INTRODUCTION

The global burden of End-Stage Renal Disease (ESRD) is rapidly rising and increasing number of patients is entering in the pool of those on renal replacement therapy (dialysis or transplant). Approximately 1.9 million ESRD patients are undergoing hemodialysis worldwide. Access to the facility of Renal Replacement Therapy (RRT) correlates directly with socioeconomic development and regional income. The initiation of RRT in developing world is restricted to fewer than a quarter of ESRD patients. In 2010, only 58.9% of ESRD patients received dialysis or had kidney transplantation. There was disparity among different parts of the world regarding access to renal replacement therapy, ranging from less than 2% in most of sub-Saharan Africa to over 70% in high-income North America, high-income Asia Pacific, and East Asia. The annual incidence of End-Stage Renal Disease (ESRD) in Pakistan is estimated at about 100 per million populations, and it is increasing with each passing year. Only 10% of renal failure patients receive renal replacement therapy.

ESRD patients have a high mortality rate during the first year of initiation of dialysis and at least 6% patients die within first 90 days. Late nephrology referral has been associated with adverse outcomes among ESRD patients. In Pakistan, till few years ago, almost 100% patients presented in emergency department with uremia and required urgent dialysis. A recent survey from Karachi (the largest metropolis of Pakistan) found that 41% of family physicians did not know when to refer a renal failure patient to nephrologist.

In late referral patients with ESRD, metabolic acidosis is present which is in most cases mild and partially or fully compensated with pH > 7.2 and may not be life threatening. However, more severe acidosis i.e. pH < 7.2 can cause hemodynamic instability (hypotension, cardiac arrhythmias), especially in patients with advanced uremia. Metabolic acidosis, however, is not the sole culprit for early mortality and morbidity whereas other factors may also contribute. During the first year of dialysis, mortality is lowest during the first month and at peak during the second and third month. Analysis of patients record from the authors institution revealed that patients were received with advanced uremia and metabolic acidosis requiring urgent hemodialysis via temporary vascular access and frequently need

ORIGINAL ARTICLE

Outcome of End-Stage Renal Disease Patients with Advanced Uremia and Acidemia

Iqbal Ur Rehman, Muhammad Khalid Idrees and Shoukat

ABSTRACT

Objective: To determine the outcome of End-Stage Renal Disease (ESRD) patients presenting with advanced uremia and acidemia requiring hemodialysis and adverse events seen within 72 hours of admission.

Study Design: Cross-sectional study.

Place and Duration of Study: Sindh Institute of Urology and Transplantation, Karachi, Pakistan, from October 2010 to March 2011.

Methodology: ESRD patients with advanced uremia and acidemia were included in the study. History, physical examination, complete blood count, serum urea, creatinine, electrolytes, arterial blood gases analysis, and ultrasound of kidneys were done in each patient. Adverse events and outcome were recorded for the next 72 hours. Data was analyzed by SPSS version (10). Mean value and standard deviation of quantitative measurements were calculated and statistical significance computed by t-test. A p-value ≤ 0.05 was taken as significant. Statistical significance of categorical variables was determined by chi-square test.

Results: Out of the 194 ESRD patients (mean age 46.54 ±14.07 years), 28 (14%) expired and 166 (86%) survived within 72 hours of admission. Hypotension requiring inotropic support was the commonest adverse event observed in 40 (20.6%) cases followed by fits in 31 (16%); and 25 (12.9%) patients required ventilatory support. Mortality was high in patients above 50 years of age. There was no statistically significant difference between two genders regarding adverse events and mortality.

Conclusion: The morbidity and mortality of patients with ESRD are serious concerns. Early referral of patients with ESRD, before they develop severe acidosis, can prevent significant morbidity and mortality.


INTRODUCTION

The global burden of End-Stage Renal Disease (ESRD) is rapidly rising and increasing number of patients is entering in the pool of those on renal replacement therapy (dialysis or transplant). Approximately 1.9 million ESRD patients are undergoing hemodialysis worldwide. Access to the facility of Renal Replacement Therapy (RRT) correlates directly with socioeconomic development and regional income. The initiation of RRT in developing world is restricted to fewer than a quarter of ESRD patients. In 2010, only 58.9% of ESRD patients received dialysis or had kidney transplantation. There was disparity among different parts of the world regarding access to renal replacement therapy, ranging from less than 2% in most of sub-Saharan Africa to over 70% in high-income North America, high-income Asia Pacific, and East Asia. The annual incidence of End-Stage Renal Disease (ESRD) in Pakistan is estimated at about 100 per million populations, and it is increasing with each passing year. Only 10% of renal failure patients receive renal replacement therapy.

