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Effect of Methylprednisolone and Cyclophosphamide on the Survival of Patients with Leptospirosis, Renal Failure and Pulmonary Hemorrhage

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Abstract

Objectives: To determine the efficacy of three day methylprednisolone plus single dose intravenous cyclophosphamide on the survival of patients with leptospirosis, renal failure and pulmonary hemorrhage.

Methods: A retrospective review of 138 patients diagnosed with leptospirosis at the National Kidney and Transplant Institute (NKTI) from August 1, 2009 to August 31, 2013 were included in the study. Patients were grouped according to those who received standard therapy with a 3-day course of Hydrocortisone (HC group) compared to a 3-day course of Methylprednisolone-Cyclophosphamide (MP-C). Patient survival, length of hospital stay and time to becoming dialysis independent were compared.

Results: There were 65 patients in the HC group and 73 patients in the MP-C group. Mean age was 35.9 years, with male predominance. The most common clinical manifestation was fever. Thrombocytopenia was the major indication to steroid therapy. Survival of patients given MP-C was significantly higher than those given HC (88% and 74% respectively; p=0.035). The post treatment activated Plasma Thromboplastin Time (aPTT) was significantly lower in the MP-C group. There was no significant difference in the length of hospital stay and time to becoming dialysis independent.

Conclusion: Three day MP-C pulsing significantly improves survival of patients with leptospirosis, renal failure and pulmonary hemorrhage.

Keywords: Leptospirosis; Weil's disease; Renal failure; Pulmonary hemorrhage; Methylprednisolone-cyyclophosphamide pulsing; Steroids

Introduction

Leptospirosis is frequently encountered in the tropical region. It is caused by the pathogenic species of leptospira, commonly *L. Interrogans*, with *L. icterohemorrhagica* causing the severe form [1]. Leptospira-infected animals are commonly rats. They shed urine into water and soil and infect humans via skin or gastrointestinal routes. The risk of infection is increased through exposure from work, household surroundings and flooding. Clinical manifestations range from sub-clinical infection, self limited febrile illness to severe and fatal disease with hemodynamic collapse and multi-organ involvement, including renal and pulmonary failure [2].

Renal involvement is common in leptospirosis. Incidence of renal failure varies from 10% to over 60% [3]. The development of nephropathy is a consequence of bacterial colonization, inflammatory process, hemodynamic changes and direct toxicity of bacterial products [3]. An inflammatory process is responsible for the pathogenesis of glomerulonephritis and interstitial nephritis, involving both T helpers 1 and 2, resulting in an immune mediated nephropathy [3].

An alkaline pH caused by ammonia generation in the proximal tubules favors bacterial growth, making it the major location of leptospiral colonization [3]. Primarily, tubular degeneration involves the proximal tubules, but distal tubular necrosis occurs later [3].

Interstitial nephritis is the fundamental pathology [3]. Glomerular changes are usually unremarkable, though mesangial proliferative glomerulonephritis has been seen [4].

Pulmonary involvement occurs in 20-70% of cases and the clinical severity ranges from mild dyspnea to pulmonary hemorrhage [5].

Treatment for severe leptospirosis includes fluid resuscitation, antibiotic therapy with penicillin or ceftriaxone and supportive renal replacement therapy (RRT). Despite standard and supportive treatment, mortality still ranges from 5-20% [6,7]. Because of the more aggressive manifestations of the disease, trends in management are currently focusing on its immune aspect as a target for therapy.

In the Philippines, after the heavy rainfall of typhoon Ondoy in 2009, there was an increase in the number of patients admitted for leptospirosis with renal failure at the National Kidney and Transplant Institute (NKTI), a tertiary referral center for patients requiring renal replacement therapy (RRT). Despite standard therapy with antibiotics and dialysis, the mortality was 26% from the initial 64 patients admitted, mainly due to pulmonary hemorrhage. Due to this high mortality, the treatment protocol was revised to include a 3-day course of hydrocortisone in those with severe leptospirosis (Appendix A). An unpublished retrospective review at the NKTI looked at the effect of this short course steroid therapy on 57 patients compared to 78 patients given standard therapy alone. The mortality rate was similar among the two groups (p=0.78), although the survival time of patients who received steroids was longer (21.9 days vs 12. 7 days). The mean time to

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death (6.6 days) among patients who received steroids was significantly longer compared to patients on standard therapy alone (4 days) (p=0.001). In view of these findings, the short course steroid therapy was incorporated into the revised hospital protocol for the treatment of severe leptospirosis (Appendix A).

