Hemostatic derangement in leptospirosis: A prospective cross-sectional study

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ABSTRACT

Context: Coagulation abnormalities have been observed among leptospirosis patients. However, coagulopathy in severe leptospirosis has not been further characterized.

Aims: The aim of this study was to evaluate conventional coagulation and rotational thromboelastometry (ROTEM®) parameters in leptospirosis patients.

Settings and Design: This prospective cross-sectional comparative study included patients presenting to a tertiary hospital in Sri Lanka with clinically and serologically confirmed leptospirosis (14 severe and 6 mild), dengue (6), sepsis (5), and 6 healthy individuals.

Subjects and Methods: Blood samples were collected between the 3rd and 10th days of illness for prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen, lupus anticoagulant, factors VII and VIII, D-dimer, platelet count, and ROTEM.

Statistical Analysis Used: ANOVA post hoc comparison using Bonferroni was applied to compare groups.

Results: PT and aPTT were prolonged in leptospirosis patients and were corrected with normal plasma. TT was not significantly prolonged in leptospirosis. Fibrinogen was significantly elevated in severe leptospirosis (P = 0.001) and sepsis (P = 0.001) compared with healthy controls and dengue. Thirty percent of leptospirosis patients had thrombocytopenia (17% in mild and 36% in severe). No significant differences were seen in inTEM clotting time (CT) and exTEM CT in leptospirosis when compared to the other three groups. inTEM clot formation time (CFT) and exTEM CFT in dengue were significantly higher compared to severe (P = 0.001) and mild (P = 0.005) leptospirosis. inTEM maximum clot firmness (MCF) (P = 0.001) and exTEM MCF (P = 0.001) were significantly lower in dengue than in leptospirosis. Only one patient with leptospirosis had bleeding manifestations.

Conclusions: Abnormalities in conventional coagulation parameters occur in leptospirosis. However, ROTEM parameters in leptospirosis are not significantly altered.

Key Words: Coagulation, hemorrhage, leptospirosis, thromboelastography

INTRODUCTION

Leptospirosis is a re-emerging zoonotic infection in Sri Lanka, with several outbreaks over the past decade. Its clinical presentation ranges from mild acute febrile illness to severe disease with organ dysfunction,
including acute renal failure, lung involvement, liver derangement, hemorrhage, and shock. Endothelial cell injury and vasculitis are known to play an important role in the pathogenesis of leptospirosis. While bleeding is a commonly seen, more complex derangement of hemostasis can occur in leptospirosis, including thrombotic episodes, or severe thrombomembranous syndromes such as disseminated intravascular coagulation (DIC), and rarely hemolytic-uremic syndrome \(^{[1,2]}\) or thrombotic thrombocytopenic purpura.\(^{[3,4]}\) Clinically evident bleeding in leptospirosis is seen in a variable proportion of patients in different studies ranging from 20% to 60%.\(^{[5,6]}\) However, most of the bleeding manifestations are not life-threatening, and their frequency is increased with increased severity.\(^{[6]}\) There is little understanding regarding the pathophysiological basis of these hemorrhagic and thrombotic manifestations in leptospirosis and whether they contribute to organ dysfunction through effects on the tissue microcirculation.\(^{[7]}\) Thrombocytopenia is seen in up to 80% of patients with leptospirosis.\(^{[8]}\) In one study from Thailand, plasma concentrations of fibrinogen, d-dimer, thrombin–antithrombin III complex, and prothrombin fragment 1 and 2 were found to be significantly elevated, with prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) in patients with leptospirosis.\(^{[9]}\) However, thrombocytopenia was the only hemostasis factor independently associated with clinical bleeding. In another prospective study limited to patients with severe leptospirosis, disorders of coagulation were seen in all patients.\(^{[10]}\) In this study, 22% of patients who had their DIC score calculated showed overt DIC. Most studies so far have used conventional static measurements of coagulation in leptospirosis, and there are no human studies on dynamic measurements of coagulation, such as thromboelastometry (TEM).

