Plasma exchange with immunosuppression in pulmonary alveolar haemorrhage due to leptospirosis


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Background & objectives: Pulmonary involvement due to leptospirosis carries high case fatality rate and is the commonest cause of death due to leptospirosis. Immune mechanisms play a key role in the pathogenesis of leptospiral pulmonary haemorrhage. As other immune pulmonary haemorrhages due to non leptospiral causes are treated with plasma exchange and cyclophosphamide we evaluated their efficacy in patient with leptospiral pulmonary haemorrhage.

Methods: Of the 602 confirmed patients of leptospirosis, 236 (39.2%) had pulmonary haemorrhage. Of these, 144 had mild haemorrhage (acute lung injury score < 2.5) and were included in the study. One hundred and fourteen patients were given two cycles of plasma exchange, 24 h apart, 25 ml/kg body weight of plasma was removed in each cycle. Cyclophosphamide (20 mg/kg body weight) was given after the first plasma exchange cycle. The remaining 30 patients were not given this treatment, and used as control.

Results: In the control group only 5 (16.6%) patients survived while in the treatment group 70 (61.40%) patients survived. Thrombocytopenia was observed in 111 (77.08%) patients. Renal and hepatic involvement was seen but did not account for mortality. Minor complications were seen in group I patients after plasma exchange and cyclophosphamide treatment, but none were serious.

Interpretation & conclusions: Our findings showed that plasma exchange with immunosuppression improved survival in patients of pulmonary alveolar haemorrhage due to leptospirosis, suggesting that immune mechanisms play a key role in the pathogenesis of the disease.

Key words Cyclophosphamide - leptospirosis - plasma exchange - pulmonary alveolar haemorrhage

Severe leptospirosis is a multiorgan dysfunction, with liver, kidneys, lungs, heart, being the principal organs involved. Pulmonary involvement occurs in the form of alveolar haemorrhage. Pulmonary alveolar haemorrhage has very high mortality all over the world. In India it accounts for majority of fatality due to leptospirosis. Immune mechanisms account for majority of pulmonary alveolar haemorrhages due to non leptospiral mechanisms. Pulmonary alveolar haemorrhage due to other immune mechanisms is treated with glucocorticosteroids, cyclophosphamide and plasma exchange alone or in combination. Several reports from India, demonstrated the efficacy of glucocorticosteroids in leptospiral pulmonary
haemorrhage\textsuperscript{6-9}. But the disease is changing pattern all over the world with pulmonary involvement becoming more frequent and more severe\textsuperscript{1}. Exaggerated immune response of the host has been postulated to be the main mechanism of changing disease pattern\textsuperscript{10,11}. The response to glucocorticosteroids is decreasing. Hence it is imperative to search for other methods of treatment. There are reports of the successful use of exchange transfusion and haemofiltration in leptospirosis\textsuperscript{12-14}, and of plasma exchange in leptospirosis\textsuperscript{15-17}. Meaudre \textit{et al}\textsuperscript{18} have postulated that immunomodulation in the form of plasma exchange, intravenous immunoglobulin or glucocorticosteroids may be useful in multiorgan dysfunction due to leptospirosis. They found intravenous immunoglobulins to be effective in leptospirosis. Plasma exchange is indicated in almost all conditions where intravenous immunoglobulin is effective.

Hence we decided to evaluate all the modalities of treatment used in immune alveolar haemorrhage due to non leptosomal causes in patients of alveolar haemorrhage due to leptospirosis.

