A Prospective Observational Study on Diabetic Foot Ulcer and Prevalence of Drug Resistant Organisms

Lavanya Gopinath[1*], D. Harindranath. H.R.[2], Vishnupriya G[3]

[1]Intern, Bangalore Medical College, Bengaluru, Karnataka
[2]Professor and Head of Department, Department of General Surgery, Bangalore Medical College and Research Institute, Bengaluru
[3]II Year MBBS Student, JSS Medical College, Mysore

Abstract:

Introduction: Diabetes mellitus is a chronic disease with chronic micro vascular and macro vascular complications. The major concern at present is the increasing incidence of multi-drug resistant organisms. The problem of multi-drug resistant organisms was poorly studied because of lack of uniform definitions and specific criteria to name an organism as multi-drug resistant. Hence this study was done to analyses the prevalence, risk factors and impact of multi-drug resistant organisms in diabetic foot ulcers at a tertiary care hospital.

Methodology: 150 diabetic patients with foot ulcer were prospectively studied. Detailed clinical history and clinical examination of the ulcer were done for all patients. The microbiological profile was analysed in detail for each patient. Using internationally accepted criteria, the multidrug resistant organisms were identified. Each patient was followed for a period of ten weeks to assess the status of wound healing.

Results: Multi drug resistant organisms were isolated from 99 patients of 150 (66%). 54.8% (153 out of 279) of isolated organisms were multidrug resistant organisms. The commonest organism isolated in our study was Escherichia coli followed by Staphylococcus aureus and Pseudomonas aeruginosa. Poor glycemic control, previous hospitalization, previous history of amputation, previous antibiotic usage, size of ulcer, higher grade of ulcer, and polymicrobial culture, were associated with multidrug resistant infected foot ulcers.

Conclusion: The prevalence of multi drug resistant organisms is alarmingly high in infected diabetic foot ulcers. Recurrent ulcers and higher grade of ulcers are more prone to acquire multi drug resistance. They are associated with longer duration of hospital stay and higher rates of amputations. The study also directs us to manage the diabetic foot ulcers with appropriate antibiotics adhering to the institutional antibiotic policy along with effective glycemic control to decrease the incidence of multi-drug resistant organisms.

Keywords: Diabetic Foot Ulcer, Multidrug Resistant Organisms.

Introduction

Diabetes mellitus is a chronic disease with chronic microvascular and macro vascular complications. India is considered by many, as the diabetic capital of the world. Like in other developing countries, complications of diabetic foot such as ulceration and infections, apart from causing high morbidity and mortality, also have social, and economic ramifications [1,2]. It has beenreported that as high as 15% of all diabetics are prone to develop ulcers in their feet during their lifetime. These can result in severe tissue destruction and can lead to some form of amputation. [3]

Diabetes-related hospital admissions are most pronounced because of infected diabetic foot ulcers. Major and minor (83% and 96% respectively) amputations have been done related to diabetic foot ulcer aggravated by infection4. On the other hand, diabetic foot osteomyelitis development is seen in around 44-68% of patients admitted to the hospital and it is the principal reason for amputation among such patients5.

A study from Nigeria revealed that the burden of diabetic foot ulcers accounts for 24.9% and that the majority of the ulcers are already infected with Wagner grade ≥ 36. In the study from Addis Ababa, diabetic foot ulcer with cellulitis was 12.2%, with toe gangrene at 16.3%, diabetic foot ulcer with foot gangrene at 18.4%, and only 31.1% with foot ulcer7. Another more recent study found that the rate of foot ulcers at Tikur Anbessa

Specialized Hospital was 26%. The major concern at present is the increasing incidence of multi-drug resistant organisms. The problem of multi-drug resistant organisms was poorly studied because of lack of uniform definitions and specific criteria to name an organism as multi-drug resistant. The European center for disease control and prevention has defined criteria, which are applicable universally. Very few studies have been done in India to analyze the prevalence and risk factors of multi-drug resistant organisms in relation to diabetic foot ulcers.

The impact caused by multi-drug resistant organism was least analyzed in Indian literature. Diabetic foot ulcer infection is essentially polymicrobial. Many complications of diabetic foot ulcers are caused by bacterial infections and can be minimized by paying due attention to the identification and control of infections. It is necessary to detect the specific pathogens and their susceptibility pattern to initiate early treatment with the appropriate antibiotics. Hence this study was done to analyze the prevalence, risk factors and impact of multi-drug resistant organisms in diabetic foot ulcers at a tertiary care hospital.

