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DOES DIURETIC REDUCE MORTALITY IN CARDIAC PULMONARY EDEMA? A PROSPECTIVE ANALYSIS AT A TERTIARY CARE CENTER

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Contribution
SFM conceived the idea and designed the study. Data collection and manuscript writing was done by NH, EG, AK, PMM, AK, SA, and SH. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Objective: Acute pulmonary edema (APE) is a common problem presenting in emergency department of cardiology units. For decades, the mainstay of treatment in APE has been loop diuretics; mainly furosemide. Studies regarding mortality benefits of diuretics in APE patient have not been conducted in our population, where other drugs of heart failure are not frequently available. Therefore, results of our study may provide justification for continued use of diuretics as mainstay treatment of APE. Aim of this prospective study was undertaken to determine the relationship between dose of furosemide and mortality.

Methodology: This prospective study was conducted at department of cardiology, SMBBMU, Larkana from June 2017 to December 2017. Patients of either gender, aged between 18 to 75 years presenting with diagnosis of APE were included in the study. Patients were followed up till time of discharge or death. Outcome variable i-e mortality was noted and recorded.

Results: A total of 402 patients were included in this study out of which 234 (58.2%) were males. In-hospital mortality was 17.9% (77). Total amount of diuretics used was significantly lesser among the patients who died (209.28 ± 134.15 ml vs. 295.18 ± 151.43 ml; p-value <0.001). Patients who received less than 300mg/day diuretics had increased mortality as compared to those who received more than 300 mg/day (59 (20.3%) vs. 13 (11.7%); p-valve 0.045).

Conclusion: Patients who received less diuretic had more mortality than those who received more diuretic.

Keywords: APE, Diuretic, Dyspnea, Furosemide, Mortality

INTRODUCTION

Treatment strategy of acute pulmonary edema (APE) is directed at reducing preload, afterload and increasing functional reserve of the heart. Unfortunately last option is often not the possibility in acute setting. Therefore agents which decrease preload and afterload have been used in management of APE for decades. Diuretic still remains mainstay of treatment in majority of centers in Pakistan. It has remained a matter of controversy whether diuretics have any role in APE.

Theoretically a diuretic, mainly furosemide is supposed to act on loop of henle and get rid of extra volume from the body. But studies have suggested that majority of patients with APE are not volume overloaded.[1,2] In fact some patients are dehydrated. In heart failure, problem is not volume overload but shifting of volume from other compartments and accumulation in lungs is the cause of APE.[3]

Many studies have concluded that chronic use of diuretic has no beneficial effect. Even chronic use of diuretics is associated with increased mortality, morbidly and resistance.[4,5] Morbidity is mainly due to adverse renal effects.[6] Even during early hospitalizations period studies have shown increased mortality with use of diuretics and a linear relationship between diuretic dose and mortality.[7]

It is proposed that diuretics activates neurohormonal system.[8] It increases serum creatinine in patients with elevated PCWP.[9] Some studies have shown beneficial role of diuretics alone.[10,11] The combination of furosemide and nitrates resulted a robust decrease in PCWP hence a decrease in preload.

These controversial results affect more resource limited facilities like us. Furosemide is cheap, easily available and easily infused drug. Other treatment modalities like nitrate which require continuous hemodynamic monitoring and dose adjustment and NIPPV which is costly and technically difficult to use. Therefore this study was conducted to determine whether furosemide has a linear relationship with mortality.

METHODOLOGY

This study was conducted at department of cardiology Shaheed Mohtarma Benazir Bhutto Medical University (SMBBMU), from 1-6-2017 to 1-12-2017. Approval of ethical review committee of the institution was taken before commencement of the study. All the patients between age group of 18-75 years presenting with diagnosis of APE were enrolled after meeting the inclusion criteria. Patients who had concurrent other sever illness like chronic obstructive pulmonary disease (COPD), cerebrovascular accident (CVA), metabolic acidosis, and sepsis were excluded

Patients were enrolled from cardiac department of SMBBMU, Larkana. After explaining the procedure and obtaining the informed consent. The investigator collected the data on prescribed questionnaires which included baseline characteristics of patients. Total dose of furosemide was recorded in proforma. Patients were followed up till discharge/mortality.

