Door-to-Dialysis Time and Daily Hemodialysis in Patients with Leptospirosis: Impact on Mortality

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Background: Leptospirosis is a public health problem, the severe form of which (Weil’s disease) includes acute respiratory distress syndrome, typically accompanied by acute kidney injury (AKI), and is associated with high mortality rates. Recent evidence suggests that dialysis dosage affects outcomes in critically ill patients with sepsis-induced AKI. However, this population varies widely in terms of age, gender, and concomitant conditions, making it difficult to determine the appropriate timing (door-to-dialysis time) and dialysis dosage.

Design, setting, participants, and measurements: It is logical to assume that increasing the dialysis dosage would minimize uremic complications and improve outcomes in such patients. Patients with Weil’s disease constitute a homogeneous population and are typically free of comorbidities, therefore presenting an ideal model in which to test this assumption.

Results: The effects of dialysis dosage were evaluated in this population, with the use of either classic or slow low-efficiency hemodialysis, and two periods/treatment plans were compared: 2002 to 2003/delayed, alternate-day dialysis (DAdD group; n = 15) and 2004 to 2005/prompt and daily dialysis (PaDD group; n = 18). Age, gender, AKI severity, APACHE score, serum urea, and time to recovery of renal function were assessed. All patients received vasoactive drugs (because of hemodynamic instability) and were on mechanical ventilation (because of acute respiratory distress syndrome). Mean serum urea during the dialysis period was significantly lower in the PaDD group than in the DAdD group. Of the PaDD group patients, three (16.7%) died, compared with 10 (66.7%) of the DAdD group patients.

Conclusions: On the basis of this result, it is believed that alternate-day hemodialysis is no longer appropriate for critically ill patients with Weil’s disease.

L leptospirosis is a spirochetal zoonosis that is caused by pathogenic Leptospira species. Leptospirosis is a public health problem worldwide and is epidemic in some areas of Brazil during the rainy season. In 2005, the reported incidence of leptospirosis cases in the city of São Paulo was 5.3/100,000 inhabitants (1). Leptospirosis typically affects young adults, mainly men (at a ratio of 9:1), in their most economically productive years (2). The most severe form of the disease (Weil’s disease) is a classic model of the type of sepsis that includes acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) (3). The mortality rates associated with Weil’s disease remain unacceptably high, reaching 55% among patients who are admitted to intensive care units (ICU) (4). The current treatment includes penicillin and supportive care (5). Weil’s disease manifests as severe lung injury (diffuse alveolar hemorrhage, pulmonary edema, ARDS, or a combination of these features) accompanied by AKI and can therefore be highly lethal (6). Patients with this form of leptospirosis typically require dialysis. In our ICU, the mortality rate among patients with leptospirosis and ARDS (on mechanical ventilation) and AKI (on dialysis) was 55% from 1994 to 1997 and 43% from 1998 to 2001 (4). Despite improvements in critical care and dialysis technology, AKI continues to be associated with high mortality (7). In patients with ESRD, a strong correlation between dialysis dosage and outcome has been established on the basis of urea reduction ratios and Kt/V. Consequently, there has been intense interest in defining a similar relationship in critically ill patients with AKI. Evidence from the studies recently conducted by Ronco et al. (8) and Schiffl et al. (9) suggests that the dosage of dialysis delivered can significantly affect outcomes in cases of AKI. Although many studies have described the incidence and outcomes associated with sepsis-induced AKI, relatively few have examined the relationship between the timing of the initiation of dialysis (door-to-dialysis time) and AKI-related mortality (10–12). The need for renal replacement therapy (RRT) in critically ill patients with AKI depends on numerous factors, including the remaining diuresis, the accumulation of uremic solutes, hypercatabolism, patient body weight, and the level of metabolic control desired. The overall effect that dialysis has on patient outcomes remains unclear. Dialysis is commonly used in the treatment of AKI. However, there is great variation in the population of critically ill patients with AKI in terms of age and gender, as well as in terms of concomitant conditions such as sepsis, predisposing factors (e.g., AIDS), hematologic disorders, chronic obstructive pulmonary disease, liver

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failure, trauma, and heart failure. Therefore, given this wide array of subject characteristics, which is not seen in the population of patients with ESRD, it is considerably more difficult to determine the appropriate timing and dosage of dialysis in patients with AKI than in those with ESRD. The hypothesis that increasing the dosage of hemodialysis delivered in critically ill patients with AKI reduces the rate of uremic complications and improves the outcome is logical yet remains unproved. Because the population of patients with Weil’s disease is extremely homogeneous and typically free of concomitant diseases, it represents an ideal model in which to test this hypothesis. Therefore, we designed this study to evaluate the effects that dialysis dosage has on survival in this population, comparing prompt, frequent (daily) hemodialysis with delayed, intermittent (alternate-day) hemodialysis. We hypothesized that the door-to-dialysis time and the frequency of hemodialysis would be associated with mortality rates.