Methodology

This study is a prospective observational study for a period of one year from February 2021 to January 2022 in a tertiary care teaching hospital conducted to find the prevalence, risk factors and the impact of multidrug resistant organisms in diabetic foot ulcers. 150 diabetic patients with foot lesions were included in the study. Diabetic patients with venous ulcers, those patients with neurological disorders and other known causes of neuropathy, other than diabetes related neurological dysfunction will be excluded from the study. Written informed consents were obtained from the patients. Detailed clinical history of the patient and other relevant data were collected using structured case report forms.

Mode of presentation of foot ulcers were classified as grade I – V as per Meggit Wagner Classification System. Presence of neuropathy was detected by assessing vibration sensation using a 128 HTZ tuning fork and a 10g Semmes - Weinstein monofilament. Wound swabs were obtained from the floor of the ulcer, before starting on empirical antibiotic therapy. Direct microscopic examination and aerobic cultures were done by standard methods. The bacteriological spectrum and the sensitive antibiotics were noted for each patient.

For each patient the following details were entered: age, sex, duration of ulcer, duration of diabetes, glycemic control, presence of retinopathy, presence of micro/macro-albuminuria, hypertension, history of smoking, history of previous amputation, duration of hospital stay, interventions (medical and surgical), organisms cultured from ulcer, antibiotic profile and status of ulcer after 10 weeks.

The data was collected and analyzed using SPSS24 software for descriptive statistics. The test variables were compared using Chi-square test for qualitative variables and Student's test for quantitative variables.

Results

In our study 150 diabetic in-patients with foot ulcers were included in the study among which 78% of the patients were 51 years or older, with the average age being 58.21. 74.6% of the patients were males, showing a distinct male preponderance. Almost all the patients had Type II diabetes, with only 4% of them having Type I. Only 19.33% of patients had a good glycemic control, with HbA1c 6 – 7 %. 40% of patients with ulcer had diabetes for less than 5 yrs. In our study 40% of patients had less than 5 years duration of diabetes.

Coming to foot ulcer detail, 68 % of patients had ulcers of less than one month duration. Less than 10% of the ulcers studied had a duration of 2 months or greater. With respect to the size of the ulcer, most were between 4 to 8 cm^2 and 8 to 16 cm^2. A majority had superficial ulcers. Most of the patients had Wagner's grade II, III, or IV ulcers. As far as the site of the ulcer was concerned, 28% were seen in the heel, followed by digits / inter digital areas (21.33 %).

Peripheral arterial disease was seen in 52.66%, retinopathy detected in 24.66 % and albuminuria suggesting nephropathy was found in 48.66%. Majority of the patients had neuropathy. In our study 61.33% were hypertensive. 50% of the patients were smokers and 41.33% alcoholics. History of previous hospital admission in the last one year was seen in 53.33%.

42% of patients required wound debridement and more than a third of the patients underwent some form of amputation. 32 of the 150 patients (21.3%) had only conservative treatment. In 10 percent of patients the ulcer healed completely by 10 weeks.

Microbiological analysis of ulcer was done and a total of 279 organisms were isolated from 150 patients. On an average 1.86 species were isolated from each patient which shows that 88 of the 150 patients had polymicrobial culture. Among the isolates, most were gram negative rods (69.89 %) and almost all the rest were gram positive cocci. Among the isolates, Escherichia coli was the most common one constituting 17.9%, followed by Staphylococcus aureus 17.6%, followed by Pseudomonas aeruginosa (16.5%). Klebsiella pneumonia (8%), Proteus mirabilis (7%) and Enterococcus feacalis (7%) were next common organisms found When we analyzed culture and

sensitivity, multidrug resistance organisms were seen in 99 of the 150 patients.

Table 1: Microbiological spectrum

	Number of patients	Percentage
Culture		
Mono-microbial	62	41.33 %
Poly-microbial	88	58.66 %
Multi Drug Resistance		
Present	99	66 %
Absent	51	34 %

As stated earlier, the frequency distribution of patients with multidrug resistant organisms among the 150 patients included in the study, was 66%, being observed in 99 out of 150 patients. 54.8% (153 out of 279) of isolated organisms were multidrug resistant organisms. Antibiotic resistance was observed in 58.6% (115 out 196) of gram negative organisms compared to 45.78% (38 out of 83) in gram positive organisms. Among the gram-positive cocci, 55% of Staphylococcus aureus species and 47.36% of Enterococcus faecalis species were multidrug resistant. Among the gram negative bacilli, multidrug resistance was noted in 78% of Escherichia coli, 74% of Pseudomonas aeruginosa, 70% of Proteus mirabilis and 61.53% of Acinitobacter baummanni, with lower percentages in other isolates.

