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Research Article

Comparison of efficacy of levofloxacin-metronidazole combination versus ceftriaxone in cases of moderate diabetic foot infection

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ABSTRACT

Background: Foot ulcers are a significant complication of diabetes and are the most common cause of non-traumatic lower extremity amputations in the industrialized world. Diabetic foot infections can be treated effectively with cephalosporins and fluoroquinolnes. The purpose of this study was to compare the efficacy, safety and microbiological outcomes of ceftriaxone and combination of levofloxacin and metronidazole.
Methods: This was a prospective, open labelled, randomized controlled trial study. Patients diagnosed of having diabetic foot infection were recruited for the study from the OPD and IPD of the surgery department of Govt. Medical College and Hospital, Miraj and PVP Govt. Hospital, Sangli from June 2007 to December 2007. Signed informed consents were obtained from the patients. The study complied with declaration of Helsinki. Enrolled patients were randomized in 2 groups. Group 1: ceftriaxone group: patients were hospitalized and received ceftriaxone 1 gm intravenously for 14 days. Group 2: levofloxacin and metronidazole group: patients were treated as out-patients and received Levofloxacin 500 mg orally once daily with metronidazole 400 mg orally thrice daily for 14 days. Detailed history and complete physical examination was done for all patients. Sequential measurement of the lesion was done, to assess the change in size. Bacteriological evaluation was done. Clinical and microbiological outcome and safety parameters were assessed after treatment.
Results: The baseline characteristics in both the groups were comparable and were not significant with each other ($p > 0.05$). In both the groups the most commonly isolated aerobe was staphylococci species followed by different species of enterobacteriacae and pseudomonas. Most commonly isolated anaerobe was bacteroides fragilis. Microbiological and clinical outcomes were assessed and the total no of patients recovered in both groups were almost similar. The percentage of wound healing in both the treatment groups was equal. None of the patients in both the groups had shown complete wound healing. The number of adverse effects associated with the therapies was also similar. The cost of therapies in both the groups were assessed and found the difference was highly significant.
Conclusions: Even though combination of levofloxacin-metronidazole and ceftriaxone alone had similar outcomes in terms of efficacy, on contrary in comparison of cost and convenience, levofloxacin - metronidazole therapy was proved better than ceftriaxone in treatment of diabetic foot ulcers.

Keywords: Diabetic foot infection, Metronidazole, Levofloxacin, Ceftriaxone

INTRODUCTION

Diabetes is rightfully called as the "disease of complications" as with every on-going year, this disease attacks almost all the target organs creating havoc. One of its complication was diabetic foot though it is not common as other complications, such as those affecting the eye but it may lead to amputation.[1] The risk of lower extremity amputation is 15 to 46 times higher in diabetics than non- diabetics.[2] Most lower extremity amputations

are preceded by skin ulcers.[3] The polymicrobial nature of diabetic foot infections is well known, with an average of 5 to 6 organisms involved.[4]

Ceftriaxone is a third generation cephalosporin with increased potency against enterobacteriacae while maintaining activity against streptococci and staphylococci species. This is highly effective in the treatment of serious skin and soft tissue infections like diabetic foot infections in a once daily regimen.[5]

Levofloxacin is a second generation fluoroquinolones having activity against gram negative bacteria and also extended activity against gram positive cocci and anaerobes.[6] As per the American diabetic association a newer fluoroquinolone plus either clindamycin or metronidazole can be used to treat diabetic foot.5 Metronidazole is a nitro imidazole with proven efficacy in anaerobic bacterial infections.[7]

This study was planned to compare the efficacy, safety and microbiological outcomes of oral antibiotics with a wide spectrum of activity like levofloxacin and metronidazole with intravenously administered regimen utilizing ceftriaxone in patients with moderate diabetic foot infections.

METHODS

The study was a prospective, open label randomized controlled trial. Patients diagnosed of having diabetic foot infection were recruited for the study from the OPD and IPD of the surgery department of Govt. Medical College and Hospital, Miraj and PVP Govt. Hospital, Sangli from June 2007 to December 2007. Written informed consent was obtained from the patients. The study complied with declaration of Helsinki and ethics committee approval was sought.