TEM provides an effective and convenient way of monitoring whole blood coagulation and provides a global assessment of hemostatic function.\(^{[10]}\) This method continuously evaluates real-time clot formation, clot strength, as well as platelet function, until eventual clot lysis or retraction. Rotational TEM (ROTEM\(^{®}\), Tem Innovations GmbH) is a point-of-care diagnostic test measuring the viscoelastic properties on multiple aspects of blood coagulation.\(^{[11]}\) ROTEM is a widely used tool in the management of patients with massive hemorrhage following trauma, peripartum hemorrhage, in the liver transplant setting, and in DIC. However, studies regarding its use in the management of bleeding due to infective causes, such as dengue and leptospirosis, are extremely scant.

TEM assesses the interaction between clotting factors, their inhibitors, platelets, and fibrinolysis. ROTEM provides the following measurements: clotting time (CT), clot formation time (CFT), alpha angle (α), amplitude 15 and 30 min after CT (A15 and A30), maximum clot firmness (MCF), lysis index 30 min after CT (Li30), and maximum lysis. When interpreting ROTEM results, it is important to be aware of the relationship of different parameters to the hemostatic system. In exTEM, coagulation is activated by a small amount of thromboplastin, and therefore, it assesses coagulation through the extrinsic pathway. In inTEM, coagulation is activated through contact phase, where the intrinsic pathway comes into play. CT is mainly dependent on coagulation factors, whereas CFT and α angle (slope of tangent at 20 mm amplitude) depend on platelets and fibrinogen. Decreased CFT or increased α angle denotes hypercoagulability. MCF is related to platelets and fibrinogen, as well as fibrin polymerization and factor XIII. With regard to fibTEM, activation is similar to exTEM, but platelets are blocked using cytochalasin D. Therefore, the resultant clot is dependent only on fibrin formation and polymerization. The A15 and A30 are able to predict the MCF at 15 and 30 min after the CT, respectively. A single sample from a patient may run in ROTEM for about 60 min until its completion. Therefore, A15 and A30 are useful parameters, which are available to within about 30 min.

We designed this study primarily to look at conventional coagulation parameters and ROTEM parameters in patients with leptospirosis, with the aim of further determining the pathophysiological mechanisms involved in the deranged hemostasis seen in the disease and its potential contribution to tissue and organ dysfunction. Identifying these changes may also be of use in managing patients with coagulopathy, especially with regard to determining whether replacement of clotting factors and platelets are necessary. Further, we intended to compare these findings with the hemostatic derangement occurring in patients with dengue and sepsis. Dengue is one of the most common acute febrile illnesses encountered in Sri Lanka as well as many tropical countries and results in significant morbidity and mortality. It shares many clinical and laboratory features with leptospirosis, including bleeding manifestations and thrombocytopenia. Similarly, bacterial sepsis also results in derangement of hemostasis. Therefore, we also compared the coagulation status of patients with mild and severe leptospirosis with patients having dengue and bacterial sepsis and also healthy individuals.

**SUBJECTS AND METHODS**

**Study design and setting**

We conducted a prospective cross-sectional comparative study recruiting patients with severe and mild leptospirosis, dengue, bacterial sepsis, and healthy individuals. The study was carried out in the National Hospital, Colombo, Sri Lanka, between September and November 2014. The National Hospital, Colombo, is a...
tertiary care hospital situated in the Western province, which was reported to have had 47% of leptospirosis patients of the country, according to a hospital-based sentinel surveillance.[8]

**Study population**

Individuals were recruited from four groups: patients with leptospirosis, dengue, bacterial sepsis, and healthy volunteers. The first three groups were recruited from the National Hospital, Colombo. Clinically suspected leptospirosis patients (based on the WHO criteria) were tested for leptospirosis microscopic agglutination test (MAT). Those who had MAT titers >400 or four-fold rise from acute to convalescent titer were considered as serologically confirmed leptospirosis patients.[8] Patients with leptospirosis were further categorized into severe and mild groups based on the criteria used in previous similar studies.[8] The criteria used to define severe cases were as follows: renal insufficiency (urine output <400 ml/day, creatinine >133 µmol/L, urea >25.5 mmol/L, and dialysis), jaundice (bilirubin >51.3 µmol/L), intensive care unit stay, prolonged hospital stay (>10 days), or death. Patients with a clinical picture compatible with dengue who were positive for dengue nonstructural protein (NS)-1 antigen were enrolled in the dengue group. Sepsis was defined as patients with clinical or laboratory evidence of bacterial infection having at least two of the features of systemic inflammatory response syndrome. Patients with clinical or laboratory evidence of coinfection, those presenting after the 10th day of illness, patients with chronic illness, and those on medicines affecting hemostasis were excluded. Healthy volunteers were from the community; the following were exclusion criteria for healthy volunteers: those with any preexisting or acute medical condition, those on medications of any sort, those reporting a febrile illness within the past 3 months, and those with any abnormalities on standard coagulation profile testing. All healthy volunteers were tested for dengue by performing dengue IgM and IgG antibodies, and leptospirosis by performing MAT, and had a CRP and full blood count to exclude ongoing sepsis.