Listing the multidrug resistant organisms isolated, MDR Pseudomonas aeruginosa was found to be the highest (34/153), followed by ESBL Escherichia coli (33/153). However, when the number of ESBL + Amp C Escherichia coli is considered together along with ESBL Escherichia coli, this would be the highest.

Table 2: Frequency distribution of multidrug resistant organisms

Organisms	N (%)	Multi drug resistance (%)
Gram- Positive Cocci		
Enterococcus faecalis	19 (6.8%)	6%
Staphylococcus aureus	49 (17.6%)	18%
Gram-Negative Rods		
Acinetobacter baumannii	13 (4.7%)	5.3%
Citrobacter diversus	9 (3.2%	2%
Enterobacter aerogenes	8 (2.9%)	2%
Escherichia coli	50 (17.9%)	26%
Klebsiella pneumoniae	24 (8.6%)	6.6%
Proteus mirabilis	20 (7.3%)	9.3%
Pseudomonas aeruginosa	46 (16.5%)	22.6%

We also analyzed the factors associated with drug resistant infections like age, sex. Depth and nature of ulcer. Glycemic control and grade of ulcer. Results of the univariate analysis showed, poor glycemic control, previous hospitalization, previous antibiotic usage, size of ulcer, higher grade of ulcer, peripheral vascular disease, neuropathy and polymicrobial culture, was significantly associated with MDRO infected foot ulcers.

The association of factors like age and sex of the patient, socio-economic status, type and duration of diabetes, presence of nephropathy, hypertension, smoking, alcohol, site andduration of the ulcer with multi drug resistant infected ulcers were statistically insignificant. Similarly he means duration of hospital stay in patient who had drug resistant infections was 15.36 days when compared to 8.88 days in non-resistant infections. We further followed the patients for 10 week's time the patients were grouped as healed and non-healed group. Healed group included the patients whose ulcers were completely healed and reduced in size. The rest were in the non-healed group. 60 patients were in healed group and 90 were in the non-healed group.

Discussion

This study presents a comprehensive clinical and microbiological profile of infected diabetic foot ulcers, especially in relation to multidrug resistant organisms. In our study the foot ulcers were more prevalent in the fifth and sixth decade of life. The average age of the patients with foot ulcer was 58.21 ± 9.3 years, which is similar to the age prevalence described in other Indian studies [2].

The foot ulcers were more common in male than female, which may be due to higher level of manual work and outdoor activity among male when compared to females. Similar gender preponderance was observed in studies conducted in India [2]. In our study, most of the patients with ulcer had diabetes of less than 5 years duration. This observation was in contrast with other studies conducted in the country [2] which showed more ulcers occurring in patients having diabetes for longer duration. This might well reflect the profile

of all diabetic patients visiting the hospital, and will need an in depth examination to ascertain this.

Most of the patients (68%) had ulcers of less than 1 month duration which is similar to the observations from a north Indian study [8]. But according to another north Indian study [2] most ulcers presented to hospital after 3 months. An early presentation is often due to the fact that ulcers with acute onset often have systemic symptoms which bring the patients to the hospital, while in chronic ulcers the symptoms are mild and localized.

Comparable with the literature [2], most of the patients in the present study had poor glycemic control. Poor glycemic control is associated with greater degree of microvascular complications. Majority of the patients in our study had higher grade of ulcers (Wagners grade III or worse) similar to the other north Indian studies [2,8]. In the present study the neuropathy was seen in 77.33% of the diabetic foot ulcer patients. The other studies reported from India [2, 8] showed a similar high prevalence (86.2%, 66.6%).Whereas studies done in other countries showed a varied prevalence.

The bacteriological evaluation of diabetic foot ulcer from our study showed that the gram-negative organisms were found have a higher occurrence than gram positive organisms in the ratio 2.3:1. Some of the other Indian studies [2,8] also showed a higher occurrence of gram-negative organisms with ratios of 1.5: 12, and 1.3: 18. Comparatively our study did show a higher ratio. A study from Malaysia9 also showed the same. However, most of the western literature showed a predominance of gram-positive organisms as supposed to gram negative organisms [10,11] this could be partly due to differences in the causative organisms occurring over time, geographical variations, or the types and severity of infection included in the studies [12]. Diabetic foot infection are usually polymicrobial in nature which is well documented in literature. In our study, 58.66% of ulcers had polymicrobial culture. Similar observations were found in other Indian studies [2, 8, 13] and western studies [12, 14].

