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Original article

SAFETY OF DIURETIC ADMINISTRATION IN EARLY DYSPNEA PATIENTS NOT FINALLY DIAGNOSED WITH ACUTE HEART FAILURE: A CLINICAL STUDY.

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Abstract

Objectives
The study aims to investigate the effect of initiating diuretic treatment in dyspnea patients without a confirmed diagnosis of acute heart failure, assessing its connection with immediate medical outcomes, mortality, and readmission rates. Additionally, the study explores potential variations in treatment effects across subgroups and provides insights into the implications of diuretic administration in the emergency department.

Methods
This study, conducted at Bhima Bhoi Medical College in Balangir, Odisha, India, employed exploratory secondary analysis of BASEL-V registry data, examining 266 dyspnoeic patients diagnosed with conditions other than AHF. The analysis assessed outcomes, categorizing patients into treated and untreated groups, with statistical methods including Wilcoxon rank-sum, chi-square tests, and t-test.

Results
Out of 533 initial patients from the BASEL-V registry, 266 were analysed, with 14.6% receiving diuretics during their ED stay. The 30-day mortality rate was 4.5%, with a 5.2% mortality rate in treated patients and 4.3% in untreated patients, resulting in a non-significant adjusted hazard ratio of 1.33 for treated patients. For the secondary outcome, 13.9% experienced readmission within 30 days, with a 14.7% rate for treated patients and 10.8% for untreated patients.

Conclusion
The study revealed that diuretic administration in dyspnoeic patients without acute heart failure had not significantly impacted on the readmission or mortality rates. While an increased hazard ratio for thirty-day mortality was observed in treated patients, it was not statistically significant, suggesting a need for cautious interpretation and further research validation.

Recommendation
The study recommends further research to validate and refine findings, emphasizing a larger sample size. Additionally, exploration of specific subgroups, such as those with COPD, and a comprehensive investigation into the impact of diuretic administration on elderly patients are advised for a more nuanced understanding of therapeutic implications.

Keywords: Dyspnoea, Diuretics, Emergency Department, Acute Heart Failure
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Introduction
Dyspnoea is a common issue among individuals visiting the emergency department (ED), with potential underlying causes including aggravations of chronic obstructive pulmonary disease (COPD), wheezing, respiratory illnesses, and acute heart failure (AHF) [1]. Various research investigations have reported dyspnoea to be the first complaint in approximately 2.7 % to 9 % of patients admitted to ED [2-5]. Some research indicates that early administration of diuretics to individuals presenting with AHF in the ED may be linked to improved outcomes, including reduced mortality rates [6-9]. Consequently, many doctors opt to initiate early diuretic therapyfor patients experiencing severe dyspnoea before a definitive diagnosis is established [10]. However, differentiating between the various conditions causing dyspnoea during the initial clinical assessment can be challenging, often resulting in significant diagnostic uncertainty.

The uncertainty surrounding the diagnosis of dyspnoea presents a dual challenge in EDs. Firstly, it may result in a delay in initiating the suitable treatment, potentially

compromising patient outcomes [11, 12]. Contrary to this, the initiation of prompt diuretic treatment before reaching a final diagnosis may mean that some patients, whose condition is ultimately identified as something other than acute heart failure (AHF), receive unnecessary diuretic doses. This unwarranted treatment may contribute to adverse events, including the development of renal dysfunction [13]. Despite these concerns, there is a paucity of work to assess the safety of using diuretics in these patients [10].

Recognizing this gap, our investigation explored the impact of acutely administering diuretics on outcomes in patients ultimately diagnosed in the emergency department with conditions apart from acute heart failure. To address this, we conducted a study using data sourced from Basics in Acute Shortness of Breath EvaLuation (BASEL-V) registry. These registries encompassed patients seeking ED care due to dyspnoea. The central hypothesis we tested was whether the use of certain diuretic doses in the emergency department is not linked with worse immediate outcomes when dyspnoeic patients are not conclusively diagnosed with acute heart failure.

The study aims to investigate the effect of initiating diuretic treatment in dyspnea patients without a confirmed diagnosis of acute heart failure, assessing its connection with immediate medical outcomes, mortality, and readmission rates.

Materials and Methods

Study design

An observational study.

Study setting

This exploratory secondary analysis utilized data obtained from BASEL-V database registries, encompassing consecutive patients admitted to the EDs with dyspnoea. It was carried out at Bhima Bhoi Medical College in Balangir, Odisha, India and the data was collected from July 2022 to July 2023, with 266 eligible patients, all diagnosed with conditions other than acute heart failure (AHF).

Inclusion and exclusion criteria

The study involved consecutive patients from BASEL-V registries. The BASEL-V registry comprised patients attending emergency departments (ED) from July 2022 to July 2023, resulting in 533 patients, of which 266 were eligible as they were diagnosed with conditions other than AHF. The primary complaint for inclusion was dyspnoea. Exclusion criteria encompassed patients lacking data on diuretic treatment at the ED, those without follow-up mortality data, and individuals on chronic diuretic treatment, considering ED diuretic administration as a potential continuation of their chronic regimen.