**Sampling**

Patients’ blood was collected into 3.2% sodium citrate (8 ml) tubes in 9:1 dilution for coagulation studies. Blood samples of all included patients were tested using conventional coagulation studies: PT, aPTT, thrombin time (TT), fibrinogen level, D-dimer level, platelet count, and lupus anticoagulant. Where PT, aPTT, and/or TT were prolonged, 50:50 correction with normal plasma was performed to confirm the presence of a factor deficiency. In those who had a prolonged PT which was corrected with normal plasma, a factor VII assay was performed, whereas in those who had a prolonged aPTT which was corrected with normal plasma, a factor VIII assay was done. TEM was performed using the ROTEM Delta® device (Tem Innovations GmbH) according to instructions provided in the manufacturer’s manual. All conventional coagulation tests and ROTEM were performed at the Haematology Laboratory at the Faculty of Medicine, University of Colombo.

**Data analysis**

IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY, USA) was used for data analysis. One-way ANOVA tests were used to determine differences between the groups.

**RESULTS**

A total of 101 patients with clinical features suggestive of leptospirosis were screened; 20 patients with laboratory-confirmed leptospirosis were included in the final analysis (85% males, mean age 43 years, standard deviation [SD]: 17.4). Only one patient had clinically overt bleeding. Six patients with confirmed dengue, five patients with bacterial sepsis, and six healthy controls were also included.

The findings of the conventional coagulation tests are shown in Table 1. One-way ANOVA with Bonferroni *post hoc* comparison was used to look for statistical significance in the observed differences.

Mean platelet counts were significantly lower in patients with dengue (61,164/mm³, SD: 27,375), compared with the other groups; this finding is in keeping with previously published literature.[12] While platelet counts were similar in patients with mild leptospirosis and sepsis, patients with severe leptospirosis had significantly lower platelet counts when compared with patients with sepsis (*P = 0.002*). Previous studies have shown much lower platelet counts in leptospirosis patients[8] and in sepsis.[13]

In both bacterial sepsis and leptospirosis, elevated D-dimer levels and prolongation of the aPTT were seen. D-dimer levels were significantly higher in patients with severe leptospirosis compared to those with mild disease (*P < 0.01*). Patients with severe leptospirosis and those with bacterial sepsis had PT prolongation and raised fibrinogen levels, compared to the other groups. Patients with mild leptospirosis had fibrinogen levels which were similar to dengue and healthy controls. There was no statistically significant difference in TT between any of the study groups.

Factor assays were performed in five patients with severe leptospirosis after correction studies. There were two patients with prolonged PT of 16 s and 18 s, respectively. Both of these were corrected by 50:50 correction studies; factor assays done revealed factor VII deficiency in these two patients. The percentage of clotting factor...
VII activity in these two patients was 30% and 15%, respectively. aPTT was prolonged in four patients, out of whom one also had prolonged PT. Their aPTT values were 40 s, 46 s, 48 s, and 80 s and all were corrected with mixing studies. Factor assays showed reduced factor VIII level, respectively, as 65%, 70%, 40%, and 30%. Lupus anticoagulant was not detected in any of the patients with leptospirosis.

For all patients and controls, ROTEM was performed, for inTEM, exTEM, and fibTEM. The results of inTEM and exTEM studies are given in Table 2. Of the inTEM parameters, CFT was significantly elevated in the dengue group compared to all the other groups (P < 0.05), but there was no significant difference between other groups. MCF was also significantly lower in the dengue group compared to all the other groups (P < 0.05). Both mild and severe leptospirosis patients had reduced MCF compared to sepsis patients (P < 0.05). Other inTEM parameters such as CT, α angle, and Li30 did not show statistically significant differences between any of the groups studied.