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In late referral patients with ESRD, metabolic acidosis is present which is in most cases mild and partially or fully compensated with pH > 7.2 and may not be life threatening. However, more severe acidosis i.e. pH < 7.2 can cause hemodynamic instability (hypotension, cardiac arrhythmias), especially in patients with advanced uremia. Metabolic acidosis, however, is not the sole culprit for early mortality and morbidity whereas other factors may also contribute. During the first year of dialysis, mortality is lowest during the first month and at peak during the second and third month. Analysis of patients record from the authors institution revealed that patients were received with advanced uremia and metabolic acidosis requiring urgent hemodialysis via temporary vascular access and frequently need
ventilatory and inotropic support with high (very early, within 72 hours) mortality. As this type of presentation is now rare in developed and Western countries, this phenomenon is not reported in the literature and its prognostic factors are not well studied.

There is lack of data regarding the outcome of patients with advanced uremia and acidemia in our population. This study was conducted to study the patients’ demographics, occurrence of adverse events (fits, hypotension requiring inotropic support and requirement of ventilatory support) and their impact on outcome (survival/expiry) of the patients who presented with advanced uremia and acidemia.

METHODOLOGY

This cross-sectional study was conducted at Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan, from October 2010 to March 2011. Patients between 15 - 60 years of age, presenting first time to emergency department of SIUT having advanced uremia (arbitrarily defined as serum urea level ≥ 250 mg/dl at first presentation at SIUT) and diagnosed ESRD on the basis of clinical features, serum biochemistry and ultrasound kidneys, were included in the study by convenience sampling technique. Patients with acute or chronic renal failure and those already on dialysis were excluded from the study. The study was approved by the Ethical Review Committee (ERC) of the institution. Informed consent was obtained.

History was taken and physical examination done. Blood samples for Complete Blood Count (CBC) and serum biochemistry (serum urea, creatinine, electrolytes) sent along with a separate heparinized sample of arterial blood for pH, PO2, PCO2, O2 saturation and bicarbonate measurement. Ultrasound of kidneys was done to see the size of the kidneys and exclude obstruction. Outcome of patients (whether the patient expired or survived) was observed for the next 72 hours after admission. Additionally, adverse events (fits, need of mechanical ventilation and hypotension) were observed. During this period, hemodialysis was done in supervision of trained physician. The dialysis was of short duration (90 - 120 minutes), with low flux hollow fibre (polysulphone) dialyzer, without any anticoagulation (saline flushes to prevent clotting of dialyzer), bicarbonate dialysate, blood flow of 250 ml/minute and dialysate flow of 500 ml/minute. Ultrafiltration was done in patients having fluid overload. All the relevant information (survival, death and adverse outcome) were recorded on the proforma.

Data was entered and analyzed in statistical software (SPSS version 10). Frequency and percentage were computed for categorical (qualitative) variables like age group, gender, outcome of end stage of renal disease patients and adverse event. Mean and standard deviation were computed for quantitative measurement like age, temperature, hemoglobin, TLC, platelet, potassium, sodium and pH. Statistical significance of these variables was determined by t-test and value of p equal or less than 0.05 was taken as statistically significant. Similarly, the statistical significance of categorical data was determined by chi-square test. Stratification was done with regard to age, gender and number of dialysis to observe the effect on outcomes.

RESULTS

This study included 194 ESRD patients (130 males and 64 females) having advanced uremia and acidemia. The average age of the patients was 46.54 ±14.07 years and most of the patients were above 50 years of age. Patients who expired were older as compared to those who survived (52.29 ±12.77 vs. 45.57 ±14.09 years) and this difference was statistically significant (p = 0.019). All the patients had fairly advanced uremia with a mean serum urea of 349.04 ±77.6 mg/dl and mean serum creatinine of 14.44 ±4.41 mg/dl respectively. About 40% patients had hyperkalemia. The patients who expired had lower pH (7.01 ±0.11) as compared to those who survived (7.14 ±0.09) and this difference was statistically significant (p=0.0005). Table I shows the descriptive statistics of study variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ±SD</th>
<th>Max - Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.54 ±14.07</td>
<td>65 - 15</td>
</tr>
<tr>
<td>Temperature*</td>
<td>98.59 ±0.98</td>
<td>103 - 98</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7.87 ±1.82</td>
<td>11 - 3</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>86.06 ±20.51</td>
<td>122 - 47</td>
</tr>
<tr>
<td>TLC</td>
<td>15.48 ±8.23</td>
<td>56 - 1</td>
</tr>
<tr>
<td>Platelet</td>
<td>246.78 ±139.95</td>
<td>716 - 5</td>
</tr>
<tr>
<td>Potassium**</td>
<td>5.41 ±1.35</td>
<td>9 - 2</td>
</tr>
<tr>
<td>Sodium</td>
<td>134.66 ±8.48</td>
<td>168 - 107</td>
</tr>
<tr>
<td>pH</td>
<td>7.12 ±0.13</td>
<td>7.29 - 6.84</td>
</tr>
<tr>
<td>H.ion (nmol/L)</td>
<td>79.15 ±21.94</td>
<td>144 - 52</td>
</tr>
<tr>
<td>Urea mg/dl</td>
<td>349.04 ±77.6</td>
<td>594 - 251</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>14.44 ±4.41</td>
<td>36.9 - 8.0</td>
</tr>
</tbody>
</table>