Collected data were entered and analyzed using SPSS 21. Mean ± standard deviation (SD) was calculated for age, duration of APE, daily dose and total dose of furosemide. Frequency and percentages were calculated for gender, type of APE, comorbid and other medications.

Kolmogorov-Smirnov test was applied to test the normality of the diuretic dosage amount and relationship between dose of furosemide and mortality was determined by applying appropriate t test or Mann–Whitney U test. Patients were divided in two groups, who were given less than 300mg total dose and those who were given 300mg or above total diuretic doses, and its association with mortality was assessed using chi square test. Effect modifiers were controlled through stratification of age, gender, type of APE and effect of these on outcome variable was assessed by applying chi square test. P-value ≤ 0.05 was taking as criteria for statistical significance.

RESULTS

A total of 402 patients were included in this study out of which 234 (58.2%) were males and 168 (41.8%) were females. In our study overall 72 (17.9%) patient died. The baseline characteristics, diuretics, and in-hospital outcome are provided in Table 1.

Table 1: Baseline characteristics of patients

Characteristics	Total (n = 402)
Gender	
Male	234 [58.2%]
Female	168 [41.8%]
Age (years)	
Mean ± SD	54.4 ± 17.73
Up to 18 years	20 [5%]
18 to 40 years	66 [16.4%]
41 to 60 years	186 [46.3%]
More than 60 years	130 [32.3%]
Cause of pulmonary edema	
Acute coronary syndrome	14 [3.5%]
Ischemia	287 [71.4%]
Valvular disease	54 [13.4%]
Cardiomyopathy	21 [5.2%]
Cause Unknown	26 [6.5%]
Diuretic dosage	
Diuretic dose day 1	121.49 ± 39.9 ml
Diuretic dose total	279.8 ± 151.95 ml
Less than 300 ml	291 [72.4%]
300 ml and above	111 [27.6%]
In-hospital Mortality	72 [17.9%]

Table 2 displays use of diuretics in various groups of patients. There was no statistically significant difference in amount of diuretics dosage used by gender and causes of APE. Total amount of diuretics dosage used was significantly lesser among the patients who died, 209.28 ± 134.15 ml vs. 295.18 ± 151.43 ml; p<0.001.

Table 3 displays the association between diuretic dose and mortality. The results suggest a strong dose response relation with mortality. Patients were divided in two groups (received less than 300mg/day vs. received more than 300 mg/day) and patients received less diuretics had increased mortality as compared to those who received more than 300 mg/day (p=0.045).

Table 2: Comparison of total diuretic dose by patient's characteristics

	Base	Total diuretic dose	P-value
Gender			
Male	234	284.4 ± 145.11 mg	0.116
Female	168	273.38 ± 161.22 mg	
Acute coronary syndrome			
No	388	241.43 ± 188.84 mg	0.145
Yes	14	281.18 ± 150.57 mg	
Ischemia			
No	115	283.34 ± 142.19 mg	0.209
Yes	287	270.94 ± 174.3 mg	
Valvular disease			
No	348	299.22 ± 217.67 mg	0.844
Yes	54	276.78 ± 139.2 mg	
Cardiomyopathy			
No	381	240 ± 72.66 mg	0.511
Yes	21	281.99 ± 154.9 mg	
In-hospital Mortality			
No	330	209.28 ± 134.15 mg	<0.001*
Yes	72	295.18 ± 151.43 mg	

P-values are based on Mann-Whitney U test
**Statistically significant at 5% level of significance*

Table 3: Association between diuretic dose risk factors and mortality

	Total diuretic dose		P-value
	< 300 mg	≥300 mg	
In-hospital Mortality			
No	232 [79.7%]	98 [88.3%]	0.045*
Yes	59 [20.3%]	13 [11.7%]	
Gender			
Male	163 [40.5%]	71 [17.6%]	0.091
Female	128[31.8%]	40 [9.9%]	
Diabetes			
Yes	89 [22.1%]	24 [5.9%]	0.046*
No	202 [50.2%]	87 [21.6%]	
COPD			
Yes	23 [5.7%]	06[1.4%]	0.261
No	267 [66.4%]	105 [26.1%]	
CKD			
Yes	14 [3.4%]	07 [1.7%]	0.355
No	276 [68.6%]	104 [25.8%]	

P-values are based on chi-square test
**Statistically significant at 5% level of significance*

DISCUSSION

There are three possible mechanism of acute pulmonary edema. Cardio-renal, cardio-circulatory and neuro-humoral. Cardio renal model was the first to be put forwarded; that undermined fluid overload by kidneys as main mechanism. This made the diuretics, drugs which wash fluid out of body, naturally number one choice.