Patients of both sexes with diabetes mellitus and with clinically infected lesion of moderate severity or at least two of the following signs - erythema, warmth, tenderness, induration, fluctuance and discharge were included in the study.

Exclusion criteria

Patients with signs of severe infection like fever, leucocytosis, suggesting limb or life threatening infection requiring prolonged parenteral antimicrobial therapy, osteomyelitis, gangrenous tissue, women who were pregnant or nursing, patients with impaired renal functions, deranged hepatic functions, history of seizure or neurological illness, advanced vasculopathy, allergic to medications, who have received prior antimicrobial therapy within previous 72 hours of enrollment or who requires concomitant antimicrobial therapy other than study drugs for any other indications.

Detailed history and complete physical examination was done for all patients. Sequential measurement of the lesion was done, to assess the change in size.

After meeting inclusion criteria a total of 60 patients were involved in the study. They were randomized in 2 groups consisting 30 in each. Group 1: ceftriaxone group- they were hospitalized and received ceftriaxone 1 gm intravenously for 14 days. Group 2: levofloxacin and metronidazole group- they were treated as out-patients and received levofloxacin 500 mg orally once daily with metronidazole 400 mg orally thrice daily for 14 days.

Bacteriological evaluation was done by collecting specimens by needle aspiration or deep tissue swabs to assess type of culture (aerobic or anaerobic bacteria). The initial susceptibility of all isolated pathogens for study drugs and other commonly used drugs was tested by the standard antibiotic disk techniques according to the modified Bauer- Kirby procedure. Cultures were repeated if necessary during treatment or after completion of therapy.

Subjects were followed every 3 to 7 days, depending on severity of the infection. Patients in both the groups were assessed on 3rd day and observed one patient in ceftriaxone group required an altogether different regime for treatment and another patient from group 2 lost follow-up on 3rd day hence they were excluded from the study. After 48 hours when culture reports were available antibiotic treatment was reassessed. Those whose culture yielded one or more pathogens that were resistant to the assigned antibiotic were assessed clinically. If their infection was improving, therapy was continued otherwise they were referred to surgery. After 2 weeks of therapy, a few patients who had improved but had some persisting infection were instructed to continue antimicrobials for additional days.

Debridement was done in patients wherever it was indicated and patient was advised to avoid unnecessary ambulation.

Clinical outcome was assessed in terms of

- Cured - if all signs of inflammation like purulence, erythema, local oedema, induration, discharge had resolved
- Improved - if at least 2 or 3 above mentioned signs had resolved
- Failed - if there was no substantial improvement in infection and change of antibiotic treatment or surgical intervention was believed necessary.

Microbiological outcome was evaluated as following

- Cured - if all the initial susceptible isolates were eradicated or there was no longer material available for a second culture

- Improved - if at least one, but not all of the susceptible isolates were eradicated
- Failed - if all the initial isolates were persisting.
- Colonization - isolation of organisms, other than the original susceptible isolates and infection has improved, or as super infection, if it has not improved.

Wound healing was regarded as following

- Healed - complete skin closure
- Healing progress - lesion has decreased in size and healthy granulation tissue has appeared
- Unhealed - lesion has no change in size and no granulation tissue.

Safety parameters were assessed by monitoring the adverse drug reactions during therapy at each follow up by inquiring the patient. Cost comparison between two therapies was done by taking into account the actual cost of the drug as well as the cost of syringe and needle, which was used for drug administration.

Statistical analysis

Quantitative data was analysed using Z test for standard error of difference between two means and two proportions.

RESULTS

A total of 58 patients were enrolled in the study and divided into two groups consisting 29 in each. Group 1 received ceftriaxone and Group 2 received levofloxacin and metronidazole. The mean age group of the patients in both the groups was 55 years. Evaluable patients included higher number of males than females in both the groups and the severity of infection evaluated in both the groups were moderate. The baseline characteristics in both the groups were comparable and there is no significant difference (p >0.05) (Table 1).