*Out of 194 patients, 66 (34%) had temperature more than 100°F
** Out of 194 patients, 78 (40.2%) had hyperkalemia

Hypotension requiring inotropic (vasopressor) support was the commonest adverse event that was observed in 40 (20.6%) patients followed by fits (seizures) in 31 (16%) patients while 25 (12.9%) patients required ventilatory support. Fits and ventilatory support were more common in patients below 30 years of age while hypotension was observed in patients above 50 years of age. Frequency of fits and ventilatory support was nearly same in male and female (p=0.46 and p=0.90, respectively) while hypotension was more common in females than males (28.1% vs. 16.9%); but this difference did not reach statistical significance (p=0.07).

Frequency of hypotension and ventilatory support was high in those cases who had only one session of dialysis as compared to those who required 2 and 3 dialysis sessions during the period of 72 hours (p=0.001 and 0.0001 respectively) while there was no statistically
significant difference in case of fits (p=0.172). These patients had more severe metabolic acidosis and consequent highest mortality as shown in Table II. Dialysis prescription varied very little from patient to patient as all the patients had short duration dialysis and dialysate flow (500 ml/minute) whereas dialysate compositions (prepared in the institution in bulk) were fixed and dialyzer used was of the same size (1.4 m²) for all the patients.

Fourteen percent (28/194) patients expired and 86% (166/194) survived within 72 hours after admission. Mortality/expiry rate was highest (20.8%) among those above 50 years of age. Mortality was statistically significantly higher in those above 50 years of age as compared to those below 50 years (p=0.029). There was no difference in both genders regarding mortality (p=0.918). Similarly, mortality/expiry rate was 100% in those cases who had only one dialysis session.

Frequencies of adverse events and mortality are summarized in Table III.

### DISCUSSION

The authors specifically studied outcome of uremic patients who were acidic and in need of emergency dialysis, which is a common scenario in Pakistan due to late diagnosis or referral. Most of those patients, who have an uneventful course within few days after starting dialysis, usually do well subsequently. The total number of patients with a span of 6 months, suggests that this is still a frequent mode of presentation in Pakistan. The average age of these patients (46.54 ±14.07 years) is much less than that reported from USA11 but close to that in other South Asian countries.12 The number of males was almost twice that of females in this study. This is contrary to the finding from community based study from Karachi13 which did not find gender difference in occurrence of kidney disease among general population. The lesser number of females in this study is probably due to gender bias and social deprivation of females.

This study included patients with severe acidosis i.e. pH < 7.3. The patients who eventually expired had more severe acidemia compared to those who survived. Acidosis of such severity may lead to adverse hemodynamic effects such as arteriolar dilatation and depression of myocardial contractility.8 In an experimental study, the effect of metabolic acidosis induced by infusion of hydrochloric acid in pigs was studied which showed that lowering of pH to 7.1 resulted in diminished cardiac contractility and increased the ventricular stroke work per minute.14 Numerous studies on patients with lactic acidosis in critical care setting have highlighted the adverse effects of profound acidemia.15 The authors were unable to find any study where effect of such profound metabolic acidosis in uremic patients has been studied.

It is difficult to compare these patients (whose acidosis is rapidly corrected by dialysis) with non-uremic patients with lactic acidosis. More than 40% patients had hyperkalemia but it had no effect on mortality. It is probably because of the rapid removal of potassium in process of hemodialysis. Patients who expired had higher temperature and higher TLC as compared to those who survived. This could be due to presence of some unrecognized infection (such as UTI) or result from systemic inflammation due to metabolic acidosis. Patients with higher PCO₂ (respiratory acidosis) had

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**Table III: Adverse events and mortality.**