\textbf{Material \& Methods}

\textit{Patient selection:} The study was carried out at a tertiary care center, New Civil Hospital \& Govt. Medical College, Surat, Gujarat during July to October in 2006 and 2007 (monsoon period). Patients of leptospirosis from a large area (three districts namely Surat, Navasari and Valsad) were referred to the hospital. Clinically suspected cases were subjected to diagnostic tests for leptospirosis. These tests included rapid diagnostic spot test and enzyme-linked immunosorbent assay (ELISA). Serion/Virion kit (Hersteller-Germany) was used for ELISA testing. World Health Organization (WHO)-International Leptospirosis Society (ILS) Guidelines 2003 were followed for the diagnosis\textsuperscript{19}. Apart from thorough clinical examination, all the confirmed cases were subjected to complete blood counts, blood urea, serum creatinine, serum bilirubin, alanine aminotransferase (ALT), serum electrolytes, arterial blood gas analysis, tests for malaria, dengue, hepatitis B and hepatitis C. Malaria was ruled out by peripheral smear and rapid diagnostic test. Immunoglobulin M (IgM) testing was done to rule out dengue. Pneumonia was ruled out by clinical features, radiological appearance and sputum examination wherever necessary. Electrocardiogram (ECG), X-ray chest and abdominal ultrasound were also carried out. Bone marrow examination was carried out on 10 patients of thrombocytopenia. Pulmonary involvement was defined as presence of respiratory symptoms (cough, breathlessness and haemoptysis) and/or presence of infiltrates on X ray chest. Similar criteria have been used by Shenoy \textit{et al}\textsuperscript{7}. Other causes of opacities in lung like pneumonia, pulmonary tuberculosis were ruled out by clinical correlation and appropriate laboratory investigations. Severity of pulmonary involvement was defined using criteria laid down by Murray \textit{et al}\textsuperscript{20}. Patients having acute lung injury (ALI) score less than 2.5 were considered to have mild disease and were included in the study.

From a total of 602 confirmed patients of leptospirosis, 236 (39.2\%) had pulmonary haemorrhage. One hundred and forty four of them had mild haemorrhage and were included in the study. Of these, the first 30 patients were given treatment with crystalline penicillin, methyl prednisolone and non invasive ventilation (group I). The next 114 were given additional treatment in the form of plasma exchange and cyclophosphamide (group I). Group II patients received injection crystalline penicillin $2 \times 10^6$ units (Pharma Impex Lab Pvt. Ltd., Kolkata) intravenously (iv) every 6 h for seven days, injection methyl prednisolone (Pfizer, USA) 1g iv daily for three days followed by tablet prednisolone 1mg/kg body weight for seven days, and non invasive ventilation with positive end expiratory pressure (PEEP) (Savina Mechanical Ventilator, Drager Medical, Germany), and blood component therapy as indicated. Only five patients in group II survived. In the remaining 114 (group I) patients, two cycles of plasma exchange, 24 h apart were given. The first cycle was given immediately on diagnosis. Twenty five ml/kg body weight of plasma was removed in each cycle. Plasma FLUX PSu 2S plasma exchange filters manufactured by the Fresenius company, Germany were used. Cyclophosphamide (20 mg/kg iv) (United Biotech (P) Ltd, Solan, HP) was given after the first exchange. Mesna (Biochem Pharmaceutical Industries, Daman) was given along with it to prevent haemorrhagic cystitis. A total of 89 units of platelets were transfused to 24 patients in group I while 30 units of platelet transfusion were given to 7 patients in group II. The study protocol was approved by the Human Research Ethics Committee of the medical college and informed consent was taken from each patient.

Daily blood counts were carried out. X ray chest was carried out at frequent intervals. Tests of hepatic and renal function were also repeated during the stay. All patients who survived, were admitted for 21 days or till total blood counts returned to normal, whichever was longer.
Statistical analysis: Test of association using chi square test was applied to assess the statistical significance between the two groups.

Results

Of the 114 patients in group I (92 males 22 females) 81 were in the age range 15-45 yr and 33 were above 45 yr age. Of the 30 patients in group I (23 males 7 females) 21 were 15-45 yr of age and 9 were >45 yr. All patients were farm workers working either in paddy or sugarcane fields which remain water logged. All patients had fever (Table I), and lungs were involved in all patient in both the groups (Table II). Renal and hepatic involvements were frequent but did not account for any mortality. In fact, none of the patients developed hepatic encephalopathy. None of the patients required dialysis. Thrombocytopenia was observed in 111(77.08 %) patients. Lowest platelet counts observed were 14,000/mm$^3$. Bone marrow examination was carried out in ten patients with thrombocytopenia. All of them showed marked increase in number of megakaryocytes. Mean platelet count (MPC) on admission was 44,500 ± 8,200/cmm while MPC on day 14 was 1,42,000 ± 8,500/cmm.