In 2012, the Monsoon rains that brought widespread flooding in Metro Manila again led to a significant increase in Leptospirosis. A total of 1,713 leptospirosis cases were reported by the department of health with 116 deaths (6.72%; range 4.5-13%) [8].

At the NKTI, 28% mortality rate was recorded among the initial 51 patients, again mainly due to pulmonary hemorrhage. Due to the very high mortality, and with the increasing trend in the use of immunosuppression in the literature, the protocol was amended to include a 3-day course of Methylprednisolone 500 mg IV followed by a single dose of Cyclophosphamide 1g/IV in cases of severe leptospirosis (NKTI 2012 leptospirosis guideline Appendix-B)

Objectives

This study aims to determine the effect of the 3-day Methylprednisolone-Cyclophosphamide in the survival of patients with severe leptospirosis, renal failure and pulmonary hemorrhage compared to those given a 3-day course of hydrocortisone. It also aims to compare the length of hospital stay, time to becoming dialysis independent and the number of fresh frozen plasma and platelet transfusions among these two groups.

Methodology

Population

Charts of patients diagnosed with leptospirosis (Based on NKTI guidelines presumptive diagnosis of leptospirosis Appendix A and B) admitted at the NKTI from September 1, 2009 to August 31, 2013 were reviewed. Sixty five patients with severe leptospirosis from Septmeber 1, 2009 to August 24, 2012 were included in the Hydrocorisone (HC) group. Seventy three patients, admitted from August 25, 2012 to August 31, 2013 composed the Methylprednisolone-Cyclosphophamide (MP-C) group.

Patient demographics such as age, sex, co-morbidities, clinical presentation and baseline blood pressure were collected. Laboratoty parameters such as serum creatinine, platelet counts, PT, aPTT, chest X-ray findings and mode of renal replacement therapy of the two groups were compared.

Inclusion criteria

Patients with a presumptive diagnosis of leptospirosis who required dialysis based on clinical signs and symptoms of anuria/oliguria not responsive to hydration with creatinine of more than 3 mg/dL plus any one of the following were considered to be having severe leptospirosis:

1. Platelet count of less than $100,000 \times 10^3$/UL

2. Systolic Blood Pressure (SBP) less than 90 mmHg after an isotonic fluid resuscitation of 2L

3. Required inotropic support to maintain SBP >90 mmHg

4. Lung infiltrates on chest X-ray without clinical history consistent with pneumonia

5. Hemoptysis or any form of bleeding

6. Prolonged Prothrombin Time (PT-4 secs from control), and activated Plasma Thromboplastin Time (aPTT-1.5x Control)

Exclusion criteria

1. Patients who expired within 24 hours from time of admission

2. Patients who were known case of Chronic Kidney Disease

3. Patients with previous history of Acute Kidney Injury requiring RRT

4. Patients were discharged against medical advice without completing the protocol steroid therapy

Definition of Terms

Standard therapy

Penicillin G 1.5 million units Intravenous (IV) every six hours or Ceftriaxone 1 g/IV once a day, fluid hydration and/or RRT.

Hydrocortisone regimen

Hydrocortisone 200 mg IV loading dose, then 100 mg/IV every six hours for 3 days.

Methyprednisolone-cyclophosphamide regimen

Methylprednisolone 500 mg/IV Once a day for 3 days followed by a single dose of cyclophosphamide 1g/IV on the 3rd day, (cyclophosphamide can be given earlier once patient develops pulmonary hemorrhage.

