

Treatment of Diabetic Foot Infections: A Prospective Study Highlighting the Efficacy and Safety of Moxifloxacin

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Abstract

Background: Foot infection involving the skin, soft tissues and bony structures, is a common complication of foot ulcers in diabetic individuals and represents a major cause of morbidity and mortality. Systemic antibiotic treatment must be given as early as possible initially on empirical basis and based on the response to empirical therapy and wound culture and sensitivity results, definitive therapy should be decided. This study was conducted to assess the efficacy and safety of moxifloxacin for treating diabetic foot infections in Pakistani population.

Methods: After taking ethical approval, an interventional phase IV study was conducted in the department of medicine and diabetic clinic, Liaquat University Hospital, Jamshoro, Hyderabad from March 2017 till August 2017. A total of 75 patients with diabetic foot infection who were sensitive to moxifloxacin on culture and sensitivity were included in the study using non-probability convenient sampling technique. All the demographic and clinical information was collected by using a questionnaire specially designed for the study. After making clinical assessment, all the patients were treated with sequential intravenous/oral moxifloxacin for 14 days. Bacteriologic response was based on the results of cultures of specimens of infected skin or soft tissue or blood. The data were analyzed on SPSS version 20.0. Chi-square test was used with significant level set at 0.05.

Results: The study results revealed that the majority of patients with diabetic foot ulcer were males with the age of greater than 45 years. Only 21.3% of them had a comorbidity, either hypertension alone or hypertension with ischemic heart disease, whereas 84% of them reported their foot ulcers to be cured at the end of treatment. Furthermore, only younger age was found to have a significant positive

association with healing of foot ulcers.

Conclusions: Moxifloxacin is effective in treating diabetic foot infections and 84% of the diabetic patients in the present study reported the healing of foot ulcers as a result of a 2-week moxifloxacin treatment. Further evaluation of the role of moxifloxacin in the treatment of diabetic foot ulcer is recommended.

Keywords: Clinical trial; Safety and efficacy; Moxifloxacin; Diabetic foot infections

Introduction

Foot infection involving the skin and soft tissues and/or bony structures, is a common complication of foot ulcers in diabetic individuals and represents a major cause of morbidity and mortality [1-3]. It is estimated to be the most common cause of diabetes-related admission to hospital and remains one of the major reasons for lower-limb amputation [4-6]. Systemic antibiotic treatment must be given as early as possible for diabetic foot infections (DFIs), initially on an empirical basis [7-9]. Based on the response to empirical therapy and wound culture and sensitivity results, definitive therapy should be decided [10]. The estimated lifetime risk of a person with diabetes mellitus developing a foot ulcer is 15% to 25%, with an annual incidence of 3% to 10% [11]. Major predisposing factors are peripheral neuropathy, peripheral arterial disease, and impaired immunity [12]. More than one-half of non-traumatic lower extremity amputations are related to DFIs, and 85% of all lower extremity amputations in patients with diabetes are preceded by an ulcer [13]. DFIs cause morbidity, limit mobility, predispose to depression and worsen patients' quality of life.

The most common pathogens in DFI are aerobic gram-positive cocci, mainly *Staphylococcus* species. Methicillin-resistant *Staphylococcus aureus* is present in 10% to 32% of diabetic infections and is associated with a higher rate of treatment failure in patients with DFI [13]. Moderate to severe infections and wounds previously treated with antibiotics are often polymicrobial, including gram-negative bacilli. Anaerobic pathogens are more commonly present in necrotic wounds and infections of the ischemic foot [12]. In the past 20 years, various fluoroquinolone agents have been used successfully for

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Table 1. Age of Participants in the Study (Years)

Mean	45.29
Median	44
Standard deviation	6.57
Minimum	35
Maximum	65

treating DFIs. Moxifloxacin is a newer fluoroquinolone with activity against most aerobic and anaerobic gram-positive and gram-negative bacteria; it is currently approved for the treatment of complicated skin and skin structure infections caused by designated susceptible pathogens, but not specifically for DFI [13].

This study therefore was carried out to assess the efficacy and safety of moxifloxacin for treating DFIs in Pakistani population so that if proven efficacious and safe, it can be recommended to be added in the treatment algorithm of DFIs specifically.