Concise Methods

Patients

The study sample was selected from among patients who were suspected of having Weil’s disease and admitted to the ICU of the Emilio Ribas Institute of Infectology, which is located in Sao Paulo, Brazil, and is a referral center for leptospirosis. Only patients who received a diagnosis of AKI and ARDS on admission to the ICU were included. To receive a diagnosis of ARDS, a patient must be intubated (receiving positive-pressure ventilation), have a partial pressure of arterial oxygen/fraction of inspired oxygen ratio of <300, and present radiologic evidence of bilateral infiltrates consistent with pulmonary edema or pulmonary hemorrhage. Because of a change in the protocol, patients who were admitted to the ICU in 2002 to 2003 (n = 15) were studied separately from those who were admitted in 2004 to 2005 (n = 18). In the 2002 to 2003 group, door-to-dialysis times were longer and subsequent dialysis sessions were performed on the traditional (alternate-day) basis. Therefore, this group was designated the delayed, alternate-day dialysis (DAdD) group. The 2004 to 2005 group, in which door-to-dialysis times were shorter and subsequent dialysis sessions were performed on a daily basis, was designated the prompt and daily dialysis (PaDD) group. The study was approved by the Ethics in Research Committee of the Emilio Ribas Institute of Infectology.

Timing and Frequency of Hemodialysis

The DAdD group patients were admitted using the traditional protocol, which involves waiting 6 h to determine whether fluid replacement and the use of vasoactive drugs increase diuresis by >1 ml/kg per h. This had the effect of delaying the initiation of dialysis. Patients in this group subsequently received alternate-day dialysis sessions. Depending on patient hemodynamic status, either intermittent classic dialysis or sustained low-efficiency dialysis (SLED) was used. The treatment strategy used for the PaDD group patients was considered aggressive: The RRT was started as soon as possible after admission to the ICU; and the subsequent hemodialysis sessions, also consisting of either intermittent classic dialysis or SLED, were conducted on a daily basis.

Hemodialysis

Hemodialysis was performed using a volumetrically controlled machine (AK 95; Gambro, Lund, Sweden). A bicarbonate dialysate was used at a dialysate flow rate of 500 ml/min. Intermittent classic dialysis sessions lasted 3 to 4 h, with a blood flow rate of 250 to 300 ml/min, whereas SLED sessions lasted 6 to 10 h, with a blood flow rate of 170 to 250 ml/min. The choice between intermittent classic dialysis and SLED was based on patient hemodynamic status. Vascular access was obtained with a dual-lumen hemodialysis catheter (Arrow Int., Reading, PA) placed in the femoral or jugular vein. Only first-use, synthetic (polysulfone) dialyzer membranes (F8, Fresenius, Bad Homburg, Germany) were used, and no anticoagulants were administered. In the first three RRT sessions, all hemodialysis procedures were performed isovolumetrically, and the net ultrafiltration volume was zero (all of the patients were considered dehydrated at admission).

Mechanical Ventilation

All of the patients were ventilated in accordance with the ARDS Network protocol (13), using the pressure-controlled mode and a tidal volume of 6 ml/kg of predicted body weight. After a recruitment maneuver, positive end-expiratory pressure was applied.

Severity of Illness and Other Variables

The severity of illness was determined on the basis of the APACHE II score (14) on the day of admission. Other variables were also evaluated on admission: Direct serum bilirubin, urea, pH, bicarbonate, creatine phosphokinase, sodium, potassium, and urinary volume. Net fluid intake per day was compared between the groups on the first 3 d in the ICU. Intradialysis episodes of hypotension, which was defined as a mean arterial pressure (MAP) of <70 mmHg or the need for intervention, were analyzed for the first three hemodialysis procedures. Mean serum urea during the dialysis treatment period was compared between the groups.

Patients were treated and monitored according to accepted intensive care practices. No patient was receiving parenteral nutrition.