Analysis of Outcomes

Primary endpoint was the overall survival of patients given MP-C compared to HC. Secondary outcomes included length of hospital stay, recovery of renal function based on the time to becoming dialysis independent, improvement of thrombocytopenia, PT and aPTT.

Statistical analysis

Sample size was computed to detect a difference in mortality of 10% between the expected group (MP-C) and the actual group (HC) using the power analysis and sample size software.

The mean and standard deviation of continuous data were computed. Frequency and percentage were used for categorical data. Z-test for two percentages was used to compare the survival of patients in the two groups. T-test was used to compare the length of hospital stay, the time to becoming dialysis independent, and the laboratory parameters among the two groups. All p-values less than 0.05 were considered significant.

Results

A total of 138 patients were included in the study, 65 patients for the HC group and 73 patients for the MP-C group. The mean age was 34.9 years, with male predominance. Most patients had no co-morbidities.

There was no significant difference in the age, sex, co-morbidities, baseline blood pressure and serum creatinine, platelet counts, PT, aPTT among the 2 groups (Table 1). All patients presented with fever. Other common signs and symptoms were calf tenderness conjunctival suffusion, and oliguria.

Majority of patients underwent hemodialysis in both groups (71% and 84% respectively (Table 2). Chest X-ray in 22 percent of patients was normal. Among the common findings were congestion and non specific infiltrates. The most common indication to steroid therapy was

Parameters	HC group (Mean ± SD) N= 65	MP-C group (Mean ± SD) N=73	P value
Age (years)	35.3 ± 12.5	34.5 ± 11.1	0.83
Male	58 (89%)	69 (94%)	0.43
Female	7 (11%)	4 (7%)	
Co-morbidities			
Diabetes	2 (3%)	3 (4%)	0.7
Hypertension	3 (4%)	4 (6%)	0.65
Blood Pressure (mmHg)			
Systolic	96.6 ± 23.4	90.27 ± 18.56	0.07
Diastolic	59.53 ± 14.51	57.53 ± 12.99	0.4
Initial Serum Creatinine (g/dL)	8.24 ± 5.6	8.11 ± 2.85	0.85
Initial Platelet (x10^3/uL)	98.94 ± 63	112.78 ± 112.39	0.3
Initial Prothrombin Time (secs above control)	2.07 ± 1.95	1.78 ± 2.12	0.44
Initial activated Partial Thromboplastin Time (times control)	1.38 ± 0.25	1.39 ± 0.34	0.46

Table 1: Baseline Demographics, Clinical and Laboratory Profile.

Mode of RRT	HC group N (Percentage) N=65	MP-C N (Percentage) N=73	P value
Hemodialysis	46 (71%)	61 (84%)	0.0657
Peritoneal Dialysis	19 (29%)	12 (16%)	

Table 2: Mode of Renal Replacement Therapy (RRT).

	Population	HC	MP-C	z value	P value
N	**138**	**65**	**73**	2.11	0.035*
Death	26 (19%)	17 (26%)	9 (12%)		
Survived	111 (81)	48 (74%)	64 (88%)		
*Statistically significant difference					

Table 3: Survival of patients among the two groups.

thrombocytopenia (88%) and hypotension (61%).

Clinical Outcomes

Among the 65 patients given HC, 48 (74%) survived, while 64 patients (88%) survived in the methylprednisolone-cyclophosphamide regimen. Overall survival rate was 81%. There was statistically significant difference in patients' survival among MP-C group compared to those in the HC group (88% vs. 74% respectively; p=0.035) (Table 3).

In both groups, the most common cause of mortality was pulmonary hemorrhage (15 of the 17 deaths in the HC and 8 0f the 9 deaths in the MP-C group). The mean platelet count of those who died was below 100,000×10^3/UL in both groups (78.29×10^3/UL and 67.55×10^3/UL for the HC and MP-C group respectively), and was lower than those who survived (109.39×10^3/UL and 126.15×10^3/UL for the HC and MP-C group respectively). Likewise the baseline Systolic and Diastolic Blood Pressure were lower among those who died compared to the survivors (Tables 4 and 5).