When exTEM parameters were considered, CFT was significantly elevated in dengue patients compared to the other groups (P < 0.005). Similarly, α angle, A15, and MCF were significantly different in dengue patients compared to the other groups (P < 0.005). CT, A30, and Li30 did not show any statistically significant differences between the groups.

The mean values and SDs of fibTEM parameters among different categories of patients and healthy controls are shown in Table 3. FibTEM α angle was significantly higher among sepsis and severe leptospirosis patients, compared to healthy individuals and dengue patients (P < 0.01). A15 was significantly higher among patients with sepsis and severe leptospirosis compared to healthy individuals.

**DISCUSSION**

Our findings suggest that the prolonged PT and aPTT seen in certain patients with leptospirosis could be attributed to clotting factor deficiency. It was noted that TT in patients with leptospirosis did not differ significantly from other groups, and this finding is in keeping with findings of previous studies.[9] Fibrinogen

### Table 1: Conventional coagulation parameters in leptospirosis patients (mild and severe), sepsis, dengue, and healthy controls (means and standard deviation)

| Test | Unit | Healthy | Mild Leptospirosis | Severe Leptospirosis | Sepsis | Dengue |
|------|------|---------|--------------------|----------------------|--------|--------|
| PT   | s    | 12.2 ± 0.4 | 14.3 ± 0.98       | 15.0 ± 1.63         | 16.7 ± 1.4 | 13.8 ± 0.8 |
| aPTT | s    | 34.7 ± 1.6 | 51.2 ± 1.54       | 43.85 ± 3.98        | 50.9 ± 7.6 | 46.2 ± 6.4 |
| TT   | s    | 23.8 ± 4.9 | 29.83 ± 8.13      | 26.84 ± 5.86        | 24.2 ± 3.3 | 35.0 ± 15.3 |
| Fibrogen | g/L | 2.4 ± 0.3 | 3.15 ± 0.51       | 3.47 ± 0.50         | 3.9 ± 0.7  | 2.4 ± 0.3  |
| Platelets | µL | 249,668 ± 56148 | 194500 ± 99480 | 146071 ± 110242 | 386,000 ± 189,672 | 61,167 ± 27,375 |

s—seconds; g/L—grams per liter

### Table 2: Mean values and standard deviations of inTEM and exTEM Parameters among patient groups and healthy controls

| Test | Unit | Healthy | Mild Leptospirosis | Severe Leptospirosis | Sepsis | Dengue |
|------|------|---------|--------------------|----------------------|--------|--------|
| inTEM CT | S | 165.3 ± 18.2 | 179.50 ± 31.3 | 163.8 ± 26.6 | 199.6 ± 22.2 | 174.7 ± 18.6 |
| inTEM CFT | S | 81.2 ± 9.7 | 105.7 ± 66.2 | 83.1 ± 71.2 | 49.3 ± 9.3 | 276.3 ± 138.1 |
| inTEM α | o | 73.8 ± 2.0 | 75.0 ± 5.5 | 78.3 ± 4.6 | 80 ± 1.9 | 161.3 ± 247.8 |
| inTEM A15 | mm | 55.3 ± 19 | 53.2 ± 10.9 | 58.4 ± 14.2 | 71.4 ± 5.3 | 35.5 ± 7.1 |
| inTEM A30 | mm | 57.5 ± 28 | 56.3 ± 10.2 | 68.5 ± 17.8 | 73.4 ± 4.8 | 115.2 ± 188.1 |
| inTEM MCF | mm | 57.2 ± 7.0 | 55.7 ± 9.7 | 62.5 ± 11.8 | 73.2 ± 4.5 | 40.7 ± 6.7 |
| inTEM Li30 | % | 99.3 ± 1.2 | 100 ± 0.0 | 99.8 ± 0.6 | 99.8 ± 0.5 | 100 ± 0 |
| exTEM CT | S | 67.2 ± 10.4 | 88.8 ± 32.5 | 81.1 ± 18.5 | 73.2 ± 22.1 | 77.5 ± 23.0 |
| exTEM CFT | S | 99.7 ± 16.6 | 111.5 ± 72. | 74.5 ± 38.3 | 50.6 ± 11.2 | 381.0 ± 234.1 |
| exTEM α | o | 70.2 ± 3.1 | 75.0 ± 4.7 | 77.9 ± 3.7 | 80.0 ± 2.6 | 50.5 ± 13.6 |
| exTEM A15 | mm | 54.0 ± 3.0 | 53.2 ± 11.3 | 58.7 ± 14.1 | 72.0 ± 5.5 | 32.5 ± 8.0 |
| exTEM A30 | mm | 56.8 ± 2.4 | 56.3 ± 9.9 | 98.6 ± 133.2 | 73.2 ± 5.4 | 37.8 ± 7.5 |
| exTEM MCF | mm | 57.2 ± 2.5 | 56.5 ± 9.1 | 61.5 ± 12.3 | 73.4 ± 5.5 | 38.8 ± 6.3 |
| exTEM Li30 | % | 99.8 ± 0.4 | 100 ± 0.0 | 99.6 ± 0.8 | 99.0 ± 1.2 | 100.0 ± 0.0 |