Outcome Measures

The primary outcome measures of the study were survival, duration of AKI, and time on mechanical ventilation. The causes of death among patients with the severe form of leptospirosis can be pulmonary hemorrhage, bleeding, shock, myocardinis, arrhythmia, and sepsis. We decided to analyze overall mortality rather than death from specific causes.

Serologic Diagnosis and Treatment

The diagnosis was confirmed by serology using microscopic agglutination test or IgM ELISA. All patients were initially treated with penicillin or ceftriaxone. In some cases, nosocomial infection occurred, and the treatment regimens were therefore modified on the basis of the culture results.

Statistical Analyses

All quantitative data are expressed as means ± SEM. Differences among the means of multiple parameters were analyzed using ANOVA followed by the Student-Newman-Keuls test. Differences between two parameters were analyzed either by unpaired t test or by nonparametric methods (Mann-Whitney test). Values of P < 0.05 were considered statistically significant.

Results

Baseline Characteristics

The study sample comprised 33 patients with leptospirosis: 15 treated in the 2002 to 2003 period and 18 treated in the 2004 to 2005 period. There was only one female patient (in the 2002 to 2003 group).

Of the Leptospira interrogans serovars identified, 70.6% were icterohaemorrhagiae, 17.6% were copenhageni, 5.8% were copenhageni, and 5.8% were castellonis.

In the DAdD group, 10 (67%) of the 15 had an APACHE II score
Table 1. Clinical characteristics of patients at admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>2002 to 2003 (n = 15)</th>
<th>2004 to 2005 (n = 18)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44 ± 4.6</td>
<td>42 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>26 ± 1.2</td>
<td>24.5 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary volume (ml/d)</td>
<td>1135 ± 539</td>
<td>1963 ± 458</td>
<td>NS</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>232 ± 19.5</td>
<td>207 ± 18.4</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>6.2 ± 0.6</td>
<td>6.6 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>136 ± 1.7</td>
<td>139 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.2 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.28 ± 0.03</td>
<td>7.26 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>18 ± 1</td>
<td>17 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>CPK (IU/L)</td>
<td>1410 ± 244</td>
<td>2069 ± 409</td>
<td>NS</td>
</tr>
<tr>
<td>Br (mg/dl)</td>
<td>15.4 ± 2.4</td>
<td>15.3 ± 2.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

aData are means ± SEM; Mann-Whitney test. Br, direct bilirubin; CPK, creatine phosphokinase.

>24, compared with 11 (61%) of the 18 in the PaDD group. As can be seen in Table 1, the two groups were similar at admission with respect to demographic characteristics, serum bilirubin, pH, bicarbonate, creatine phosphokinase, sodium, potassium, and urinary volume. Table 1 also shows the degree of azotemia at admission.

Respiratory Function and Time on Mechanical Ventilation

Ventilator settings and respiratory function at admission are shown in Table 2, which also shows the time on mechanical ventilation. There were no statistically significant differences between the groups in any of the variables evaluated.

Net Fluid Intake

By day 2, urinary output, which had been normal at admission, had dropped (to <500 ml) in both groups (data not shown). None of the patients received furosemide or any other diuretic during their stay in the ICU. The net fluid intake (cumulative fluid intake minus fluid output) is shown in Table 3. There were no statistically significant differences between the groups.

Hemodynamic Status

We compared the predialysis MAP, the lowest intradialysis MAP, and the postdialysis MAP in each session for the first three sessions given to the two groups (Table 4). For a given dialysis, there were no statistically significant differences in MAP among the three time points (predialysis, intradialysis, and postdialysis), among the three sessions, or between the two groups. All patients were receiving norepinephrine (10 to 80 μg/min).

Table 2. Respiratory function and time on mechanical ventilation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2002 to 2003</th>
<th>2004 to 2005</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2/FIO2</td>
<td>212 ± 25</td>
<td>168 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>PEEP (cmH2O)</td>
<td>12 ± 0.7</td>
<td>12 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>PIP (cmH2O)</td>
<td>30 ± 0.9</td>
<td>30 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Time on MV (d)</td>
<td>8 ± 1.8</td>
<td>11 ± 1.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

aMV, mechanical ventilation; PaO2/FIO2, partial pressure of arterial oxygen/fraction of inspired oxygen ratio; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.
bCounted from the day of intubation to the day of extubation.