Table 1: Baseline characteristics.

Characteristics	Group 1 n = 29	Group 2 n = 29
Age (years) mean±SD	55.34±7.31	55.96±5.91
Sex	M - 23 (79.31%)	M - 24 (82.75%)
	F - 06 (20.69%)	F - 05 (17.24%)
Duration of diabetes (years) Mean±SD	7.48±3.42	7.24±2.69
Uncontrolled diabetics r	24 (82.75%)	25 (86.20%)
Smokers n (%)	11 (37.93%)	13 (44.82%)
Neuropathy n (%)	16 (55.17%)	17 (58.62%)
Vasculopathy n (%)	6 (20.68%)	8 (27.58%)
h/o Trauma n (%)	20 (68.96%)	19 (65.51%)
Severity of infection	moderate	moderate

Out of all the 58 specimens sent for culture only 1 culture yielded monomicrobial infection whereas rest all cultures had polymicrobial growth. In ceftriaxone group, total isolates were 72 in number which comprised of 63 aerobes and 9 anaerobes. In levofloxacin - metronidazole group, total isolates were 72 in number which comprised of 62 aerobes and 10 anaerobes. In both the groups the most commonly isolated aerobe was *Staphylococci* species followed by some *Enterobacteriaceae* and *Pseudomonas*. Most commonly isolated anaerobe was *Bacteroides fragilis.* There was no significant difference in microbiological characteristics of both the groups at the baseline (p >0.05) as given in Table 2.

Table 2: Microbiological characteristics.

Isolates	Group 1 * n=29	Group 2* n=29
Staphylococcus aureus	18	15
Coagulase-negative Staphylococcus	5	6
Streptococcus spp	2	3
Pseudomonas aeruginosa	7	10
Escherichia coli	11	8
Proteus mirabilis	7	9
Proteus vulgaris	5	4
Klebsiella pneumoniae	3	4
Klebsiella oxytoca	1	2
Citrobacter koseri	2	0
Citrobacter freundii	2	1
Total aerobes	63 (87.5%)	62 (86.11%)
Bacteroide fragilis group	5	5
Peptococcus spp	4	4
Peptostreptococcus spp	0	1
Total anaerobes	09 (12.5%)	10 (13.88%)

*(p >0.05) no significant difference in both the groups.

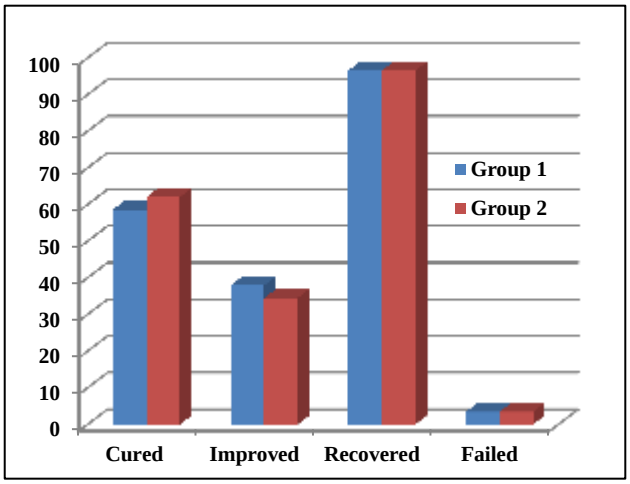

Figure 1: Comparison of microbiological outcome between two groups (n = 29 in both groups).

Figure 1 demonstrates the microbiological outcome and found that Group 1 patients achieving microbiological cure were 17 (58.62%), improvement in 11 patients (37.95%) failure in 1 patient (3.44%). In group 2, 18 (62.06%) were cured microbiologically, 10 were

improved (34.48%) and 1 had failure (i.e.3.44%). The total no of patients recovered in both groups were 96.55% and 96.54% respectively and the difference was not significant in the study groups (p >0.05).