Three patients were complicated by Hospital Acquired Pneumonia (HAP) in the methylprednisolone group, while there were four cases of HAP in the hydrocortisone group.

There was no significant difference in the length of time of recovery (hospital days), mean time to death, time to becoming dialysis independent, post treatment values of platelet count and PT and the number of FFP and platelet concentrate among the two groups. However, the aPTT post treatment was significantly lower in those treated with MP-C than those treated with HC (P=0.018) (Table 6).

Discussion

The survival of patients given the MP-C regimen was significantly higher (88%) compared to that of the HC group (74%) in our study. This finding is comparable with a recent study in India that showed an overall mortality of 18% (3 of 17) in patients who received methylprednisolone, compared to 62% (8 of 13 patients) in those who received standard therapy alone (p=0.02). In patients with established acute lung injury, five of eight patients survived in the subgroup with corticosteroids (37% mortality) while only one of nine patients survived in the standard therapy alone (89% mortality) [1].

Cyclophosphamide was likewise investigated as a treatment for leptospirosis with pulmonary hemorrhage. A study by Trivedi et al. [6] showed that among 33 patients treated with cyclophosphamide, 22 (66.7%) survived, while in 32 patients given standard therapy plus methylprednisolone alone, only three (9.4%) survived. Trivedi et al. concluded that cyclophosphamide improved survival in cases of severe alveolar hemorrhage due to leptospirosis [6]. The improvement in survival of patients using an immunosuppressive regimen, as shown in our study, further strengthens the possibility that an immune mechanism plays a key role in the pathogenesis of the disease.

Our results showed that the most common cause of mortality in both groups was pulmonary hemorrhage (88%). This is consistent with previous studies showing a poor prognosis for patients with pulmonary

Parameters	HC N (percent) N=17	MP-C N (percent) N=9
Mean time to death (Days)	2.58 ± 2.26	3.22 ± 3.31
Death due to Pulmonary Hemorrhage	15 (88%)	8 (88%)
Platelet		
Mean + SD (×10^3/uL)	78.29 ± 46.83	67.55 ± 53.65
>100×10^3/uL	5 (29%)	2 (22%)
100-50×10^3/uL	6 (35%)	3 (33%)
<50×10^3/uL	6 (35%)	4 (44%)
SBP		
Mean+SD	85.88 ± 20.32	74.54 ± 15.89
>90 mmHg	7 (42%)	3 (33%)
<90 mmHg	10 (58%)	6 (77%)
DBP		
Mean+SD	52.35 ± 9.7	47.77 ± 10
>60 mmHg	7 (42%)	3 (33%)
<60 mmHg	10 (38%)	6 (77%)
Mode of RRT		
Hemodialysis	16 (94%)	9 (100%)
Peritoneal Dialysis	1 (6%)	0
Blood Transfused	6 (35%)	2 (22%)
total	1 (6%)	1 (11%)
FFP+Platelet	3 (18%)	1 (11%)
FFP+platelet	2 (12%)	0
CXR		
Infiltrates, non-specific	10 (35%)	6 (67%)
Congestion	4 (24%)	0
No active infiltrates	3 (18)	3 (33%)
PT seconds above control (Mean+SD)	2.91 ± 1.91	1.51 ± 1.33
PTT times control	1.46 ± 0.18	1.44 ± 0.18

Table 4: Clinical and Laboratory parameters of mortality.

Parameters	HC N (percent) N=48	MP-C N (percent) N=64
Hospital days	6.86 ± 3.77	6.44 ± 3.05
Hospital day RRT free	4.2 ± 1.68	3.95 ± 1.9
Platelet		
Mean ± SD (x 103/uL)	109.39 ± 96.31	126.15 ± 83.78
SBP		
Mean ± SD	96.45 ± 23.45	95.26 ± 18.46
DBP		
Mean ± SD	59.03 ± 15.35	60.78 ± 12.6
Mode of RRT		
Hemodialysis	30 (62.5%)	52 (81%)
Peritoneal Dialysis	18 (37.5%)	12 (19%)
Blood Transfused total		
FFP	6 (35%)	2 (22%)
Platelet	1 (6%)	1 (11%)
FFP+platelet	3 (18%)	1 (11%)
PT seconds above control (Mean+SD)	2 (12%)	0
PTT times control	1.42 ± 0.23	1.41 ± 0.33

Table 5: Clinical and Laboratory parameters of Survived patients.