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Number</th>
<th>Fits</th>
<th>Hypotension</th>
<th>Ventilatory support</th>
<th>Expired</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 30 years</td>
<td>36</td>
<td>7 (19.5%)</td>
<td>8 (16.7%)</td>
<td>5 (13.8%)</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>31 to 50 years</td>
<td>82</td>
<td>11 (17.8%)</td>
<td>7 (11.3%)</td>
<td>7 (11.3%)</td>
<td>5 (6.1%)</td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td>96</td>
<td>13 (13.5%)</td>
<td>27 (28.1%)</td>
<td>13 (13.5%)</td>
<td>20 (21.3%)</td>
</tr>
<tr>
<td>Number of adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>130</td>
<td>19 (14.6%)</td>
<td>22 (16.9%)</td>
<td>17 (13.1%)</td>
<td>19 (14.6%)</td>
</tr>
<tr>
<td>Females</td>
<td>64</td>
<td>12 (18.8%)</td>
<td>18 (28.1%)</td>
<td>8 (12.5%)</td>
<td>9 (14.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>31 (16%)</td>
<td>40 (20.6%)</td>
<td>25 (12.9%)</td>
<td>28 (14%)</td>
</tr>
</tbody>
</table>

* Significant
higher mortality. Patients with pure metabolic acidosis have lower PCO\(_2\) due to respiratory compensation but exhaustion of respiratory muscles leads to concomitant respiratory acidosis (more pronounced among diabetic CKD patients) and consequent higher morbidity and mortality.\(^{16}\)

Hypotension was the commonest adverse event observed in 20.6% cases followed by fits (16%) and 12.9% patients required ventilator support. High mortality rate (60%) observed in patients who were on ventilator followed by hypotension (47.5%) and fits (2.3%). Seizures are not uncommon in patients with advanced uremia on presentation and are multi-factorial in causation. Seizures in uremic patients can be a manifestation of uremia, metabolic derangements or the treatment of these derangements.\(^ {17}\) Bergen and colleagues reported the incidence of seizures (fits) of approximately 10% in patients with chronic renal failure.\(^ {18}\) The lower frequency of seizures among our study participants may be due to short period of observation (72 hours).

Mechanical ventilation was required in 12.9% patients which is less than 26% as reported by Rocha\(^ {19}\) among maintenance dialysis patients admitted in ICU. Patients with advanced uremia often have pulmonary edema, inability to clear upper airways and exhaustion due to respiratory muscle fatigue. Similarly, 20.6% of our patients had hypotension and required inotropic support compared to 24% as reported by Rocha.\(^ {19}\) The difference in the two study populations is that there was high proportion of patients with sepsis in the study of Rocha while these patients had severe metabolic acidosis.

The outcome of ESRD patients with advanced uremia was quite dismal in this study. Fourteen percent patients expired within 72 hours of admission. This is much higher than the 6% mortality during first 90 days of start of dialysis in USA.\(^ {5}\) In Canada,\(^ {20}\) early 90-day mortality after initiation of dialysis was up to 34.7% of one year mortality. However, there is wide variation in patient mortality in different parts of the world. DOPPS found that one-year mortality rates were 6.6% in Japan, 15.6% in Europe and 21.7% in the USA and variability in demographic and co-morbid conditions at inception of dialysis could explain only part of the differences in mortality rate between these countries.\(^ {21}\) It has been observed that both cardiovascular and non-cardiovascular mortality risk factors are equally increased among dialysis patients and should be focused.\(^ {22}\)

In this study, frequency of expired patients was high in above 50 years of age. This is well known phenomenon that mortality increases with increasing age.\(^ {20}\) Mortality rate was similar in male and female patients in this study. Gender difference has been reported in the survival of new ESRD patients. Bloembergen et al. found that males receiving chronic dialysis had a 22% higher mortality than females, mostly because of excess risk of acute myocardial infarction and malignancies.\(^ {23}\) However, another study from European cohort showed that young and diabetic women starting dialysis had higher non-cardiovascular mortality risk than men while females of 45 years old and above had lower cardiovascular mortality than men.\(^ {24}\) The authors did not find such gender difference in this study. This may be because of smaller number of females. Higher frequency of hypotension, need of ventilatory support and 100% mortality among patients, who survived to have only one dialysis session, reflects that these patients were more seriously sick. The dialysis prescription was more or less the same among all the patients and it is not possible to judge the effect of dialysis on survival or mortality in this small single centre study.

This study is, to the best of authors' knowledge, the first of its kind from this part of the world which highlights the high mortality rate among ESRD patients presenting with advanced uremia and metabolic acidosis/acidemia during first 72 hours of admission. It highlights the importance of accurate reporting of events during initial days of start of dialysis. Early referral to nephrologist and attendance of pre-dialysis clinics may facilitate the avoidance of central venous catheters, timely creation of AV fistula, correction of anemia, mineral bone metabolism and malnutrition, which ultimately improve survival on dialysis.\(^ {25}\)

It is a single center study and observation period was only 3 days, so co-morbid conditions other than ESRD could affect the outcome and adverse events.

**CONCLUSION**

The morbidity and mortality of patients with ESRD are serious concerns for patients presenting late with advanced uremia and severe metabolic acidosis. Early referral of patients, with ESRD before they develop severe acidosis, will prevent significant morbidity and mortality.

**REFERENCES**