
Muscle Spasm	1	2.44%
Restlessness	1	2.44%

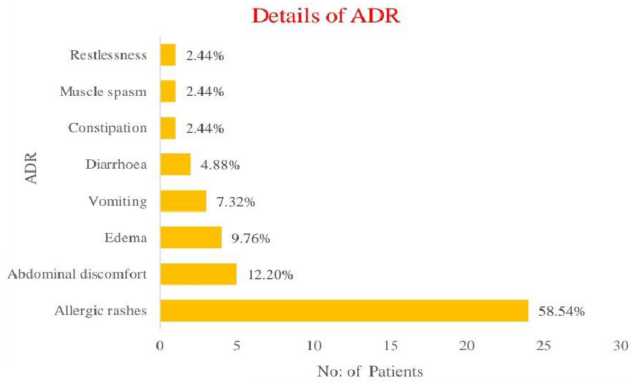

Figure 6: Describes the Details of ADRs.

abdominal discomfort, edema, vomiting, diarrhoea, constipation, muscle spasm, restlessness (Table 7). The most common adverse event observed was allergic rashes 24 (58.54%) followed by abdominal discomfort 5 (12.20%) and it was clear from Figure 6.

DISCUSSION

Complications

The major complications that was encountered include hyponatremia, arrhythmia, and acute kidney injury. The presence of hyponatremia during hospitalization could have a more unfavorable impact in patients with HF. This has a prognostic impact on an increased risk for in-hospital morbidity, mortality longer hospital stay reflecting the severity of HF, or a direct effect of hyponatremia. Several clinical conditions and cardiovascular risk factors, such as diabetes mellitus, chronic obstructive pulmonary disease, and alcohol consumption may also be associated with hyponatremia. A similar study by Velat Ivan *et al*.[6] reveals that high doses of furosemide and spironolactone, or concomitant use of these diuretics, seem to be an important cause of hyponatremia in HF patients, particularly in combination with advanced age, diabetes, and alcohol consumption. Diuretic dose reduction may help to avoid hyponatremia and improve clinical status and prognosis in such patients. Our findings were consistent with the study of Velat Ivan *et al*. The severity of hyponatremia was also evaluated and it was found that most of them had mild hyponatremia, and were managed with sodium bicarbonate. A similar study by Hoss *et al*.,[7] states that non-potassium sparing diuretics increased the risk of arrhythmic death in HF patients whereas, potassium supplementation improved the outcomes. These results were found to be in accordance with this study. According to Mehta *et al*.[8] diuretic use was associated with non-recovery of renal function. The recent SPARK study by Bagshaw *et al*.[9] concluded that furosemide neither prevents worsening AKI nor reduces renal replacement therapy use. These Findings were also in concordance with the study.

Side Effect Profile of The Drugs

In the comparison of Furosemide with Torsemide, it was recognized that the incidence of ADR remained high with Furosemide. In particular, these were allergic rashes 24(58.54%) followed by skin reactions, GI disturbances, electrolyte abnormalities, *et al*.[10] conducted a similar study and the results were inconsistent with the findings of the study for the reason that there was no difference in the medication side-effects.

CONCLUSION

The study concludes that the hypokalemia is a more prevalent condition in HF patients. There is a shred of increasing evidence that the serum potassium level should be maintained above 4.0 mmol/l to minimize the risk of sudden cardiac death. To avoid fluctuations in ECG, it is desirable to maintain serum potassium levels within the normal limit to minimize life-threatening arrhythmias like ventricular arrhythmias. The confounding factors like age, DM, HTN and the development of AKI relative to the potassium levels were independent predictors for the worsening of outcomes. Although it remains unclear to what extent hypokalemia is a risk factor for the worsening of AKI. Symptomatic HF patients (NYHA class III-IV) should be prescribed the lowest possible dose of diuretic to avoid a higher incidence of Hypokalemia. Mild Hypokalemia may be corrected by the use of aldosterone receptor antagonists such as Spironolactone. Thus the associated complications like Arrhythmia, hyponatremia or Renal dysfunction and the side effect profile of loop diuretics used in the treatment of ADHF/LVF patients are been understood from this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ADHF/LVF: Acute Decompensated Heart Failure/ Left Ventricular Heart Failure; **HF:** Heart Failure; **TDS:** Torsades-de Pointes; **VF:** Ventricular Fibrillation; **APD:** Action Potential Duration; **CHF:** Congestive Heart Failure; **AKI:** Acute Kidney Injury; **ADR:** Adverse Drug Reaction.

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