The clinical outcome in both the groups were compared and there was no significant difference in both therapies (p >0.05) as in Figure 2. In group of patients received ceftriaxone, 19 patients were cured at the end of 14 days (65.51%), improved were 8 (27.58%) and therapy failed in 2 patients (6.89%) and in Group 2 clinical cure was seen in 21 patients (72.41%), improvement in 7 (24.13%) and failure in 1 patient (3.44%). The number of patients recovered in both the groups was 93.09% and 96.54% respectively and the statistical difference was p >0.05.

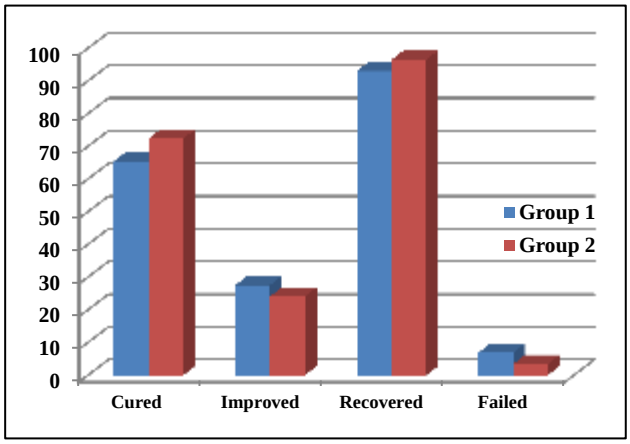

Figure 2: Comparison of clinical outcome between two groups (n = 29 in both groups).

The percentage of wound healing in both the treatment groups was given in Figure 3. A complete skin closure was not seen in both the treatment groups. But healing progressed in 27 patients (93.10%) and 28 patients (96.55%) in both groups respectively. The wound did not heal in 2 patients (6.89%) and 1 patient (i.e.3.44%) in ceftriaxone and levofloxacin-metronidazole group correspondingly and p value is >0.05.

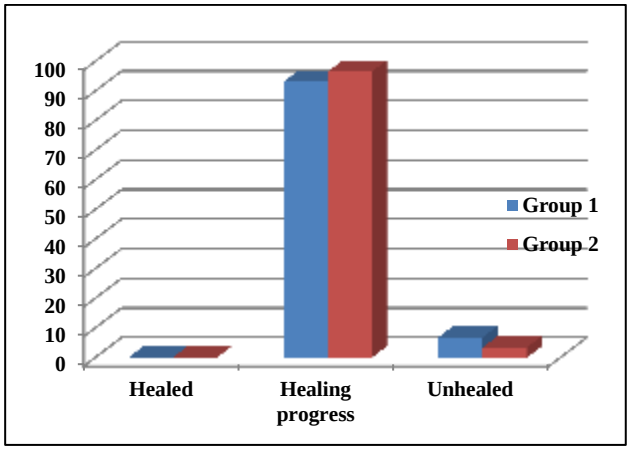

Figure 3: Comparison of percentage of wound healing between two groups (n = 29 in both groups).

The numbers of adverse drug events were similar with both the therapies and were of minor severity as presented in Table 3.

Table 3: Incidence of adverse events in both the study groups.

Adverse drug reactions	Group 1 n = 29	Group 2 n = 29
Nausea	4	5
Vomiting	2	1
Headache	1	1
Diarrhea	2	1
Abdominal discomfort	0	2
Thrombophlebitis	1	0
Others	1	1
Total events	**11***	**11***

*p >0.05 when compared between two groups.

The total cost of parenteral ceftriaxone therapy given to a single patient per day was rs. 37 and cost of levofloxacin - metronidazole therapy to a single patient per day is rs. 5.10 paisa. So the cost of therapy in group 1 patients was significantly greater than the cost of therapy in group 2 patients (p >0.05) as in Figure 4.