### Table 3: Mean values and standard deviations of fibTEM Parameters among patient groups and healthy controls

| Test | Unit | Healthy | Mild Leptospirosis | Severe Leptospirosis | Sepsis | Dengue |
|------|------|---------|--------------------|----------------------|--------|--------|
| fibCT | S | 57.8 ± 7.9 | 72.7 ± 4.8 | 75.6 ± 17.2 | 91.0 ± 7.1 | 66.3 ± 5.0 |
| CFT  | S | NA | 302.5 ± 316.1 | 216 ± 343.7 | 54.0 ± 8.5 | NA |
| α    | o | 66.6 ± 5.4 | 72.5 ± 5.1 | 77.66 ± 2.6 | 79.5 ± 2.1 | 61.0 ± 4.7 |
| A15  | mm | 11.6 ± 0.5 | 18.5 ± 9.3 | 28.9 ± 7.6 | 42.0 ± 9.9 | 13.0 ± 1.4 |
| A30  | mm | 12.0 ± 0.7 | 22.0 ± 6.5 | 29.6 ± 7.9 | 43.5 ± 9.2 | 14.0 ± 1.4 |
| MCF  | mm | 11.8 ± 0.4 | 22.3 ± 6.5 | 29.9 ± 7.9 | 43.5 ± 9.2 | 13.8 ± 1.3 |
| Li30 | % | 99.8 ± 0.9 | 80.5 ± 39.0 | 99.9 ± 0.3 | 100.0 ± 0.0 | 100.0 ± 0.0 |
levels are elevated in severe leptospirosis and sepsis. Similar findings were obtained in other studies as well,[13] and this finding has been attributed to severe tissue injury, vascular involvement, and increased production of fibrinogen by the liver. However, previous studies also demonstrated that *Leptospira* can increase the consumption of fibrinogen either by sequestration or degradation. A previous study has concluded that fibrin clot formation is likely to be reduced in leptospirosis.[14]

In our study population of leptospirosis patients, although there were some factor deficiencies causing prolonged PT and aPTT, there were no major alterations in ROTEM parameters. There was prolonged CFT with reduced MCF in inTEM in dengue patients. In exTEM also, CFT was increased and α angle was prolonged in dengue patients. These abnormalities were corrected in fibTEM, suggesting that the changes are likely to be related to platelet-related factors. In inTEM, MCF was reduced in leptospirosis compared to sepsis patients. In fibTEM studies, it was shown that α angle was higher in sepsis and severe leptospirosis patients, suggesting a hypercoagulable state. The fact that most of the parameters in leptospirosis patients were normal in exTEM and inTEM might be explained by the possibility that hypercoagulability due to hyperfibrinogenemia is compensated by hypocoagulability due to thrombocytopenia and clotting factor deficiency. There were no significant abnormalities in ROTEM parameters related to fibrinolysis in any of the patient groups.

Our study has several limitations. The sample size was small. Bleeding manifestations were rare, which maybe a reason for the relatively normal coagulation studies. This is, however, the first study to assess ROTEM in leptospirosis and compare the findings in leptospirosis with other groups. Further in-depth studies are planned. Future studies will concentrate on larger groups of patients with leptospirosis, with greater correlation with other clinical characteristics.

**Research quality and ethics statement**

The authors of this manuscript declare that this scientific work complies with reporting quality and formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require the Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is University of Colombo, Faculty of Medicine Ethics Review Committee EC-12-056.

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**Conflicts of interest**

There are no conflicts of interest.

**Ethical conduct of research**

This study was approved by the Institutional Review Board / Ethics Committee. The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines during the conduct of this research project.

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