The commonest organism isolated in our study was Escherichia coli followed by Staphylococcus aureus, Pseudomonas and Klebsiella pneumoniae. This is similar to the observations from a south Indian study [13]. But most of the other studies from India [2,8] and other countries [9,12] showed Staphylococcus aureus as the commonest isoloate from diabetic foot ulcers.

In our study, the third predominant organism was Pseudomonas (16.5%). Two other studies [15] also showed higher recovery of Pseudomonas. The gram negative bacilli, Pseudomonas, which were once considered as normal flora of the skin, may cause severe tissue damage in diabetics and should

never be regarded as insignificant in diabetic foot ulcers

In our study 66% of the ulcers grew multi-drug resistant organisms and 54.8% of isolated organisms were multi drug resistant. Apart from the multi-drug resistant organisms like MRSA, ESBL, and VRE which were extensively studied in literature, other groups of organisms like MDR Pseudomonas, Acinetobacter, Enterococcus, Enterobactereciae were also identified in our study. The higher prevalence of multidrug resistant organisms was also observed in another north Indian study [2]. The higher degree of antibiotic resistance in tertiary care hospitals, could be because, with widespread usage of broad-spectrum antibiotics, there occurs selective survival of drug resistant organisms.

Our study showed that 75% of all drug resistant isolated were gram negative organisms. It is a fact that higher degree of antibiotic resistance is observed in gram negative organisms when compared to gram positive organisms. This is because gram negative organisms have a unique outer membrane which does not allow certain antibiotics to penetrate. 55% (27 out of 49 isolates) of Staphylococcus aureus isolated from our study were methicillin resistant. A similar observation was found in the north Indian study 8 which showed 57.1%, and in the south Indian study alluded to earlier, it was 42% 16. MRSA was seen in 18% of the patients in our study. These results were similar to the previous Indian studies. 17.5% and 23.3% were seen respectively in the two north Indian studies [2,8]. With regard to the gram negative organisms in our study, E.coli showed greater antibiotic resistance, followed by Pseudomonas aeruginosa. 78% of isolated E. coli and 74% of isolated Pseudomonas were multi-drug resistant.

In our study, univariate analysis showed that, poor glycemic control, previous hospitalization, previous history of amputation, previous antibiotic usage, size of ulcer, necrotic ulcer, recurrent ulcers, higher grade of ulcer, presence of osteomyelitis, presence of retinopathy, peripheral vascular disease, neuropathy and polymicrobial culture, were significantly associated with multi drug resistant infected foot ulcers. Another study from India [12] showed that presence of neuropathy and ulcer size > 4 cm2 were significantly associated with multi-drug resistant organism infections. Previous hospitalization was again significantly associated in another study from France [17].

In our study, the presence of MDRO in foot ulcers significantly increased the duration of hospital stay and the associated cost. The mean duration of hospital stay in MDRO infected ulcer group was 15.36 days and that of non-MDRO group was 8.8 days. Interestingly, the other two Indian studies

Gadepalli et al [2], Mohammed zubair8 found no difference in the duration of hospital stay with MDRO infected ulcers. We also made an effort to analyze the factors involved in determining the healing time of infected foot ulcers. We found by multi-variate analysis, the factors which determine the wound healing were, the age, presence of peripheral arterial disease, osteomyelitis, nephropathy, interdigital ulcers, poor glycemic control and grade of ulcer.

Conclusion

The prevalence of multi-drug resistant organisms is alarmingly high in infected diabetic foot ulcers. Recurrent ulcers are more prone to acquire multi-drug resistant organisms. Higher grade of ulcers are more prone to acquire multi-drug resistant organisms. Escherichia coli is commonest isolate from all the ulcers. ESBL Escherichia coli is the commonest multi-drug resistant organism derived from infected diabetic foot ulcer. Multi-drug resistant organisms in diabetic foot ulcers are associated with longer duration of hospital stay.

There is a paucity of data regarding the actual burden of multi-drug resistant organisms in diabetic foot ulcers in our country. The findings from the present study suggest that prospective multicentre studies have to be done to assess the nationwide prevalence and to frame an effective antibiotic policy. The study also directs us to manage the diabetic foot ulcers with appropriate antibiotics adhering to the institutional antibiotic policy along with effective glycemic control to decrease the incidence of multi-drug resistant organisms.

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