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Progression of Infected Diabetic Foot Ulcers to Amputation Cases; A Comparative Study of Meropenem vs Linezolid Treatments

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ABSTRACT

Objective: To study the effectiveness of Linezolid in comparison to Meropenem for diabetic foot disease in terms of decreasing the number of amputations and infection clearance.

Study Design: Quasi Experimental Study.

Place and Duration of Study: Department of General Surgery, Combined Military Hospital, Rawalpindi Pakistan, from Jan 2020 to Apr 2021.

Methodology: A total of 188 patients suffering from diabetic foot disease who met the inclusion criteria were included. Patients were divided into two Groups, Group A received Linezolid while Group B received Meropenem at standard doses. Patients were evaluated after 10 days of antibiotic therapy. All patients received testing for pre- and post-treatment C-reactive protein levels and progression to amputation within 6 months which were checked across both Groups for improvement as an indicator of treatment effectiveness. Data was analyzed by SPSS 26.0.

Results: The mean C-reactive protein level on enrollment for Group A was 84.71±27.29 mg/L, while the same was 83.33±26.74 mg/L in Group B (p=0.73). These levels were 6.84±5.5 mg/L and 8.94±8.73 in Groups A and B, respectively, post-treatment (p=0.049). Treatment was declared successful in 84(89.4 %) with Linezolid, while in 72(76.6%) on Meropenem (p=0.02). A total of 6(6.4%) patients underwent amputation at 6 months in the Linezolid Group versus 2(2.1%) in the Meropenem Group, p=0.14.

Conclusion: Linezolid is an effective drug for which can be used in the management of diabetic foot disease with different clinical manifestations. It demonstrates superiority to Meropenem in terms of clearance of infection and progression to amputation.

Keywords: Amputations, Diabetic Foot Disease, Linezolid, Meropenem.

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INTRODUCTION

Diabetes mellitus is a disease with a prevalence of 11.77% in Pakistan, a fairly significant number.[1] The yearly incidence of foot ulcers in diabetics ranges between 9.1 and 26.1 million, globally, and approximately 15-25% of all diabetic patients develop a foot ulcer during the course of their lives.[2,3] Poorly controlled diabetes and persistent hyperglycemia lead to the development of foot ulcer formation. These ulcers serve as a nidus of infection which, if not promptly treated, may result in local tissue ischemia and death and a constant source of sepsis endangering the life of the individual thus, resulting in the requirement for amputation.[4,5] The multipronged management of diabetic ulcers require good glycaemic control, apt use of antibiotics, cure of vasculopathy, moist wound dressings, exudate control and surgical debridement.[6] Antibiotics form the mainstay of treatment with the choice of regimen may be aimed at the most likely infective agent, or having a culture-proven pathogen, local antibiotic resistance patterns, disease severity, history of the patient including previous antibiotics, co-morbidities, financial status and drug availability.[7]

Meropenem is a drug which belongs to the carbapenem Group, has a wide-spectrum of activity, which includes both Gram-positive and Gram-negative bacteria (even some resistant ones), as well as against acid-fast bacilli and anaerobic organisms. Having effective activity against number of organisms, it is recommended both empirically and as a targeted agent in the treatment of diabetic foot.[8] Linezolid, an oxazolidinone, is also getting its ever-increasing share as an anti-microbial agent for infected wounds in patients who are suffering from diabetes mellitus. It is

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highly beneficial in treating Gram-positive organisms, especially those resistant ones e.g glycopeptide-resistant gram-positive bacteria as well as methicillin-resistant Staphylococcus aureus, and thus the importance of this drug therapy cannot be underrated in diabetic skin and superficial soft tissue disease.[9,10]

Diabetic foot disease is a pathology encasing a hefty load of surgical patients, and the incidence is deemed to rise as the global diabetes mellitus pandemic worsens. As such, early and prompt institution of the appropriate antibiotic is paramount. The ever-changing challenge of antibiotic resistance in bacteria presents a constantly evolving landscape, which forms an uphill task to the treating clinician. Thus, it is crucial to select the appropriately active antibiotic regimen. This study was conducted with the view of understanding the role of Meropenem and linezolid, two important weapons in the surgeons repertoire, in the management of this increasing common disease.