Bias

Potential bias was minimized at the onset of the study through the implementation of measures aimed at ensuring impartiality. Specifically, all participants were provided with uniform information, and the allocation of groups was concealed from the data-collecting nurses.

Study size

The study began with a total of 533 patients, out of which 267 were excluded, resulting in 266 individuals who met the eligibility criteria due to their diagnosis of conditions distinct from AHF.

Sample setting

Acute heart failure diagnoses relied on the treating physicians' clinical assessment. Patients lacking data on diuretic treatment, follow-up mortality data, or on long-term diuretic therapy were not included in this study. The analysis categorized patients into two sub-groups: treated patients (those receiving diuretic therapy at the ED) and untreated patients (those not receiving diuretics).

The primary immediate outcome under scrutiny was thirty-day mortality, providing a crucial metric for evaluating the impact of early diuretic intervention on patient survival. The secondary result was the necessity for readmission within the 30 days of discharge due to any reason. The diverse methods employed across centers to follow up on the patient's health were medical records review, telephone contact, and consultation of regional health insurance and death registries. This meticulous examination of outcomes aimed to shed light on the potential benefits or risks associated with early diuretic administration in dyspneic patients with diagnoses other than AHF.

Statistical Analysis

Continuous variables were summarized using mean range. Group comparisons employed Wilcoxon rank-sum, chi-square tests, or t-test while missing data were addressed through multiple imputation. Significance was set at $P < 0.05$.

Ethical considerations

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

Results/Outcomes

Participants

Out of the initial 533 patients sourced BASEL-V registry, 267 were excluded, leaving 266 patients for the final analysis. In this group, 39 patients (14.6 %, $p<0.001$) received diuretics during their ED stay. Examination of patient characteristics revealed that factors such as age, sex, and previous medical history influenced the likelihood of administering diuretics. The most prevalent final diagnoses were COPD (33.4 %, $p=0.09$) and pulmonary infection (24.6 %, $p=0.16$) (Table 1).

Table 1: Attributes of Non-Acute Heart Failure Patients in Cohorts with or without ED Diuretic Therapy

	Total, N = 266, n (%)	Untreated, N = 227, n (%)	Treated, N = 39, n (%)	*p*-value
General Characteristics				
Age (yrs)	61.0	58.4	68.6	<0.001*
Female	150 (56.5 %)	130 (57.5 %)	20 (50.7 %)	0.02*
Co-existing illness				
High blood pressure	120 (45.1 %)	95 (42.1 %)	25 (64.6 %)	<0.001*
Diabetes mellitus	51 (19.4 %)	36 (16.1 %)	15 (37.9 %)	<0.001*
Atrial fibrillation	32 (11.9 %)	22 (9.6 %)	10 (25.8 %)	<0.001*
Peripheral arterial disease	7 (2.7 %)	6 (2.6 %)	1 (3.3 %)	0.56
COPD	82 (30.8 %)	73 (32.1 %)	9 (23.8 %)	0.002*
Active neoplasia	17 (6.4 %)	15 (6.8 %)	2 (6.1 %)	0.69
Chronic heart failure	26 (9.8 %)	19 (8.4 %)	7 (18.7 %)	<0.001*
Ultimate diagnosis for the present episode of dyspnea				
COPD	89 (33.4 %)	83 (36.7 %)	6 (15.7 %)	0.09
Pulmonary infection	65 (24.6 %)	59 (25.9 %)	6 (15.7 %)	0.13
Pulmonary embolism	17 (6.4 %)	16 (7.2 %)	1 (2.7 %)	0.16
Rapid atrial fibrillation	17 (6.3 %)	13 (5.7 %)	4 (10.5 %)	<0.001
Bronchitis or influenza	7 (2.8 %)	6 (2.6 %)	1 (2.7 %)	0.004*
Others	33 (12.8 %)	30 (13.2 %)	3 (7.8 %)	0.78
Unclear diagnosis after ED attendance	32 (12.3 %)	26 (11.7 %)	6 (15.6 %)	0.03*

Over the 30-day follow-up, 12 patients (4.5 %, p=0.16) experienced mortality, with 2 deaths (5.2 %, p=0.14) among those treated with diuretics and 10 deaths (4.3 %, p=0.01) among untreated patients. The unadjusted analysis showed a hazard ratio (HR) of 1.33 for thirty-day mortality in treated patients cohort compared to its counterpart. After adjustments, the difference in thirty-day mortality between both cohorts was not statistically significant.

On a different note, data on the secondary outcome were gathered for 266 patients, revealing that around 37 individuals (13.9 %, p=0.78) experienced readmission within 30 days after discharge. Among them, 33 patients belonged to the treated cohort (readmission rate: 14.7 %, p=0.61), and 4 to the other cohort (readmission rate: 10.8 %, p=0.03).