Materials and Methods

After taking ethical approval, an interventional phase IV study was carried out in the department of medicine and diabetic clinic, Liaquat University Hospital, Jamshoro, Hyderabad. The duration of study was from March 2017 till August 2017. A total of 75 patients with DFI who were sensitive to moxifloxacin on culture and sensitivity were included in the study through convenient sampling technique after seeking their informed consent. Patients willing to undergo screening, belonging to either gender, aged 18 or above, with any foot infection with a history of diabetes or any foot infection with a documented foot ulcer with a history of diabetes, and with at least three of the following signs or symptoms of wound infection were included in the study: drainage or discharge, erythema, fluctuance, localized heat or warmth, pain or tenderness, swelling or induration, fever, leukocytosis or 15% immature neutrophils on peripheral blood smear. Patients with human immunodeficiency virus (HIV), vasculitis, connective tissue disorders, received antibiotic therapy for 24 h within last 3 days or needed concomitant systemic antibiotic therapy for treatment of other infections, a DFI with suspected or documented osteomyelitis, unless the infected bone was fully or partially resected and any residual soft tissue infection could be adequately treated with study drug for 14 days, major learning barriers such as visual or hearing impairment or dementia, history of arthritis or history of cardiac arrhythmias including prolonged QT were excluded from the study.

All the demographic and clinical information was collected by using a questionnaire specially designed for the study. After making clinical assessment, all the patients were treated with sequential intravenous/oral moxifloxacin for 14 days. Clinical assessments were made prior to antibiotic therapy, and at the end of therapy on the 14th day. Clinical response was defined as cure when resolution of all acute signs and symptoms related to the infection or sufficient improvement such

Table 2. Participants Profile

Variables (n = 75)	Frequency	Percentage
Gender		
Male	46	61.3%
Female	29	38.7%
Age groups		
≤ 45 years old	22	29.3%
> 45 years old	53	70.7%
Comorbidity		
Hypertension	13	17.3%
Hypertension and IHD	3	4 %
None	59	78.7%
Foot ulcer cured		
Yes	63	84.0%
No	12	16.0%

IHD: ischemic heart disease.

that additional antimicrobial therapy not required and failure was defined as insufficient resolution of the signs and symptoms of acute infection, necessitating additional or alternative antimicrobial therapy. Bacteriologic response was based on the results of cultures of specimens of infected skin or soft tissue or blood. The bacteriologic response was categorized as confirmed eradication (if all of the original pathogens are absent from a post-baseline specimen); presumed eradication (if there was no post-baseline culture but the patient had clinically responded to study therapy); persistence (presence of a baseline pathogen in a post-baseline specimen from a tissue biopsy or needle aspiration of fluid contiguous to the primary infected area in a patient who failed clinical therapy, or from blood); or indeterminate (inability to determine the bacteriologic response to treatment).

The data were entered and analyzed on SPSS version 20.0. Means and standard deviations were calculated for continuous variables whereas frequencies and percentages were generated for categorical variables. Chi-square test was applied to check for associations and the significance level was set at 0.05.

Results

The study results revealed that the mean age of the study participants was 45.29 ± 6.57 years with the range being from 35 to 65 years (Table 1). Totally 61.3% of them were males whereas 70.7% of them belonged to > 45 years age group. Only 17.3% of them had hypertension as comorbidity whereas 4% of them had both hypertension and ischemic heart disease. About 84% of them reported their foot ulcers to be cured at the end of treatment (Table 2; Fig. 1).

The study results further revealed that among gender, age and comorbidity, only age had a statistically significant association with healing of foot ulcers ($P = 0.002$) where patients who belonged to ≤ 45 years age group were more likely to

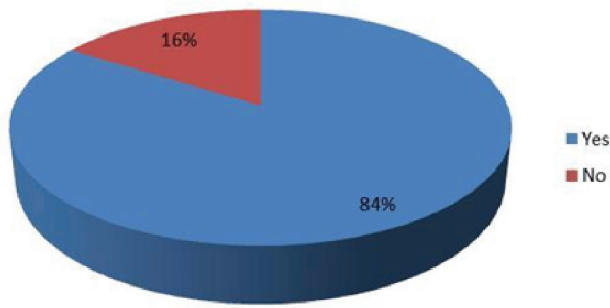


Figure 1. Cure of foot ulcer.

have their foot ulcers cured than those who belonged to > 45 years age group (66.7% vs. 33.3%) (Table 3).

Discussion

The study results revealed that the majority of patients with diabetic foot ulcer were males and > 45 years old. Only 21.3% of them had a comorbidity, either hypertension alone or hypertension with ischemic heart disease, whereas 84% of them reported their foot ulcers to be cured at the end of treatment. Furthermore, among gender, age and comorbidity, only age was found to have a significant association with healing of foot ulcers where younger patients were more likely to have their foot ulcers cured than the older ones.