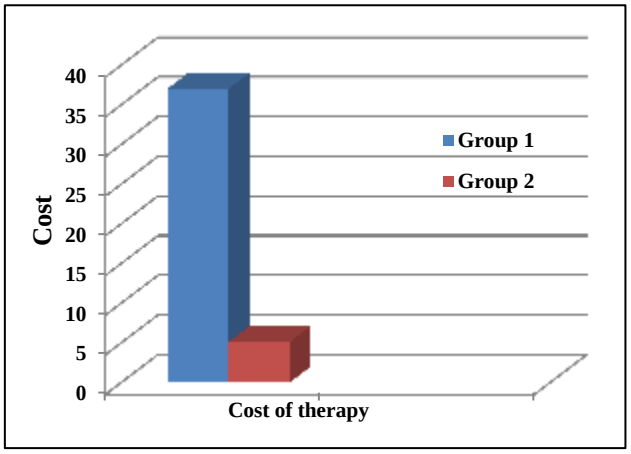

Figure 4: Comparison of cost of therapy in both the study groups (n = 29 in both groups).

DISCUSSION

Lower extremity infections are an important cause of hospitalization, disability; morbidity and mortality among patients with diabetes mellitus.[8] Neuropathy, infection, deformity and ischemia are major threats to the diabetic foot and the overall functional well-being of the diabetic patient. The cost associated with adequately caring for these problems represents a significant monetary impact to the health care system.[9]

In the present study, 60 diabetic foot ulcer patients were randomized, 30 each to two groups i.e. ceftriaxone group (parenteral therapy) or levofloxacin-metronidazole group (oral therapy) to receive the respective study drugs for 14

days. As seen in Table 1 the baseline characteristics like age, sex, duration of diabetes, uncontrolled diabetes and other variables were equally distributed in both the study groups and was not significant with each other. In this study a variety of pathogens were isolated, total of 144 comprising 72 isolates of aerobes, anaerobes and mixture of them in each group. Most commonly isolated aerobe being Staphylococci species in both the groups followed by isolation of *Proteus species* and E. coli. Most common anaerobe was *Bacteroides fragilis* in both the groups. Our results are similar to those reported by Kelker et al, who studied 50 patients with diabetic foot ulcers and isolated total 150 organisms comprising of 125 aerobes and 25 anaerobes with S. aureus as most common aerobe and *Pepto streptococcus* as most common anaerobe.[10]

In the present study the microbiological out come in both the groups were 96.55% and 96.54% respectively and this management of ceftriaxone and fluoroquinolones against microbiological eradication was already demonstrated in previous studies of Robert et al.[5] There was significant increase in the frequency of colonization with ceftriaxone therapy (17.24%) compared to levofloxacin-metronidazole group (10.34%). This might be due to hospitalization in ceftriaxone group which makes them more prone to hospital acquired infections as compared to outpatient treatment in the second group. In the present study it was observed that the efficacy of both therapies in two groups was similar and the clinical outcomes were in concordance with the studies of Jose et al.[11]

In this study wound healing was assessed by the decrease in size of the ulcer and appearance of healthy granulation tissue. There was no patient in both ceftriaxone group and levofloxacin-metronidazole group, who achieved complete skin closure. But healing progressed in 93.10% of patients in ceftriaxone group and 96.55% of patients in levofloxacin-metronidazole group. These results are similar to the studies of Freykberg.[12]

Adverse drug events were monitored throughout the study. Overall incidence of adverse events in both the groups was similar. All events were mild in nature and resolved after a short duration. None of the event required discontinuation of the study medication or additional hospitalization. Most commonly reported events were nausea and vomiting in both the groups. Other complaints in both the groups were diarrhoea and headache and these findings were in accordance with the studies of Robert et al.[5] In the present study cost of therapy was also assessed by taking into account the actual cost of the drug and the cost incurred for administering the drug like cost of syringe and needle. The total cost of ceftriaxone therapy and levofloxacin-metronidazole therapy for single patient per day is Rs. 37 and Rs. 5.10 paisa respectively and this difference in cost of treatment were highly significant.

CONCLUSION

We found that both ceftriaxone and combination levofloxacin and metronidazole had similar efficacy and safety but the cost and convenience of antimicrobial therapy with levofloxacin-metronidazole fares better than ceftriaxone in treatment of diabetic foot ulcers.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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