In a congested patient increased pressure along renal veins reduces the net pressure gradient across the glomerulus. End result is diminished renal excretion of water and sodium.[12] Therefore it was suggested that relief of systemic congestion is an important step key target in management of APE.

Latter on cardio circulatory model became popular. That model emphasized the role of pre and afterload as causes of pulmonary edema. Extravasation of fluid across alveoli is determined by forces at local level. Increased hydrostatics pressure in capillary will give rise to fluids leakage in interstitial spaces.[13] Still latter neuro-humoral model highlighting the role of vasoactive agents became popular.

Diuretics has been considered first line agent in treatment of acute pulmonary edema. But recently conflicting evidence has been reported regarding role of diuretics in APE. In our setup diuretics are still considered drug of first choice in patients with APE.

But many of the researchers have proposed that patients with APE are not necessarily volume overloaded. Their total water content may be normal or even less. Then what makes these patients dyspnea? It is proposed that actually there is shift in water content of different compartment that cause APE.

In our set ups, There may be various reasons for over reliance of clinicians on diuretics in APE. First; furosemide has been used for so many years that many of doctors who have been using it since their training period are still using it and are not aware of the recent guidelines. Second; easy availability and low cost. Other medications of APE, mainly nitrates are comparatively costly and difficult to use [continuous I/V infusion and constant need of monitoring for hypotension]. Third; other anti-heart failure medications like ACE are not available in I/V form. During acute APE, doctors psychologically prefer I/V medications thinking that it will bring prompt relief of symptoms.

Our study showed that in patients with mortality diuretics were used less than those who survived. These patients received not only lesser total dose but day 1 dose too is lesser than other group. We have calculated total dose only up to day 4 because death usually occurred in patients with 4 days of admissions. If total hospitalization dose was considered it obviously have been more in surviving patients.

Many studies have shown that diuretics improve symptomatic relief when prescribed in heart failure patients.[14] In the congested patient, diuretics lower filling pressures, reduce lung water content, and are the most efficacious drugs available to relieve symptoms rapidly. Relief of congestion not only results in improvement of dyspnea and recurrent hospitalization but this is also reno-protective by reducing renal venous congestion. When diuretics were compared with additional ACEI; patient were found better when increased dose of diuretics as compared to those who had additional ACEI.[15] In the same way other study showed that when diuretics were stopped patient had worsening of symptoms.[16] A meta-analysis including eighteen studied (928 patients) has also shown that use of diuretics improved both morbidity and mortality in patients with heart failure.[17] Benefit is seen more in symptomatically worse patients.[18] A meta analysis of the placebo-controlled trials suggested 8% reduction in absolute risk of mortality in patients treated with diuretics compared with placebo.[17]

As a result of these studies diuretics are largely considered as an agent of symptomatic relief in patients with APE. Neither guidelines nor large scale studies have proved their role in decreasing mortality. But various studies have shown contradictory results, such as, data from the ADHERE registry reported worse in hospital outcomes such as length of hospital stay, length of intensive care unit stay, and mortality in patients treated with intravenous diuretics.[19] Analysis of the Left Ventricular Dysfunction (SOLVD) trial data demonstrated higher rates of mortality, both cardiovascular and all-cause, in patients receiving a diuretic at baseline.[20] Not only diuretics have shown to worsen acute outcomes, studies in the chronic HF population have also shown an independent association between diuretic use and increased mortality.[20,21]

Limitations

Though we have proposed statistically significant results our study is not without limitations. First we did not have record of pre hospitalization status of patients. Therefore we did not risk stratify them according to their disease severity. Secondly we did not account other comorbid like anemia, infection and hypernatremia. Thirdly we did not offer the patients mechanical ventilation. Latter two confounders may have affected the results.

CONCLUSION

Patients who received less diuretic had more mortality than those who received more diuretic. Difference was seen more pronounced in patients who presented with acute coronary syndrome. ACS patients also had higher mortality as compared to Non-ACS patients. Therefore it is reasonable to treat patients presenting with acute pulmonary edema with high dose diuretic along with other routine medications.

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