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LINEZOLID VERSUS CIPROFLOXACIN - METRONIDAZOLE IN THE TREATMENT OF DIABETIC FOOT INFECTIONS

Naresh Thondepu*, P. Ranjith Kumar, P. Suneetha, C. K. Dhanapal and R. Manavalan

Division of Pharmacy Practice, Department of Pharmacy, Annamalai University, Annamalai Nagar, Chidambaram, Tamilnadu, India.

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ABSTRACT

Diabetic Foot Infections are a common cause of morbidity in both the community and the hospital. Diabetic Foot Infection is classified as complicated if the infection has spread to the deeper soft tissues, if surgical intervention is necessary, or if the patient has a co morbid condition hindering treatment response (e.g., diabetes mellitus or human immunodeficiency virus). The prospective comparative study was conducted in the surgery department attach to medical college situated in Tamilnadu, with 1210 bedded Hospital. The purpose of this study was to compare use of linezolid with ciprofloxacin-metronidazole in the treatment of proven gram positive and gram negative complicated diabetic foot infections requiring hospitalization. In current study Wagner's ulcer grade classification scale was used to find out the degree and severity of foot infections on basis of the scale the treatment was selected. Majority of the patients with foot problems were of Grade II to Grade IV. The overall mean treatment was longer for control group (Ciprofloxacin-Metronidazole treated) than for the test group (Linezolid treated). The mean duration of treatment was 10.9±5.3 days in Test Group and 11.8±4.9 days in Control group. The treatment duration was significantly ($P<0.01$) shorter for diabetic foot infection patients in Test (Linezolid) group. Linezolid showed more therapeutic efficacy than combination of Ciprofloxacin and Metronidazole. A Significant difference ($P<0.01$) was observed in test group (Linezolid treated) compared to the control group in diabetic foot infections. Drug related adverse events more in control group than test group were observed.

Keywords: Wagner's Ulcer Grade Classification, Linezolid, Ciprofloxacin, Metronidazole.

INTRODUCTION

Infections usually represents the ulceration and destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limb of the leg. (WHO,1985). The term "diabetic" foot indicates that there are specific qualities about the feet of people with diabetes that sets this disease apart from other conditions that affect the lower extremity" (Habershaw & Chzran, 1995). Foot infections are the most common problems in people with diabetes. Diabetic foot infections are infections that can develop in the skin, muscles, or bones of the foot as a result of the nerve damage and poor circulation that is associated with diabetes. People who have diabetes have a greater than average chance of developing foot infections because a person who has diabetes may not feel foot pain are discomfort, problems can remain undetected until fever, weakness, or other signs of systemic infection appear. As a result, even minor irritations occur more often, heal, more slowly, and or more likely to result in serious health problems.[1] In terms of the infecting microorganisms and the likelihood of successful treatment with antimicrobial therapy, acute osteomyelitis in people with diabetes is essentially the same as in those without diabetes. Chronic osteomyelitis in patients with diabetes mellitus is the most difficult infection to cure. Adequate surgical debridement, in addition to antimicrobial therapy, is necessary to cure chronic osteomyelitis. Patients with diabetes also can have a combined infection involving bone and soft tissue called fetid foot. This extensive, chronic soft tissue and bone infection causes foul exudates and usually requires extensive surgical debridement and or amputation. Except for chronic osteomyelitis, infections in patients with diabetes are caused by the same microorganisms that can infect the extremities of those without diabetes.

In general, people with diabetes have infections that are more severe and take longer to cure than equivalent infections in other people. The epidemiology of the diabetic foot infections was 252 million people across the world. Foot infections increases drastically in hospital stays. In this 4% of diabetics develop foot ulcer annually, 25% in lifetime, 45-75% of all lower extremity amputations are in diabetics, 85% of these preceded by foot ulcer, two-thirds of elderly patients undergoing amputation do not return to independent life, studies have shown less cost for saving a limb than amputation.

Diabetic foot infections result from the simultaneous action of multiple contributing causes. The major underlying causes are noted to be peripheral neuropathy and ischemia from peripheral vascular disease.[2] More than 60% of diabetic foot ulcers are the result of underlying neuropathy. The development of neuropathy in affected patients has been shown in animal and in vitro models to

***Corresponding Author:**
Naresh Thondepu
Division of Pharmacy Practice, Department of Pharmacy,
Annamalai University, Annamalai Nagar, Tamilnadu, India.
Contact no: +91-9994338657
Email: naresh99pharma@gmail.com

be a result of hyperglycaemia induced metabolic abnormalities. Peripheral arterial disease (PAD) is a contributing factor to the development of foot ulcers in up to 50% of cases. It commonly affects the tibial and peroneal arteries of the calf. Endothelial cell dysfunction and smooth cell abnormalities develop in peripheral arteries as a consequence of the persistent hyperglycaemic state. There is a resultant decrease in endothelium-derived vasodilators leading to constriction.