Parameters	HAA (Mean ± SD) N=65	MP-C (Mean ± SD) N=73	P value
Hospital days	6.86 ± 3.77	6.44 ± 3.05	0.49
Mean time to death(days)	3.29 ± 2.61	4.33 ± 3.67	0.38
Hospital day RRT free	4.2 ± 1.68	3.95 ± 1.9	0.46
Creatinine Post treatment	2.32 ± 1.78	1.98 ± 1.19	0.21
Platelet Post treatment	253.1 ± 128.01	249 ± 131	0.78
PT post treatment (secs above control)	1.003 ± 1.28	0.87 ± 1.84	0.74
PTT post treatment (Times control)	1.15 ± 0.23	1.04 ± 0.25	0.018*
Transfusion	20 (31%)	18 (27%)	
FFP (Number of patients transfused)	7 (11%)	5	1
FFP number of units (mean ± SD)	4.8 ± 1.09	5 ± 2	0.85
Platelet (Number of patients transfused)	10 (15%)	10	1
RBC (number of patients transfused)	3 (5%)	3	1
PRBC number of units (mean ± SD)	6.57 ± 1.51	6.2 ± 0.63	0.89
*statistically significant at 95 percent confidence interval			

Table 6: Comparison of Outcomes.

hemorrhage [6]. Gancheva in their study on the hemorrhagic syndrome of leptospirosis showed that hemorrhages were found in 75% of death and were risk factors for death [9]. Proposed mechanism for the pulmonary involvement includes a direct action of the bacteria on the membrane of parenchymal cells. The antigenic materials' affinity for cell membranes suggests an interaction with surface proteins, causing functional disorders of the membranes, leading to necrosis [7]. Leptospiral toxin also causes endothelial damage to the pulmonary capillaries which can lead to generalized vasculitis [10]. Findings of antibodies and complement gives strength to the hypothesis that the infection can precipitate an immune response [11].

Majority of the patients who died had platelet counts below 100× 10^3/uL and lower than those who survived. Sharma in their study in 2009 concluded that thrombocytopenia was an important contributory factor in the pathogenesis of hemorrhage in leptospirosis [12]. Trevendi in 2010 also noted that there is an increase in the megakaryocytes in the bone marrow of patients with thrombocytopenia, suggesting peripheral destruction of platelets, which is most likely immune-mediated brought about by vasculitis [13]. Furthermore, the study by Gancheva et al. [9] demonstrated the presence of anti-thrombocyte antibodies causing platelet destruction in severe leptospirosis [9].

Severe vascular injury as a consequence of vasculitis can also cause destruction of the hepatic architecture, which could cause derangements in the clotting factors as manifested by prolonged PT and aPTT. Furthermore increased blood nitrogen products brought about by endothelial and tissue damage can lead to changes in the concentration of coagulation factors [9]. In the current study, the pre-treatment PT and aPTT were prolonged in both groups. However, the post treatment aPTT was significantly lower in patients treated with MP-C compared to the HC group. This could have played an essential role in decreasing the hemorrhagic syndrome of patients, thus lowering mortality.

Although not statistically significant, the mean time prior to death was longer in the MP-C compared to HC group. Since infection might precipitate an inflammatory and immune response, the immunosuppression brought about by cyclophosphamide and methylprednisolone might have caused the delay in the deterioration of the patients. However, in a study in 2012 have shown that the infiltration of monocytes and neutrophils, which characterizes the inflammatory reaction, is mild compared to the vascular damage, making the pulmonary involvement primarily hemorrhagic rather than inflammatory [10]. This might have caused severe hemorrhage in some of our patients despite immunosuppression. Timing of administration of cyclophosphamide can also be an important factor. Visnith et al. [3] stated that vasculitis is often seen early in the course of the disease and is seldom seen late [3]. In our study, administration of cyclophosphamide in the protocol was after the third day of the pulsing or anytime only when the patient developed hemorrhage, which could have already been too late for some patients.

