DIURETIC RESISTANCE IN PATIENTS PRESENTING WITH HEART FAILURE TO CARDIOLOGY DEPARTMENT OF A TEACHING HOSPITAL

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ABSTRACT

Objective: To determine the frequency and outcome of Diuretic Resistance (DR) in patients with heart failure admitted in the Cardiology Department of a Tertiary Care Hospital.

Material and Methods: This observational study was conducted at Cardiology Department, Khyber Teaching Hospital, Peshawar, Pakistan from January 2014 to December 2014. Adult patients admitted with diagnosis of heart failure during this duration were five hundred and sixty. Patients discharged within 24 hours (n=152) and/or having incomplete information (n=113), were excluded from our study, the remaining two hundred and ninety five were included in the study. Patients received I/V furosemide dose of 160 mg per day was considered as cut off value between diuretic responders [using < 160 mg furosemide per day (group I)] and diuretic resistant [using ≥ 160 mg furosemide per day (group II)].

Results: Out of two hundred and ninety five patients, 175 (59.33%) were male and 120 (40.67%) were female. Mean age of study population was 65±7 years. Patients responding to diuretics (group-I) were 190 (64.1%), while patients resistant to diuretics (group-II) were 105 (35.9%). Among group-I male were 114 (60%) and female were 76 (40%) while among group-II male were 61 (58%) and female were 44 (42%). Patients with DR (group II) were having significantly higher CAD and diabetes as compared to group I. Patients in group II were significantly more anemic, hypokalemic, hyponatremic and were having higher creatinine and cholesterol level as compared to group I. Blood pressure was lower in group II but raised JVP and edema were more common in group I. Total duration of hospital stay is >3 days in DR group.

Conclusion: Diuretic resistance is a common problem in patients presenting with uncontrolled comorbidities in heart failure patients. Early recognition of this problem and prompt aggressive treatment may help shorter stay of hospitalization.

Key Words: Diuretic Resistance, Heart Failure, Frequency.


INTRODUCTION

Heart failure is a common cause of morbidity and mortality. When heart failure is acutely decompensated, it is a life threatening condition and need immediate hospitalization. The most effective and rapid acting drugs for relieving signs and symptoms of acute heart failure are loop diuretics given up to 90% of admitted patients. Many patients do not respond promptly even to higher doses of diuretics. These patients have poor clinical outcomes in form of higher mortality and recurrent hospitalization. Early recognition of such patients may help physician to adapt aggressive treatment strategies right from start and may help early relief of symptoms and shorter stay of hospitalization. The exact prevalence of diuretic resistance (DR) is unknown because of different pathophysiologic mechanisms in different patients and different definitions used for diuretic resistance by previous researchers.

The exact pathophysiology behind diuretic resistance (DR) is still not well understood. In normal subjects the amount of diuresis following a given dose of diuretic declines over time as a result of breaking
phenomenon. This is mainly due to neurohormonal activation, triggered by reduction in extra cellular fluid volume as a result of the initial diuretic effect. Another cause of diuretic resistance in heart failure is delayed absorption of diuretics, which result in lower peak drug level in ascending loop of henle that are insufficient to induce maximum natriuresis.

As heart failure advances there is loss of renal responsiveness to endogenous natriuretic peptides. Distal tubular compensation has also been shown to be the primary mechanism of DR. Due to chronic use of diuretics, there is increase solute delivery to distal segments of nephron causing hyperplasia and hypertrophy of epithelial cells in distal nephron. This in turn increases the solute resorption capacity of the kidney as much as three fold and thus nullifying the effect of diuretics.

Apart from these mechanisms a decline in cardiac or renal function, noncompliance with diuretic doses, concurrent use of drugs like NSAIDS, COX inhibitors and thiazolidinediones can also cause impaired diuretic response. These may also result renal function deterioration and development of cardiorenal syndrome.

Regarding the definition, a patient with heart failure may be considered diuretic resistant, when moderate doses of loop diuretics do not achieve the desired reduction of extra cellular fluid volume. Reduced diuresis and natriuresis upon repeating dosing and persistent congestion despite increasing daily diuretics (more than 80 mg oral furosemide) have also been termed diuretic resistance. Knuaf H et al expressed diuretic resistance as a fractional sodium excretion (FE Na\(^+\)) of < 0.2%. FE Na\(^+\) represent the amount of sodium excreted (mmol / time) as a percentage of filtered load (plasma Na\(^+\) concentration x GFR). Testairn et al suggested a metrical index of diuretic efficiency, which was defined as net fluid loss per milligram of loop diuretics. The most commonly used parameter for fluid congestion is body weight and heart failure guidelines also recommend using weight loss for volume status. More recently a definition of DR was introduced, combining weight loss and diuretic dose, thus creating a quantitative indexed measure of diuretic response.

Most of the previous research have focused on finding the pathophysiologic mechanisms or tried to find a solution for DR and only few authors have mentioned the prevalence of the problem. Domeni A. Sica et al have mentioned that poor diuretic response occurs in one out of three patients with congestive heart failure. Neuberg GW et al found 402 out 1153 patients to be diuretic resistant.