Diabetic foot infections can be measured by one of the most popular systems of classification is the Wagner Ulcer Classification System, which is based on wound depth and the extent of tissue necrosis and also different classifications available like University of Texas wound Classification system but in our study we followed the Wagner's ulcer classification system, it explain in the Table **1**.

Table No. 1 Wagner's Ulcer Classification System

GRADE	LESION
Grade 0	High risk foot and no ulceration
Grade 1	Superficial ulcer
Grade 2	Ulcer extension involving ligament, tendon, joint, capsule, or fascia with no abscess or cellulitis
Grade 3	Deep ulcer with abscess or Osteomyelitis
Grade 4	Gangrenous Patches, partial foot gangrene
Grade 5	Extensive gangrene of foot

Linezolid is a synthetic antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics. It is a novel oxazolidinone agent that has demonstrated activity against antibiotic susceptible and antibiotic resistant gram positive and gram negative organisms.[3,4] The oral form of linezolid is 100% bioavailable,[5-7] allowing for an early switch from i.v. to oral therapy. Linezolid has a unique mechanism of action whereby it selectively binds to the 50S ribosomal unit and prevents cross-resistance with other antimicrobial agents[8]. The main indications of linezolid are infections of the skin and soft tissues, although off-label use for a variety of other infections is becoming popular. When administered for short periods, linezolid is a relatively safe drug; it can be used in patients of all ages and in people with liver disease or poor kidney function. Common adverse effects of short-term use include headache, diarrhoea, and nausea. Long-term use, however, has been associated with serious adverse effects; linezolid can cause bone marrow suppression and low platelet counts, particularly when used for more than two weeks. If used for longer periods still, it may cause peripheral neuropathy (which can be irreversible), optic nerve damage, and lactic acidosis (a build-up of lactic acid in the body), all most likely due to mitochondrial toxicity.

Ciprofloxacin is a fluoroquinolone also called 4-quinolone or quinolone carboxylic acid. It is one of the second generations of quinolones, which have substantially enhanced antibacterial activity. It has good tissue penetration and high potency against most Gram-negative pathogens with lesser activity against staphylococci .In general, ciprofloxacin has 2 to 4 fold greater antimicrobial potency than norfloxacin and considerably greater activity than cephalosporins and amino glycoside against Gram-negative bacilli.[9]

Metronidazole is an antibiotic effective against anaerobic bacteria and certain parasites. Anaerobic bacteria are single-celled, living organisms that thrive in environments in which there is little oxygen (anaerobic environments) and can cause disease in the abdomen (bacterial peritonitis), liver (liver abscess), and pelvis (abscess of the ovaries and the Fallopian tubes). Giardia lamblia and ameba are intestinal parasites that can cause abdominal pain and diarrhoea in infected individuals. Metronidazole selectively blocks some of the functions within the bacterial cells and the parasites resulting in their death.

METHODOLOGY

A prospective and comparative study was carried out and patients were randomly selected from surgery ward in Rajah Muthiah Medical College and Hospital, Chidambaram, having 1210 bedded. Most of the Diabetic Foot Infection patients are the concurrent users of different antibiotics to treat the Diabetic Foot Infection.

The sample comprised 108 patients who met the initial inclusion criteria. Patients were selected for the study during the study period of 1 year from July 2009 to June 2010. Prescription data were collected from medical records that contains all the prescriptions for each patient, providing information about the drug prescribed, its dosage and duration, the diagnosis of the patient, and all these details collected for analysis from diabetic foot infection patients been diagnosed and treated between July 2009 to June 2010. In current study, it was observed that diabetic foot infection patients were referred broadly to use different class of antibiotics in different group of patients.

For evaluation purposes the patients were divided into two groups i.e., Test group and control group. In Test group of patients received Linezolid 600mg IV for every 12 hours initial 2 days and switch to oral therapy up to 21 days, and Control group of patients receive combination of ciprofloxacin 500mg (oral) and metronidazole 500mg IV for every 12 hours up to 21 days. Improvement in patient condition was compared on the basis of clinical findings and investigations.