METHODOLOGY

This was a Quasi experimental study conducted between Jan 2020 to Apr 2021 in the Department of General Surgery, Combined Military Hospital, Rawalpindi Pakistan, on 188 patients diagnosed with diabetic foot ulcers, chosen via non-probability consecutive sampling, after informed consent. The study was formally approved by ethical committee of CMH Rawalpindi vide IRB no. EC/25/2 dated 3 May 2021. The WHO sample size calculator was used to calculate the sample size, keeping a level of significance (α) of 10%, power of the test (1–β) of 90%, anticipated population proportion 1 of 0.87 placed in Group A, and anticipated population proportion 2 of 0.72 placed in Group 2.[11]

Inclusion Criteria: Patients between the ages of 18-75 years, with ASA class II to IV, who had diabetic foot disease were included, which was defined by clinical signs and symptoms and included septic ulcers, cellulitis, septic arthritis, osteomyelitis, abscess formation or paronychia.

Exclusion Criteria: Patients who had undergone previous surgical intervention for the same episode, another focus of infection, history of autoimmune disease, had critical limb ischemia, received antibiotic therapy within 1 week of enrollment, were pregnant or lactating, or allergic to the drugs under study were excluded.

All patients underwent evaluation with a thorough history taking, clinical examination and investigations, and were tested for c-reactive protein levels (CRP) on enrollment. Culture specimens were drawn from all patients on admission, via either debridement, biopsy or curettage for open wounds and fine-needle aspiration or biopsy for closed wounds on enrollment. Any patient with a resistant pathogen cultured subsequently was withdrawn from the study. Patients were divided into two Groups: Group A received Linezolid at a dose of 600 mg twice daily for 10 days while Group B received Meropenem thrice daily for 10 days. All patients received a further CRP level test on completion of antibiotic course, and a combination of a CRP level of less than 10 mg/L and clinical improvement was taken as an indication that the infection had been cleared. All patients were followed for six months for progression to amputation. All patients received local wound care such as dressing and debridement as needed.

Data was analyzed using SPSS version 26.0. Mean and SD was calculated for quantitative variables like age, body mass index (BMI), duration diabetes, CRP at start of treatment and CRP at the end of treatment. Qualitative variables like gender, ASA class, type of infection, whether culture was positive or not and progression to amputation were recorded in terms of frequency and percentage. Chi square test was applied for all qualitative variables while independent samples t test was applied to all quantitative variable. The *p*-value of ≤0.05 was considered significant.

RESULTS

A total of 188 patients were studied which included 87(46.3%) males and 101(53.7%) females with a male to female ratio of 1:1.16. The mean age of the sample was 51.04±14.95 years. The pre-treatment characteristics of patients are shown in Table-I. The mean BMI of the sample of 25.31±3.57 kg/m2. The mean duration of diabetes mellitus was 15.66±5.48 years. Patients who were allocated to ASA II numbered 68(36.2%), 106(56.4%) landed in ASA III and 14(7.4%) patients had characteristics which placed them in ASA IV scale. A total of 74(39.4%) suffered from cellulitis, 81(43.1%) had developed foot ulcers while 12(6.4%), 10(5.3%), 7(3.7%), and 4(2.1%) had abscess formation, paronychia, septic arthritis and osteomyelitis, respectively. None of the pre-treatment variables had a statistically significant difference across both Groups.

Results for post-treatment evaluation and statistical significance are shown in Table-II. A total of 156(82.9%) patients were treated successfully across both Groups, while only 37.2% of patients had a positive culture sample. Linezolid appeared to be more effective in the treatment of diabetic foot disease in terms of treatment success (p=0.02) as well reduction in CRP levels post-treatment (p=0.049). The rate of progression to amputation was similar across both Groups i.e. there was no statistical difference (p=0.14).

Table-I: Patient Pre-Treatment Characteristics

Variable	Group A	Group B	*p*-value
Gender			
Male	41(43.6%)	46(48.9%)	0.46
Female	53(56.4%)	48(51.1%)	
Age (years)	53.14±14.43	48.95±15.23	0.054
Body Mass Index (kg/m2)	25.52±3.36	25.09±3.37	0.40
Diabetes Duration (Years)	15.50±5.67	15.82±5.29	0.69
American Society of Anesthesiology (ASA) Scale			
ASA II	36(38.2%)	32(34.0%)	0.82
ASA III	51(54.4%)	55(58.6%)	
ASA IV	7(7.4%)	7(7.4%)	
Type Of Infection			
Cellulitis	34(36.2%)	40(42.6%)	0.58
Foot Ulcer	39(41.6%)	42(44.7%)	
Abscess Formation	7(7.4%)	5(5.3%)	
Paronychia	7(7.4%)	3(3.2%)	
Septic Arthritis	5(5.3%)	2(2.1%)	
Osteomyelitis	2(2.1%)	2(2.1)	