On literature review we couldn’t find any local study highlighted prevalence of diuretic resistance in our setup. Hence, present study was conducted to determine the frequency and outcome of Diuretic resistance (DR) in patient with heart failure admitted in the Cardiology Department of a Tertiary Care Hospital.

**MATERIAL AND METHODS**

This observational study was conducted at Cardiology Department, Khyber Teaching Hospital, Peshawar, Pakistan from January 2014 to December, 2014. Adult patients admitted with diagnosis of heart failure during this duration were five hundred and sixty. Patients discharged within 24 hours (n=152) and/or having incomplete information (n=113), were excluded from our study, the remaining Two hundred and nifty five (295) were included in the study.

In all included patients data was documented and reviewed for demographic, clinical, laboratory variables, for the treatment received during hospitalization and their outcome in the form of improvement of clinical sign symptoms, duration of hospital stay and mortality. Patients I/V furosemide dose on day 2 (after 48 hours of admission) of 160 mg per day was considered as cut of value between diuretic responders [using < 160 mg furosemide per day (group I)] and diuretic resistant [using ≥ 160 mg furosemide per day (group II)].

All the data was entered and analyzed in SPSS vs 14. Mean ± standard deviation was calculated for continuous variables and were compared using students T test. Categorical variables were expressed as frequencies / percentages and statistical comparison were made by the chi-square test. P value of less than .05 was considered significant difference between the groups.

**RESULTS**

Out of Two hundred and nifty five patients, 175(59.33%) were male and 120(40.67%) were female. Mean age of study population was 65 ± 7 years. Patients responding to diuretics (group-I) were 190 (64.1%), while patients resistant to diuretics (group-II) were 105 (35.9%). Among group-I male were 114 (60%) and female were 76 (40%) while among group-II male were 61 (58%) and female were 44 (42%).
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Differences in clinical and biochemical characteristics between the two groups are shown in Table 1. Patient with DR (group II) were having significantly higher CAD and diabetes as compared to group I. Patients in group II were significantly more anemic, hypokalemic, hyponatremic and were having higher creatinine and cholesterol level as compared to group I. Blood pressure was lower in group II but raised JVP and edema was more common in group I. Total duration of hospital stay is 3.5 days more in DR group.

DISCUSSION

Previous research on diuretics in heart failure showed a wide range of prevalence of Diuretic Resistance (DR), which might be due to the different definitions used for Diuretic Resistance the different populations studied and the different pathophysiology mechanisms underlying DR.

In our study we took furosemide daily dose of 160 mg as cut off value and found 105 (35.9%) patients to have DR. The finding of this high frequency rate correlates well with the results of other studies.18

Vallente MA et al examined diuretic response (defined as change in weight on day 4 / 40mg furosemide) in 1745 patients with acute heart failure. They found 226 (13%) patients to have no reduction in weight during 4 days of furosemide therapy.19 In relax AHF trial change in weight per 40 mg furosemide was used for defining DR and found 366 / 1161 patients to be DR.20 Djenamba K et al examined record of 490 patients and divided them into three groups according to the daily diuretic dose (i.e.<80mg, 80 to 120 mg and > 120 furosemide per day). They found 242 (49%) patients to be DR (using > 120mg). The cause of this high frequency may be the relatively low threshold of diuretic dose used for defining DR.23 Elezabeth J et al found 41.7% patients to be DR. They defined DR as urine output of less than 1 liter within 4 hours of receiving I/V diuretics.24

Previous researchers used weight loss, diuretic dose or both weight loss plus diuretic dose to see the diuretic response. Each individual parameter i.e weight loss or diuretic dose, if used alone has intrinsic bias. One may think that a sicker patient may have accumulated more weight and they have potential to lose more weight, hence it may be the best parameter for diuretic response. Current guidelines also recommend change in weight to see diuretic response. However previous studies showed inconsistent association between weight loss and outcomes – better in DOSE25 and PROTECT26, while no differences in ESCAPE27. Similarly if diuretic dose is used alone, it may have patient and physician related factors and examining dose alone without its effect can also lead to bias.

Many other researchers, used weight loss per unit loop diuretic for DR. We used only furosemide dose (160 mg) as cut off for DR, because data on daily weight monitoring was not available for all of our patients. Previously researchers have also used only furosemide dose as cut off for DR.25,26

We used 160 mg dose on day 2 (48 hours after admission). This was done because many of our patients were discharged within 24 hours (n=152) were excluded from the study. Second, many patients were initially started on lower doses and their diuretic dose