In current study, patients in both test and control group are treated for diabetic foot infections and monitored (both test and control group) using 'pus culture' 'wound status' (pus healing granulation), glycaemic control. In contrast, culture monitoring was done regularly by collecting swabs on Day 0, Day 3, Day 7, Day 10, Day 14 and Day 21. All the patients (both test and control groups) are closely monitored and recorded for the duration of stay in hospital in both groups.

Inclusion Criteria

- Patients from diabetic out patients.
- Patients with age of above 30 years.
- Patients with diabetes with diabetic foot infections.
- Patients with the complaints of hypertension, Bronchial asthma, Pulmonary Tuberculosis with clinical diagnosis of diabetes were included.

Exclusion Criteria

- Patients below the age of 30 years.
- Patients without diabetes.
- Patients who are not willing to participate in the study.
- Patients with Type I diabetes.
- Patients with diabetes Type II without foot ulceration.

RESULTS

Table **2** shows that in current study male population was 70 (64.81%) and female was 38 (35.19%). Hence in comparison with other study data male population is found to be more predominant compared to females. Test

group male population was 26 (54.17%) and female was 22 (45.83%). Control group male population was 44 (73.33%) and female was 16 (26.66%).

Table No. 2 Gender Distribution in Test and Control Groups

Gender	Test Group Patients		Control Group Patients		Total Patients	
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)
Male	26	54.17%	44	73.33%	70	64.81%
Female	22	45.43%	16	26.66%	38	35/19%

Table **3** shows majority of the patients fall between 32.4% (51-60) age group and mean age of these patients were 55 ± 5 years. This signifies that foot problems are common in the age group between 51-60 years. In comparison with above studies the mean age of our population are the same. In test group majority of patients fall between 35.41 % (61-70) age group and mean age of these patients were 65±5 years. In control group majority of patients fall between 35 % (51-60) age group and mean age of these patients were 55 ± 5 years.

Table 3. Age Distribution in Test and Control Groups

	Age Distribution of Patients		Test Group Patients		Control Group Patients	
Age in Years	No. of Patients	percetage	No. of Patients	percetage	No. of Patients	percetage
30-40	9	8.33	4	10.41	4	6.66
41-50	20	18.51	9	18.75	5	18.33
51-60	35	32.4	10	29.16	15	35
61-70	34	31.4	14	35.41	12	28.33
71-80	9	9	3	6.25	4	10
81-90	1	1	0	0	1	1.66

Table **4** explains with diabetic foot ulceration majority of the study population had a duration of diabetes for 5.2 years which signifies that as the duration of diabetes increases, the foot is prone for problems. In comparison to above studies patients with diabetes tend to develop foot ulceration little earlier.

Table 4. Patients with Diabetes Mellitus (in years)

Diabetes Duration (years)	Number of patients	Percentage
0-2	35	32.4
2-4	20	18.51
4-6	31	28.70
6-8	7	6.48
8-10	8	7.40
10-12	1	0.92
12-14	2	1.85
14-16	2	1.85
18-20	1	0.92
28-30	1	0.92

Table **5** shows the Wagner's grades, Grade 0 (5.55%), grade I (6.48%), grade II (36.11%), Grade III (23.14%), grade IV (27.77%), grade V (0.9%). In test group Grade 0 (8.33%), grade I (10.41%), grade II (43.75%), Grade III (25%), grade IV (25%), grade V (0%) and control group distribution of grades are Grade 0 (3.33%), grade I (3.33%), grade II (30%), Grade III (21.66%), grade IV (30%), grade V (1.66%). This signifies that the grade II to IV is common grades. Majority of patients with diabetic foot infection were present within this grade. The importance of grading is, with increase in grade the disease is worsening and prognosis is poor. So grading the diabetic foot ulcer is important.

Table 5. Grade of Diabetic Foot Infections in Test and Control Groups

Wagner grade	Diabetic foot infections		Test group		Control group	
	No of Patients	%	No of Patients	%	No of Patients	%
G0	6	5.55	4	8.33	2	3.33
GI	7	6.48	5	10.41	2	3.33
GII	39	36.11	21	43.75	18	30
GIII	25	23.14	12	25	13	21.66
GIV	30	27.77	12	25	18	30
GV	1	0.9	0	0	1	1.66

Table **6** shows the test group *Klebsiella* (12.5%), *Proteus* spp. (18.75%), *Streptococcus aureus* (31.25%), *E. coli* (22.91%), *Pseudomonas* spp.(20.83%), *Staphylococcus aureus* (20.83%). In control group *Klebsiella* (18.33%), *Proteus* spp. (21.66%), *Streptococcus aureus* (33.33%), *E. coli* (26.66%), *Pseudomonas* spp. (10%), *Staphylococcus aureus* (16.66%). By comparison of both groups the common organisms were found to be *Streptococcus aureus*, *E-coli* and *Staphylococcus aureus*.