Diuretic administration appeared to have a potentially favorable impact on 30-day mortality in COPD patients in contrast to those without the disease. Regarding the secondary outcome (readmission), an interaction was observed between administration of diuretics and patient age, indicating improved results when diuretics were given to patients aged above 80 years in contrast to those aged 80 or less. Other examined variables for interaction did not significantly influence the 30-day readmission rate.

Discussion

Results from the analysis of 266 patients showed that 14.6% (p<0.001) received diuretics during their ED stay, and there was no significant difference in 30-day mortality between treated and untreated patients. However, an interaction was observed between diuretic administration and patient age, with improved outcomes for those aged above 80 years. Subgroup analysis suggested potential benefits of diuretic therapy in COPD patients.

Our key finding is that, for individuals assessed in the emergency department (ED) due to dyspnoea without a definitive prognosis of the cause, the initiation of empiric diuretic therapy does not correlate with worse immediate medical results in those without a final diagnosis of acute heart failure. The selective prognosis for dyspnoea in the emergency department encompasses a broad spectrum, including potentially life-threatening conditions. A Danish study revealed a thirty-day fatality rate of 13 % in dyspnoea patients diagnosed with respiratory diseases, a notably higher figure than what our study observed [14]. Consequently, it is common to employ a broad treatment protocol for individuals with severe dyspnoea while awaiting additional test results to get a conclusive diagnosis [15-17]. This approach may involve the administration of medications not specifically indicated for the underlying cause of dyspnoea. For instance, studies have shown that approximately 18 % of dyspnoea patients ultimately prognosed with acute heart failure were treated

using bronchodilators, while 14 % of AHF patients receive corticosteroids [17, 18].

In our stratified analysis, no subgroup exhibited a significant association with either worse or improved outcomes. Notably, the only sub-analysis that approached statistical significance involved patients with COPD, showing improved health outcomes for those on diuretic therapy. This aligns with the notion that in some dyspnoea patients diagnosed with COPD or asthma exacerbation, there may be concurrent congestion, potentially linked to abnormal left ventricular diastole or right heart failure [19-21]. Patients with COPD face an elevated risk of developing heart failure (HF) [22]. Consequently, individuals with a primary prognosis of COPD might have concealed slight congestion. Certain studies suggest that patients with a final prognosis of COPD or asthma exacerbation may experience improved outcomes with nebulized diuretic therapy, although the mechanisms behind these effects remain unclear [23, 24].

Conversely, our observation of a varied impact of diuretic usage on the readmission rate based on patients' age is noteworthy, particularly due to the more favourable trend observed in the older age group. This is intriguing as one might anticipate that older patients, often characterized by frailty or dependency, would be at a higher risk of reconsultation, given the recognized impact of these conditions on prognosis [25, 26]. However, dyspnoea stands out as the predominant symptom linked to the thirty-day readmission rate in geriatric patients, with 1 in 4 readmitted patients exhibiting this symptom in a previous study [27]. Similarly, the likelihood of concurrent respiratory and cardiac diseases is presumed to be higher in the elderly. Furthermore, the underutilization of evidence-based medication treatment, a phenomenon more prevalent in the geriatric cohort, could contribute to early rehospitalizations [28, 29]. Therefore, in our geriatric cohort, the use of diuretics could be a contributing factor to their reduced rates of readmission.

Conversely, the disparate effects of use of diuretics on fatality (increased, albeit statistically non-significant) and readmission (reduced, albeit statistically non-significant) could reflect the well-established understanding that these two medical outcomes have no common predisposing factors in dyspnoea patients [30-32].

Conclusion

The exploratory study focussing on "safety of diuretic administration during the early management of dyspnoea patients who are not finally diagnosed with acute heart failure" suggests that initiating diuretic therapy in dyspnoea patients without a confirmed diagnosis of acute heart failure (AHF) does not associate with worse short-term outcomes. Notably, the use of diuretics showed a potential benefit in reducing thirty-day readmission rates in elderly patients. However, due to study limitations and the need for further research, these findings should be interpreted cautiously, emphasizing the need for additional investigations to validate and expand upon these preliminary results.

Limitations

The limitations of the study include its exploratory nature, absence of sample size calculation, potential type-II errors due to limited sample size, caution needed in interpreting subgroup analyses, and the lack of recorded time to readmission, clinical criteria-based diagnoses, and potential coexisting heart failure worsening.

Recommendations

The study recommends further research with a larger sample size to validate findings and enhance statistical power. Additionally, prospective investigations into dyspnea diagnoses and comprehensive documentation of treatments and clinical parameters during emergency department evaluation are advised for a more nuanced understanding of therapeutic approaches.

Acknowledgement

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List of Abbreviations

ED – Emergency Department
AHF - Acute Heart Failure
COPD - Chronic Obstructive Pulmonary Disease
HF – Heart Failure
BASEL-V – Basics in Acute Shortness of Breath EvaLuation

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No source of funding.

Conflict of interest

No conflict of interest.

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