Table 3. Net fluid intake on the first 3 d after admission

<table>
<thead>
<tr>
<th>Day</th>
<th>DAdD Group (ml/d)</th>
<th>PaDD Group (ml/d)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1817 ± 366</td>
<td>1521 ± 241.5</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>1971 ± 277</td>
<td>1524 ± 242</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>1865 ± 475</td>
<td>1664 ± 363</td>
<td>NS</td>
</tr>
</tbody>
</table>

aDAdD, delayed, alternate-day dialysis; PaDD, prompt and daily dialysis.
was 6.3 ± 1.6 d for those in the DAdD group and 10.7 ± 9.7 d for those in the PaDD group. For those who survived, the mean time of hospitalization (time to hospital discharge) was 22 ± 3.3 d for those in the DAdD group and 35.3 ± 2.0 d for those in the PaDD group \((P = 0.01)\), and the mean stay in the ICU was 13.6 ± 3.1 d for those in the DAdD group and 20 ± 1.3 d for those in the PaDD group (NS). Although time to hospital discharge was significantly shorter in the DAdD group, it must be borne in mind that mortality was significantly higher in this group (only five of the 15 DAdD group patients survived).

Discussion

Weil’s disease is a classic model of sepsis. Patients with Weil’s disease typically develop severe lung injury (diffuse alveolar hemorrhage, pulmonary edema, ARDS, or a combination of these features) accompanied by AKI. It has been demonstrated that respiratory insufficiency and renal failure are independently associated with mortality (15,16). The mortality rate among such patients remains unacceptably high (3). In our study, there was a clinically relevant difference in mortality between the PaDD group patients and the DAdD group patients. This suggests that more frequent hemodialysis decreases the risk for fatal complications in patients with Weil’s disease. In general, it is difficult to analyze the impact of aspects such as dialysis dosage in patients with sepsis. This is due to the heterogeneous nature of the population in terms of age and underlying conditions: predisposing factors (e.g., AIDS), hematologic disorders, chronic obstructive pulmonary disease, liver failure, trauma, and heart failure. However, the population of patients with Weil’s disease is homogeneous. The typical patient with leptospirosis is a previous healthy middle-aged man with no history of serious disease. Therefore, leptospirosis is a near-perfect human model of sepsis. Schiffl et al. (9) reported that daily intermittent hemodialysis is superior to conventional (alternate-day) hemodialysis in critically ill patients with AKI and concomitant acute tubular necrosis. The authors found that daily hemodialysis was associated with better control of blood urea nitrogen and creatinine, as well as with higher survival rates. In addition, Ronco et al. (8) showed that a filtration rate of 35 ml/h per kg was associated with improved 15-d survival in patients who were treated with hemofiltration. In an analysis of retrospective data from the Cleveland Clinic Founda-
tion registry, it was suggested that, in ICU patients with AKI, survival is improved for those who receive a higher dosage of intermittent RRT or continuous RRT (CRRT) in comparison with those who receive a lower dosage (17). Honore et al. (18) showed that short-term, high-volume hemofiltration was well tolerated and improved survival in patients with septic shock. However, in another study of such patients, no association was found between dialysis dosage and survival (19). This discrepancy is likely due to the heterogeneous nature of the populations studied.

<table>
<thead>
<tr>
<th>Dialysis Session</th>
<th>DAdD Group</th>
<th>PaDD Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predialysis</td>
<td>Intradialysis</td>
</tr>
<tr>
<td>First</td>
<td>82 ± 3</td>
<td>70 ± 5</td>
</tr>
<tr>
<td>Second</td>
<td>83 ± 6</td>
<td>67 ± 4</td>
</tr>
<tr>
<td>Third</td>
<td>81 ± 6</td>
<td>74 ± 7</td>
</tr>
</tbody>
</table>

*Intradialysis is the lowest value registered. MAP, mean arterial pressure.*

Figure 1. (A) Door-to-dialysis time (from intensive care unit admission to the initiation of dialysis); (B) mean serum urea during the dialysis treatment period.

Figure 2. Mortality according to treatment group.
In this study, the door-to-dialysis time was significantly shorter in the PaDD group than in the DAdD group. Studies have shown that door-to-dialysis time is associated with the degree of azotemia and with mortality (11,12,20). Hemodynamic stability was maintained during SLED treatments in both groups. The SLED method has been shown to be a viable alternative to traditional CRRT techniques for critically ill patients (21). In addition, SLED provides solute clearances similar to those obtained with intermittent classic hemodialysis and eliminates the need for expensive CRRT machines, as well as reduces the costs related to anticoagulation, customized solutions, and trained personnel (22). These are important issues in developing countries. Although this study involved the use of hemodialysis only, there are some interesting data in the literature regarding the use of hemofiltration in patients with leptospirosis (23).