A majority of the patients with diabetic foot ulcer in the study were males. Likewise, foot ulcers have been reported earlier to develop more frequently in males ($P < 0.001$) [14]. Contrary findings have been reported though, with an earlier study finding the prevalence of diabetic peripheral neuropathy, the cause of subsequent foot ulcers, to be similar in both genders [15]. This difference in findings could be attributed to different study methodologies of both studies.

Interestingly, and as expected, a majority of the patients with diabetic foot ulcer belonged to older age groups. Similarly, old age has been reported earlier to be a risk factor for development of diabetic foot ulcer ($P < 0.001$) [16]. Another

study found age to be an independent predictor of foot ulceration in diabetic patients ($P < 0.01$) [17]. Literature though reports dissimilar findings as well [14]. This difference in findings could be due to different population characteristics of both the studies.

Gender was not found to be significantly associated with wound healing in this study. Likewise, an earlier meta-analysis also reported gender to be unassociated with the probability of wound healing (OR = 1.02; 95% CI, 0.69 - 1.50) [18]. Moreover, the study results found younger age to be positively associated with wound healing. However, literature reported contrary findings with age of the patients reported to be unassociated with the probability of wound healing [18]. This difference in findings could be due to smaller sample size of this study.

The Infectious Diseases Society of America recommends an initial antibiotic course of 1 - 2 weeks for mild soft tissue infections and 2 - 3 weeks for moderate to severe soft tissue infections [3]. In this study, 84% of the patients had their foot ulcers healed by the end of 14-day treatment with moxifloxacin. This finding was highly suggestive of the efficacy of moxifloxacin in the treatment of DFIs. An earlier clinical trial reported intravenous and/or oral moxifloxacin to be as effective as intravenous piperacillin-tazobactam and/or amoxicillin-clavulanate in treating moderate to severe DFIs with similar clinical cure rates (68% vs. 61%) thereby indicating the potential of moxifloxacin as a monotherapy regimen for such infections [19]. Another clinical trial reported similar overall bacteriological success rates in groups of patients treated with intravenous/oral moxifloxacin or intravenous piperacillin-tazobactam followed by oral amoxicillin-clavulanate (71.7% vs. 71.8%) for DFIs [20]. Moxifloxacin has also been shown to exhibit good to excellent antimicrobial activity against most aerobic and anaerobic microorganisms in surgical isolates from patients with intra-abdominal infections and DFIs [21].

The qualitative approach of this study has assured that we have assessed the wide range of patients and their response to the treatment. Nevertheless, the study might not be immune from selection and observer bias. Considering the views and observations of this study and to what extent it would be consistent with the other antibiotic therapies would be revealing to discover more facts about the effective treatment in patients with DFIs.

Table 3. Association of Participants' Characteristics With Healing of Foot Ulcer

Variables (n = 75)	Foot ulcer		P value
	Cured frequency (%)	Not cured frequency (%)	
Gender			
Male	40 (63.5)	6(50.0)	0.286
Female	23 (36.5)	6(50.0)	
Age group			
≤ 45 years old	42 (66.7)	2(16.7)	0.002
> 45 years old	21 (33.3)	10(83.3)	
Comorbidity			
None	51 (81.0)	8(66.7)	0.228
Hypertension and IHD	12 (19.0)	4(33.3)	

Conclusions

Moxifloxacin is effective in treating DFIs and 84% of the diabetic patients in the present study reported the healing of foot ulcers as a result of a 2-week moxifloxacin treatment. Further evaluation of the role of moxifloxacin in the treatment of diabetic foot ulcer is recommended.

Limitation

Due to resources constraints, the study could not be conducted with a larger sample size and using a random sampling technique. In light of the study findings, it is recommended that the role of moxifloxacin in the treatment of diabetic foot ulcer is worth evaluating further as an exceedingly high majority of the patients reported their foot ulcers healed as a result of moxifloxacin treatment in this study.

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Disclosure

Professor Dr. Bikha Ram as the principle investigator had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including adverse effects.

Conflict of Interest

Hilton Pharma Pvt Ltd was involved in organizing, evaluating and interpretation of the data with writing of the manuscript. NM is full-time employees of Hilton Pharma Pvt Ltd. The writers project no encounters of interest. The morality of the revision was not operated for any financial assistance. Furthermore, the observers were provided with the reward for their involvement in examination of the patients and data entry during the study period.

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