Of the 114 patients in group I, one developed allergic reaction after plasma exchange and hypotension was seen in four. Leucopenia was observed in 14 patients. The lowest total count noted was 1400/mm$^3$. The median time required for the lowest total count to occur was 11 days. Median duration after which the counts returned to normal was 16 days. None of the patients developed secondary infection nor was there any death attributable to leucopenia. Platelet counts improved in patients who survived. Haemorrhagic cystitis, a known complication of cyclophosphamide therapy, was not observed in any patient. Median duration for which mechanical ventilation was required in patients who survived was 118 h in group I patients and 122 h in group II patients. Mean duration was 118.6 ± 23.2 h in group I patients and 124.3±10.2 h in group II patients. Mean duration of intensive care unit (ICU) stay was 168 ± 18.4 h in group I patients while it was 180.5 ± 20.5 h in group II. Average time taken for clearance of opacities was six days. Co-infections were noted in two patients. One patient was tested positive for hepatitis B and the other had Plasmodium vivax malaria.

In the control group (group II) 5 of the 30 patients (16.6%) survived while in the treatment group (group I) 70 of the 114 patients (61.4%) survived. Eighty (55.5%) patients had one quadrant involvement on X-ray chest and had a mortality of 37.5% while the remaining patients had two quadrants involved and had mortality of 61 per cent. As only mild cases (ALI score <2.5) were included in the study, there were no patients with three and four quadrant involvement. The mortality in group I was proportional to severity of thrombocytopenia (Fig.).

Association between performance of plasma exchange with administration of cyclophosphamide and survival was found to be significant ($P<0.01$).

Discussion

Leptospirosis occurs mainly among farm labourers of paddy and sugarcane fields. As these fields are water logged, the bare footed farm workers working in these
fields are easily infected. The male preponderance can be explained by the preponderance of males among farm labourers.

Haemoptysis was present in only 25.44 per cent of group I patients in our study. A study published from Thailand showed haemoptysis in 17-29 per cent patients with leptospirosis. Shenoy et al observed haemoptysis in 50 per cent of patients, while in a Spanish series of 26 patients with leptospirosis, 17 had pulmonary symptoms but only seven had haemoptysis.

Immune mediated pulmonary haemorrhage is treated with glucocorticosteroids, cyclophosphamide and plasma exchange either alone or in combination. Glucocorticosteroids have been found to be useful in leptospirosis pulmonary hemorrhages in many studies.

Plasma exchange has been found to be useful in leptospirosis. It removes offending antibodies or immune complexes from plasma, but at the same time it also removes certain useful substances like coagulation factors and platelets from body leading to dilutional coagulopathy and thrombocytopenia. This is hazardous for patients of alveolar haemorrhage due to leptospirosis. Thus we removed only 25 ml/kg of plasma and selected only mild patients for the study because of two reasons; (i) it takes some time before improvement occurs in pulmonary haemorrhage. Severe patients having LIS>2.5 succumb in very short time and plasma exchange may not have enough time to act, and (ii) removal of coagulation factors and platelets can lead to transient worsening of pulmonary function in a subset of patients. Severe cases may not be able to withstand the transient worsening of hypoxaemia.

We selected a dose of cyclophosphamide which gives high peaks earliest because most of the patients who died, succumbed within first forty eight hours. It is obvious that low-dose long-term regimen is meaningless in such situations. Main concern with cyclophosphamide is bone marrow suppression. We did observe leucopenia in 12.28 per cent patients which was reversible. The increase in megakaryocytes observed on bone marrow examination in patients with thrombocytopenia indicates the mechanism of thrombocytopenia to be increased peripheral destruction. This could most likely to be immune destruction secondary to vasculitis. Platelet counts improved in all patients who survived. Quadrant involvement on X-ray chest on presentation was also found to be an important prognostic marker, which corroborates with the earlier findings. Sharma & Suryavanshi also found high (86.6%) incidence of thrombocytopenia in pulmonary haemorrhage due to leptospirosis. Thrombocytopenia was found to be an important marker of poor prognosis in the present study. This corroborated with results of some previous studies.

Our findings demonstrated the efficacy of plasma exchange with cyclophosphamide in pulmonary alveolar haemorrhage due to leptospirosis. The study was carried out on only mild cases but as the control group also had mild cases, the better survival in the treatment group indicates that plasma exchange with immunosuppression was useful. APACHE III score was not used in the present study, which is a better tool to assess severity of the cases.

In conclusion, plasma exchange with cyclophosphamide may be useful to treat mild cases of pulmonary alveolar haemorrhage due to leptospirosis.

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References