In this study, the time to the recovery of renal function did not differ significantly between the PaDD group and the DAdD group. We also found no statistically significant difference between the groups in terms of the time on mechanical ventilation. The higher mortality rate in the DAdD group might explain the lack of any differences in these two parameters, because patients who died were excluded from the analyses. All of the patients who died did so while on mechanical ventilation and while still being treated with dialysis.

We found no statistically significant difference between the two groups in terms of net fluid intake during the first 3 d after admission to the ICU. For patients with leptospirosis, we recommend low daily net fluid intake because of the risk for pulmonary hemorrhage. The ARDS Clinical Trials Network study showed that using a conservative fluid management protocol with the objective of achieving lower central venous pressure or lower pulmonary artery occlusion pressure resulted in a greater reduction in the net fluid intake without an increase in adverse events, as compared with a liberal fluid management protocol aimed at achieving higher intravascular volume and cardiac filling pressures. The conservative strategy improved lung function, shortening the duration of mechanical ventilation and ICU stay without increasing nonpulmonary organ failure. These results lend credence to the idea that a conservative strategy of fluid management should be used in patients with acute lung injury (24). Mitchell et al. (25) randomly assigned 89 patients with pulmonary edema to receive either diuretics with fluid restriction (based on extravascular lung water) or routine fluid management. The authors found that the patients who were subjected to fluid restriction presented lower net fluid intake, less time on mechanical ventilation, and shorter ICU stays. Pulmonary symptoms, even severe symptoms (ARDS), are being reported with increasing frequency in patients with leptospirosis (26). The cause of pulmonary edema in ARDS is unclear. It has been reported that pulmonary edema clearance is greatly affected by active sodium transport out of the alveoli rather than by reversal of the Starling forces (27–29). In a previous study, we showed that leptospirosis decreases protein expression of the α subunit of the epithelial sodium channel (ENaC) in the lungs of hamsters. We also found upregulated protein expression of basolateral Na-K-2Cl (NKCC1) in the lungs. The data obtained in that study show that leptospirosis has a profound influence on the sodium transport capacity of alveolar epithelial cells (30). We hypothesized that leptospirosis induces a decrease in alveolar clearance by reducing ENaC protein abundance, which inhibits the transport of sodium, as well as the movement of water, from the lumen into the interstitial space, thereby lowering the osmotic gradient. The cell shrinkage that is induced by this mechanism can stimulate NKCC1 protein expression in the basolateral membrane. In turn, NKCC1 mediates the coupled influx of sodium, potassium, and chlorine into the epithelial cells. The decreased influx of sodium from the lumen into the cells (induced by the lower levels of human ENaC), together with the increased influx of sodium from the interstitial space into the cells (induced by the higher levels of NKCC1), can block the net influx of sodium and water from the alveoli (30). These effects would be expected to increase susceptibility to ventilator-induced lung injury, an entity that is of increasing concern in intensive care settings (31,32).

In patients with Weil’s disease, using daily hemodialysis to maintain strict control of azotemia and fluid volume can improve survival, especially for patients who have the potential for pulmonary hemorrhage and are at high risk for death, such as those who were evaluated in this study. Reports of “prophylactic dialysis” and intensive dialysis span decades.

Early initiation of hemodialysis followed by daily hemodialysis sessions seems to be extremely important. However, because patients with AKI constitute a population that is heterogeneous, it is very difficult to prove that such treatment has an impact on recovery of renal function and on survival. In this study, we evaluated intensive dialysis treatment in a highly homogeneous group of patients who had a single disease. We found that the prompt initiation of dialysis, together with daily dialysis sessions, seems to reduce ICU mortality. We cannot entirely rule out the potential effect of improvements in standards of care during the course of the study, although the majority of treatment protocols that were used in our ICU remained unchanged during this period.

Conclusion
On the basis of these results and the results of other studies, we believe that alternate-day hemodialysis should no longer be considered appropriate for critically ill patients with Weil’s disease. We can further speculate that undergoing dialysis early and often would also be beneficial for other patients with sepsis, regardless of the underlying disease.

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Disclosures
None.

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