<table>
<thead>
<tr>
<th></th>
<th>Group-I (n= 190)</th>
<th>Group-II (n= 105)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD n (%)</td>
<td>81 (43.15%)</td>
<td>58 (55.23%)</td>
<td>0.019</td>
</tr>
<tr>
<td>HTN n (%)</td>
<td>155 (81.57%)</td>
<td>88 (83.80%)</td>
<td>0.183</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>76 (40%)</td>
<td>51 (48.57%)</td>
<td>0.027</td>
</tr>
<tr>
<td>HB(mg/dl)</td>
<td>12.20 (± 1.4)</td>
<td>11.92 (± 1.5)</td>
<td>0.029</td>
</tr>
<tr>
<td>Sodium mmol/L</td>
<td>140 (± 3.5)</td>
<td>137.0 (± 3.9)</td>
<td>0.045</td>
</tr>
<tr>
<td>Potassium mmol/L</td>
<td>4.39 (± 0.69)</td>
<td>4.07 (± 0.53)</td>
<td>0.008</td>
</tr>
<tr>
<td>Chloride mmol/L</td>
<td>108 ± 7</td>
<td>105 ± 8</td>
<td>0.064</td>
</tr>
<tr>
<td>Creatinine mg/dl</td>
<td>1.2 ± (0.3)</td>
<td>1.5 ± 0.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>138 ± 13</td>
<td>159 ± 21</td>
<td>0.009</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>148 (± 15)</td>
<td>140.5 ± 14.9</td>
<td>0.006</td>
</tr>
<tr>
<td>JVP ≥ 10 cm-n (%)</td>
<td>150 (78.9)</td>
<td>73 (69.52 %)</td>
<td>0.009</td>
</tr>
<tr>
<td>Edema ≥ + 2-n (%)</td>
<td>155 (81.57)</td>
<td>73 (69.52%)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
was gradually increased depending on their improvement in symptoms and signs.

Various mechanisms behind diuretic resistance have already been discussed in the introduction. The effect of diuretics is exerted via the kidney, relying on secretion and to some extent on glomerular filtration to achieve therapeutic concentration in tubule. Atherosclerosis and diabetes both can damage glomerulus and cause glomerulosclerosis, thus decreasing GFR. Both the diseases also cause RAS activation and inflammation, which can also contribute to the reduce response.\(^{28,29,30}\)

Our study also showed CAD and DM to be significantly more common in patients with DR, thus supporting the above studies and might be the underlying mechanism for the high frequency of DR.

Hypotension in heart failure cause reduced renal perfusion and congestion, while feedback mechanism designated to reserve renal blood flow, GFR and sodium level further worsens renal function and further congestion.\(^{28}\) In our study the DR patients were also more hypotensive as compared to group I, which might be a contributing factor for DR.

Diuretics in the beginning can decrease congestion for short term, and can actually lower certain neurohormones levels\(^{31}\), but chronic use of diuretics can cause structural changes in tubular epithelium, which result in sodium retention and worsening congestion, neurohormonal activation, necessitating higher diuretic doses.\(^{32}\)

Like our study majority of other researchers have shown that patients with DR have poor renal function, but this doesn’t necessarily mean that poor renal function is the only mechanism behind DR. Testani JM et al\(^{17}\) and Valente MA et al\(^{19}\) showed renal disfunction explain only part of DR. This may be due to number of reasons. Our study as well as other researchers\(^ {19}\), demonstrated that DR patients more often had heart failure of ischemic origin and signs or markers of atherosclerosis (e.g old MI, DM, dyslipidemia). In these patients the kidneys might also be atherosclerotic that are less likely to respond to diuretics. Additionally prevalence of renal artery stenosis may be higher in patients with ischemic heart disease33 which may cause poor DR.

Like our study other researchers\(^ {34}\) also showed that DR patients were having fewer signs of congestion (JVP and Edema). Thus there heart failure worsening may be due to fluid redistribution, rather than fluid accumulation and therefore they may not respond to diuretics. Loop diuretics may not be the best treatment option in these patients as they are not volume overload and they may even be deleterious causing relative dehydration and worsening renal function. So it can be suggested that diuretic response is better in more congested patients with more peripherals edema.

Different treatment strategies have been suggested to over come DR e.g combining different groups of diuretics, continuous infusion of furosemide, ionotropic support for hypotension and ultra filtration\(^ {12}\). Zachari LC et al recommended therapeutic strategies based on resistance etiology to improve diuretic response in acute decompensated heart failure\(^ {34}\). Kevin T. et al concluded that among hospitalized patients with heart failure and loop DR both oral HCTZ and IV CTZ are effective in augmenting diuresis. Although CTZ was associated with higher enhancement of urinary output, no corresponding improvement in length of stay or mortality was recorded\(^ {35}\).

CONCLUSION

Diuretic resistance is a common problem in patients with heart failure. Early recognition of this problem and prompt aggressive treatment may help shorter stay of hospitalization.

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AUTHOR’S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Ashraf A: Conceived the idea and planned the Study.

Faheem M: Drafted the manuscript and collected data.

Dar H: Helped in data collection.

Haq MR: Helped in data Collection.

Shah SS: Statistical analysis.

Ahmad F: Helped in bibliography.

Shah J: Final Review.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.