Table-II: Treatment Results

Variable	Group A	Group B	*p*-value
Treatment Success			
Yes	84(89.4 %)	72(76.6 %)	0.02
No	10(10.6 %)	22(23.4 %)	
Culture Positive			
Yes	31(32.9%)	39(41.5%)	0.22
No	63(67.1%)	55(68.5%)	
CRP Pre-Treatment (mg/L)	84.71±27.29	83.33±26.74	0.73
CRP Post-Treatment (mg/L)	6.84±5.5	8.94±8.73	0.049
Amputations	6(6.4%)	2(2.1%)	0.14

DISCUSSION

We studied a population that was predominantly female. Female to male ratio was 1.16:1 with females accounting for 53.8% of the population, the difference in gender was not statistically significant (p=0.46). Lipsky et al conducted a similar study and reported on a population that was predominantly male: 71.2%, the difference occurred likely because the study was in a veterans' affairs hospital, with a preponderance of male patients.[11] It is quite evident that the risk factors for development of diabetic foot progressing to amputation differ between genders with females having a greater risk if they are old, have calluses or neuropathy, while risk factors for men include insulin use, ulcer formation and joint stiffness.[12]

The mean age of our sample was 51.04±14.95 years and the difference across the Groups did not approach statistical significance, (p=0.054). Wilcox et al studied a population with a mean age of 54±19 years which was similar to our study.[13] Lipsky et al studied a population of which had an older mean age of 62.5±12.5 years.[11] The difference in the studies may be attributable to better glycaemic control and podiatric care in the western study. We studied a population with a mean duration of diabetes of 15.66±5.48 year (p=0.69). Research has shown that increasing duration of diabetes mellitus is associated with a greater risk of developing diabetic foot disease.[14]

We documented the type of infection our patients presented with: Cellulitis occurred in 74(39.4%) patients, foot ulcers in 81(43.2%) which was a majority, abscess formation in 12(6.4%), paronychia 10(5.3%), septic arthritis 7(3.7%) and osteomyelitis in 4(2.1%) patients. The difference in complications across both Groups was not statistically significant: p=0.58. The majority of cases in other studies have also reported a preponderance of foot ulcers: a frequency of 33% ulcers, 19.1% gangrene, 9.6% cellulitis/abscess formation, 6.8% osteomyelitis, and 0.5% paronychias were reported by Fincke *et al.*,[15] while a Pakistani also reported a majority with ulcer formation in their diabetic foot study.[16]

Treatment was declared successful in 84(89.4%) of patients treated with Linezolid, while it was successful in 72(76.6 %) of patients treated with Meropenem, the difference between the Groups was statistically significant, p=0.02, in our study. In Lipsky et al Linezolid successfully cleared infections in 81% of cases while β-lactam antibiotics shown efficacy in 72% of cases.[11] Linezolid has good activity against gram positive organisms but gives poor coverage against gram negative organisms. In one study, the majority of diabetic foot infections were caused by Gram-negative organisms: 56%, versus 44% caused by Gram-positive organisms, however, in this study, Staphylococcus aureus was found to be the most common infective pathogen: 28% of all cases.[17] Nageen *et al.*, reported that 95% of the organism in their sample infecting diabetic foot ulcers were susceptible to Meropenem, as

most of the organisms infecting foot ulcers in their study were Gram-negative. Conversely, Wu *et al.*, reported a higher incidence of Gram-positive organisms i.e. 54%.[18] Thus, local infection patterns play a big part in successful empirical treatment of diabetic foot. We report a total of 8(4.3%) patients progressing to amputations, the difference between the Groups was not statistically significant (p=0.14).

Linezolid can be used effectively for the varied manifestations of diabetic foot disease. It demonstrates similar or better efficacy when compared to already established antibiotics such as carbapenems/β-lactam antibiotics when it comes to infection clearance as well as progression to amputation in our study. However, this may be dependent on local causative organisms and antibiotic susceptibilities. Regardless, the drug is gaining rapid popularity for its good gram-positive cover, and minimal emergence of resistance. Our study did not look at the antibiotic susceptibility of infective organisms in diabetic foot disease: resistant infections were automatically excluded, furthermore adverse effects associated with the drugs themselves were also not studied, and as such further research is required into these two factors to see how they might play a role in antibiotic selection for patients with diabetic foot disease.

CONCLUSION

Linezolid is a safe and effective drug which can be used for infections of the foot occurring in diabetic patients. It shows marginally statistically improved activity when compared to Meropenem when it comes to these infections. Moreover, it has the added versatility of being available in both oral and intravenous formulations which can translate into the benefit of out-patient administration and improved compliance which can help in improved infection clearance rates resulting in a decrease in morbidity, mortality and financial costs as well as an improvement in quality of life.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MZF & KM: Data acquisition, data analysis, critical review, approval of the final version to be published.

MAZ & SSC: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MFS & TMQ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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