EDITORIAL

Prophylaxis and Treatment for Leptospirosis: Where are the Evidences?

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Leptospirosis is a zoonosis of worldwide distribution, caused by infection with pathogenic spirochetes of genus leptospira. The disease is maintained in nature by chronic renal infection of carrier mammals like rats, cattles, dogs etc, which excrete the organism in their urine.[1]

Humans get infection when come into contact with the contaminated environment like water or vegetation and the organism penetrates through the broken skin or mucosa.[2]

Leptospirosis is one on those many diseases which expresses itself in the form of outbreaks associated with seasonal variations like rainfall. Pathogenic organism responsible for this disease is a spirochete of genus Leptospira which exists in around 300 serovars.[3] Leptospirosis presents itself in a wide spectrum of clinical presentations frequently mimicking other diseases, so frequently it is misdiagnosed or under diagnosed. Spectrum of disease may range from mild infection to life threatening pulmonary and renal complications and case fatality may goes up to 20%.

Numbers of leptospirosis outbreaks have occurred during the past few years in various place of world, such as Nicargua, Solvador, Rio de Janeiro in Brazil and in India. In India outbreaks of Leptosirosis have been reported from Gujarat, Kerala, Tamilnadu, Karnataka , Assam and Andhra pradesh.[4]

Guidelines and protocol for prevention and treatment of leptospirosis is made by International as well as national agencies.[2, 5] As per the available guidelines, antibiotics are posed as major drugs for the prevention (chemoprophylaxis) and treatment of leptospirosis. Guidelines cite Doxycycycline as drug of choice for chemoprophylaxis and Penicillins as drug of choice for treatment.[2, 5]

Keeping in view of the epidemic potential of the disease, it is essential to assess and generate new evidences so that there finding can be incorporated to update the policies for treatment and prevention (chemoprophylaxis) of Leptospirosis. We searched various database including PubMed, Cochrane clinical trial register, Google scholar and also websites of some infectious disease societies (American society of tropical medicine and hygiene, International society of travel medicine, Infectious disease society of America) to find articles related to role of antibiotics and other intervention undertaken for treatment of leptospirosis, to assess evidences quotient of presently available guidelines at national and international level. We also searched cross references of primary articles to find more articles which can be useful in synthesis of this manuscript. Narrative findings of available evidences are discussed below under separate headings:

CHEMOPROPHYLAXIS OF LEPTOSPIROSIS

Very few studies are available related to chemoprophylaxis of leptospirosis. Studies narrate use of two antibiotics for chemoprophylaxis of leptospirosis, namely Doxycycline and Penicillin. Till date only 4 trials are available related to role of antibiotics in chemoprophylaxis of leptospirosis.

Takafuji et al (1984) explored the prophylactic effect of doxycycline in a double blind clinical trial where doxycycline (200 mg) and placebo was given weekly to US soldiers who posted to panama for three weeks. Twenty cases of leptospirosis observed in placebo group (Attack rate =4.2%) but only one case was observed in doxycycline group (Attack rate = 0.2%). It was concluded by the authors that doxycycline had 95% efficacy against the prevention of leptospirosis.[6]

In another study (Gonsalez et al, 1988) the prophylactic effect of doxycycline was explored in peoples who had already been exposed to contaminated water. 40 participants were given doxycycline (200 mg) and 42 were given placebo. Both groups were followed up for 45 days, it was observed that confirmed cases of leptospirosis were more in placebo group as compared to drug group (5 Vs 2) and protective effect of doxycycline was documented (RR = 2.3) which although was not significant.[7]

Sehgal et al evaluated the effect of doxycycline prophylaxis in people of North Andman in a randomised controlled trial. 782 patients were randomised into two group one group was given 200 mg doxycycline per week and another group was given placebo. Participants were followed up for 12 weeks. It was observed that there was no statistical difference in both groups for infection rate but there was significant difference in reducing morbidity and mortality during outbreaks.[8]

A Cochrane review and metaanalysis was done based on above three studies. This review concludes no significant role of doxycycline in prevention of leptospirosis (Odds ratio 0.28 (95% CI 0.01 to 7.48) but it was significantly associated with adverse effects like nausea and vomiting 11 (95% CI 2.1 to 60).[9]

In a placebo controlled field study done in Srilanka by lllangasekera et al (2008) 800 farmers were divided randomly into two groups one group was given oral penicillin 500 mg twice a day and second group was given similar placebo. This intervention was given for one month. Data of 602 participants were available at the end of study. Out of these 602, good compliance was observed in only 319 participants (152 from penicillin group and 167 from placebo group). Only three cases of confirmed leptospirosis were noted and all were in placebo group hence authors concluded that oral penicillin may have some protective role, however fewer outcome in both group questions the validity of findings.[10]

It can be concluded on the basis of available literature that role of antibiotics in chemoprophylaxis of leptospirosis is uncertain due to lack of large scale trials. More evidence based studies are required to generate evidence for antibiotics being used as chemoprophylaxis.