Those treated with MP-C had a shorter overall recovery period and became dialysis free earlier than those treated with HC. More patients were also transfused with fresh frozen plasma in the hydrocortisone group. However, these results were not statistically significant.

In the present study, majority of patients underwent hemodialysis in both groups (71% for HC and 84% for the MP-C), however there were more peritoneal dialysis patients in the HC group (29%) compared to those of the MP-C group (16%). Recent studies recommended the use of hemodialysis and hemofiltration in patients with leptospirosis and renal failure. But a recent review in 2011 stated that there is still room for peritoneal dialysis in management of acute kidney injury if done optimally. More studies are still needed, especially randomized control trials to fully support these conclusions. Although the difference in mode of RRT between the HC and MP-C group in our study is not statistically significant (P=0.0657), our study design cannot make conclusions on the effect of mode of renal replacement therapy on the survival of our patients, further investigation is still warranted to explore this area.

Conclusion

The three day course of methylprednisolone plus single dose intravenous cyclophosphamide significantly improves survival among patients with leptospirosis, renal failure and pulmonary hemorrhage compared to a 3-day course of hydrocortisone. There is likewise a

significant improvement in the levels of aPTT in patients treated with methylprednisolone.

Recommendation

A randomized control trial should be done to determine whether MP-C significantly improves survival in severe leptospirosis, renal failure and pulmonary hemorrhage. And risk factors associated with survival such as mode of RRT should also be investigated.

References

1. Shenoy VV, Nagar VS, Chowdhury AA, Bhalgat PS, Juvale NI (2006) Pulmonary leptospirosis: an excellent response to bolus methylprednisolone. Postgrad Med J 82: 602-606.
2. Kaspe DI, Braunwald E (2011) Harrison's Principles of Internal Medicine. New York: McGraw Hill.
3. Visith S, Kearkiat P (2005) Nephropathy in leptospirosis. J Postgrad Med 51: 184-188.
4. Boonpucknavig V, Soontornniyomkij V (2003) Pathology of renal diseases in the tropics. Semin Nephrol 23: 88-106.
5. Dolhnikoff M, Mauad T, Bethlem EP, Carvalho CR (2007) Pathology and pathophysiology of pulmonary manifestations in leptospirosis. Braz J Infect Dis 11:142-148.
6. Trivedi SV, Vasava AH, Patel TC, Bhatia LC (2009) Cyclophosphamide in pulmonary alveolar hemorrhage due to leptospirosis. Indian J Crit Care Med 13: 79-84.
7. Carvalho CR, Bethlem EP (2002) Pulmonary complications of leptospirosis. Clin Chest Med 23: 469-478.
8. Republic of the Philippines Department of Health.
9. Gancheva G, Ilieva P, Atanasova M, Tzvetanova Chr, Simova I (2005) Hemorrhagic Sydromes in Leptospirosis. Trakia Journal of Sciences 3: 10-12.
10. Helmehorst HJ, van Tol EN, Tuinman PR, de Vries PJ, Hartskeerl RA, et al. (2012) Severe Pulmonary manifestation of leptospirosis. Neth J Med 70: 215-220.
11. Nally JE, Chantranwat C, Wu Xy, Fishbein MC, Pereira MM, et al. (2004) Alveolar septal deposition of immunoglobulin and complement parallels pulmonary hemorrhage in a guinea pig model of severe pulmonary leptospirosis. Am J Pathol 164: 1115-1127.
12. Sharma J, Suryavanshi M (2001) Thrombocytopenia in leptospirosis and role of platelet transfusion. Asian J Transfus Sci 1: 52-55.
13. Trivedi SV, Vasava AH, Batia LC, Patel TC, et al. (2010) Plasma exchange with immunosuppression in pulmonary alveolar haemorrhage due to leptospirosis. Indian J Med Res 131: 429-433.