TREATMENT OF LEPTOSPIROSIS

Antibiotics

Although antibiotics like penicillins, cephalosporins, azithromycine, tetracyclines, quonolones, macrolides etc are tested on animals and in vitro models of leptospirosis but well designed clinical studies are scarce.[11 - 17]

A study was conducted by Fairburn and Semple (1956) amongst patients of leptospirosis which were divided into three groups, first group was considered as control and was given no antibiotics (n= 31), second group was given intravenous penicillin 600000 unit every six hour (n = 21) and third group was given Chloramphenicol 0.5 gm every 6 hourly (n= 31). After a follow up for 5 to 6 days, no significant difference was observed for endpoints (time (in

days) from start of symptoms to symptom free day, average time (in days) from start of sign to sign free day and total symptom free and sign free days). It was also observed that there was no significant difference in endpoints when treatment start early (within four days) as compared to when treatment starts after 4 days.[18]

Ross Russel (1958) conducted a study to explore the role of oxytetracycline in leptospirosis. In treatment group (T) oral oxytetracycline was given in the dose of initially 1.5 gm and than 0.5 gm every six hourly (n = 27) and placebo group was given oral ascorbic acid 50 mg thrice a day. After follow up of 5 days it was observed that average duration of pyrexia after treatment, average duration of symptoms after starting of treatment and average total duration of pyrexia (before treatment and after treatment) was significantly less in oxytetracycline group.[19]

Effect of doxycycline on various parameters of leptospirosis was also explored in a study done by McClain JB et al (1984). Study participants were divided into two groups, doxycyline group (n =14) and placebo group (n = 15). After follow up period of 2 to 3 weeks it was observed that doxycycline reduces the illness days, fever, fever days and other parameters (myalgia, malaise, GI symptoms, conjunctival suffusion) significantly as compared to placebo.[20]

Penicillin was compared with the placebo in a study done by Watt G et al (1988). Penicillin was given through intravenous route (6 million unit/day) to participants of group one and second group was given normal saline. After 7 days of treatment it was observed that penicillin shortens the fever days as well as duration of hospital stay significantly.[21] In a similar study done by Edward CN et al (1988) same dose of penicillin was given to drug group and intravenous fluid was given to control group. After 5 days of observation no significant difference was observed between two groups for time for defervesence, mortality and other biochemical parameters.[22] Daher et al (2000) compared effect of intravenous penicillin group with those with no treatment and observed that after 8 days of study duration no difference was observed between drug and control group for predecided endpoints like mortality, fever days, number of patients needed dialysis, days of hospitalization and days needed for normalization of biochemical parameters.[23] A similar study conducted by Costa et al in 2003 observed no significant difference between penicillin group and control group for mortality, hospital days and number of patients needed dialysis.[24]

Penicillin was compared with ceftriaxone in a trial (Thanachai Panaphut et al, 2003) where one group (P) (n=86) was given intravenous penicillin G 1.5 million unit/ 6 hour and second group (C) (n = 87) was given intravenous ceftriaxone 1 gm daily for 7 days. After 7 days follow up no significant difference was observed for median duration of fever, mortality and complications like renal failure, jaundice and thrombocytopenia.[25]

Suputtamongkol et al (2004) evaluated effects of three antibiotics (penicillin, cefotaxime and doxycycline) on various parameter of leptospirosis. In penicillin group (n = 87) 1.5 million unit dose was given every 6 hourly through intravenous route. In cefotaxime group (C) (n= 88) 1 gm dose was given every 6 hourly through intravenous route. In doxycycline group (n =81) initially 200 mg doxycycline is given intravenously in 30 minutes which was followed by 100 mg intravenous infusion 12 hourly. Parenteral therapy was given till patients condition improved (afebrile) and then oral therapy was started. After 7 days there was no significant difference observed between three groups for mortality, time to differevescence and duration of hospitalization.[26]

Doxycycline was compared with azithromycine in a trial done by Kriangsak Phimda et al (2007). Doxycycline was given in the dose of 100 mg twice a day by oral route while in azithromycine group) (n =35) azithromycine was given 1 gm initially followed by 500 mg once daily for 2 days by oral route. After the study period of 7 days

there was no significant difference observed for endpoints (No. of patient showing defervescence within 5 days and median time to defferevescence in hours).[27] Recently published Cochrane review based on 7 clinical trials[28] and one non Cochrane review based on 10 clinical trials (Unpublished, under communication) concluded that penicillin is not better than placebo in the treatment of leptospirosis. Also there is no superiority of one antibiotic over another.

So on the basis of available clinical studies, there inadequate evidences about role of antibiotics in the treatment of leptospirosis. Though, Penicillin is considered as first line therapy for leptospirosis but out of available five studies only one study shows favourable effect of penicillin. More so, there is no clear evidence of superiority of any one antibiotics based on available research findings. Doxycycline and Oxytetracycline are promising drugs but as only one trial is available for each of these drugs hence there superiority cannot be established with certainty. It was also observed that majority of the clinical trials reviewed in present study lack appropriate methodological qualities and the sample size is less in each group posing a question on validity of study. There is an urgent need to conduct methodologically strong clinical trials exploring effects of various antibiotics in different patients groups.

Glucocorticoids and other Immunosuppressants

Recently it has been documented that pulmonary involvement is more and pulmonary haemorrhage is considered as major cause of mortality in patients with leptospirosis.[29,30] Role of corticosteroids in the treatment of acute lung injury and acute respiratory distress syndrome (ARDS) is well accepted hence advantage of giving corticosteroids in pulmonary involvement of leptospirosis has been studied by some researchers. However, majority of these studies explore role of corticosteroids in leptospirosis are descriptive studies or case series having without defined control group for comparison.

In a study done by Trivedi SV et al (2001) for evaluating role of high dose glucocorticoids pulse (GPT) therapy in patients of leptospirosis with pulmonary involvement, out of 13 such patients only 8 were given GPT. Mortality was observed in 2 patients of GPT group and 4 patients in no GPT group.[31] In another pilot study 7 out of 8 patients given methyl prednisolone with noninvasive ventilation were survived. There was no control group in this study.[32] In a case series by Shenoy et al (2006) out of 30 individuals with leptospirosis , initial 13 patients were treated with standard antibiotic without corticosteroids treatment but remaining 17 patients were given methylprednisolne (1 gm IV for 3 days followed by 1 mg /kg for 7 days) along with standard treatment. Overall mortality in the methyl prednisolone group was less as compared to control (18% vs 62%).[33]

In a retrospective study by Russell Villanueva et al (2010) charts of 36 patients of severe leptospirosis were reviewed. 16 of them were given steroids and 20 were not given steroids. Ten patients out of 16 steroid group and 11 patients of second group without steroid were having pulmonary involvement. No significant difference could be found between both groups for mortality, need of assisted ventilation and complications.[34] In similar descriptive study in Srilanka significant beneficial effect of bolus methylprednisolone was observed in patients of leptospirosis.[35]

Only one clinical trial is available which explores the role of steroid in leptospirosis. In this open labelled randomised trial 68 patients of leptospirosis with pulmonary involvements was randomised to three groups one was given desmopressin with standard treatment, another group was given pulse dexamethasone with standard treatment and third group was given standard treatment only. There was no significant difference between three groups for mortality by both leptospirosis confirmed (per protocol) and intention to treat basis.[36]

Role of Cyclophosphamide is also explored in pulmonary involvement of leptosprirosis by

various researchers. In a study done by Trivedi SV et al (2009) out of 65 patients admitted with severe pulmonary involvement with confirmed leptospirosis, only 33 were given parenteral cyclophosphamide 60 mg/kg stat on diagnosis however both groups receive intravenous penicillin, methyl prednisolone pulse therapy and non invasive mechanical ventilation. Cyclophosphamide was significantly found to be associated with protective effect as survival in this group was significantly more (66.7% Vs 9.4%).[37]

On the basis of available evidence it can be concluded that role of immunosuppressants like glucocorticoids and cyclophosphamide are still in formative stage to generate enough evidences to be incorporated at policy level for treatment of Leptospirosis. Along with, lack of sufficient studies to ascertain role of glucocorticoids in leptospirosis with pulmonary involvement, studies with strong methodological component are missing. There is an urgent need of quality clinical trials to explore the role of immunosuppressant in leptospirosis with or without pulmonary involvement.

CONCLUSION

Looking into Leptospirosis as an emerging infectious disease with global importance and in absence of enough scientific evidence for currently available guidelines, there is an urgent need for quality clinical trials to explore the role of all possible antibiotics and other agents like glucocorticoids and cyclophospamide for treatment of Leptospirosis.

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