Table 6. Distribution of Organism in Test and Control Groups

Microorganism	Test Group		Control Group	
	No. of patients	%	No. of Patients	%
Klebseilla	6	12.5	11	18.33
Proteusmirabblius	9	18.75	13	21.66
Streptococcus species	15	31.25	20	33.33
E-coli	11	22.91	16	26.66
Pseudomonas	6	12.5	6	10
Staphylococcus aureus	10	20.83	10	16.66

Table **7** shows the drug response on organisms of test group was Good (68.75%), Fair (6.25%), Poor (25%) and control group was Good (58.33%), Fair (13.33%), Poor (30%). In current study, we found that good response was obtained when test drug (Linezolid) was administered compared to control drug (Ciprofloxacin and Metronidazole). The Percentage sensitivity to organisms was found to be in test group 68.75% and control Group 61.66%. In current study the eradication rates of organism of linezolid treated group (test group) out of 48 cases are group *klebsiella* (50%), *Proteus* spp. (66.66%), *Streptococcus aureus* (66.66%), *E-coli* (36.36%), *Pseudomonas* spp.(16.66%), *Staphylococcus aureus* (90%) and control group eradication rates are group *klebsiella* (36.66%), *Proteus* spp.(61.53%), *Streptococcus aureus* (50%), *E-coli* (68.75%), *Pseudomonas* spp.(66.66%), *Staphylococcus aureus* (40%). When both test and control group compared with each other the spectrum of test is found to be more than control. However since the study had been conducted in small population, further evaluation should be made to state, test treatment is more effective than control. Table **8** shows the healing of wounds in test group is more than that of control group in contrast of unhealed wound is control group is more than that of test group. Table **9** explains drug related adverse events, in test group. Major adverse event were nausea followed by dyspepsia, headache, and dizziness in contrast to control group headache major adverse event followed by dyspepsia, nausea, vomiting and dizziness. In our study,

adverse events were reported more in control group than test group. Table **10** explains the duration of hospital stay during treatment; patients were more than 14 and less than 21 days staying more both in control and test groups.

Table 7. Comparison of Eradication of Organism between Test and Control Group

Microorganism	Test Group				Control Group			
	Good	Fair	Poor	% Eradication	Good	Fair	Poor	% Eradication
Klebsiella	3	2	1	50	4	2	5	36.36
Proteus species	6	1	2	66.66	8	1	4	61.53
Streptococcus species	10	1	4	66.66	10	6	4	50
E-coli	4	0	7	36.36	11	2	3	68.75
Pseudomonas	1	0	5	16.66	4	0	2	66.66
Staphylococcus aureus	9	1	0	90	4	0	6	40

Table 8. Comparison of Wound Healing in Test and Control Groups

Status	Test Group		Control Group		Significance (P) CI 95%)
	No. of patients	%	No. of patients	%	
Healed	36	75	42	70	<0.01
Unhealed	12	25	18	30	

Table 9. Distribution of Adverse Drug Reaction in Test and Control Groups

Adverse drug events	Test Group		Control Group	
	No. of patients	Percentage	No. of patients	Percentage
Nausea	8	16.6	6	10
Headache	2	4.1	10	16.66
Vomiting	0	0	3	5.1
Dyspepsia	2	4.1	7	11.66
dizziness	1	2.08	2	3.3

Table 10. Duration of Hospital Stay

Duration of Treatment (Days)	Test Group (48)		Control Group (60)	
	No. of Patients	Percentage	No. Of Patients	Percentage
0—7	3	6.25	0	0
7—14	15	31.25	10	6
14—21	18	37.5	32	53.33
> 21	12	25	18	30

DISCUSSION

Diabetic foot infection generally develops as soft tissue skin infection (STSI) afterward skin integrity is interrupted. Cause of soft tissue skin infections involves both gram positive bacteria and Methicillin resistant *Staphylcoccus aurerus* (MRSA). The injury allows organisms commonly found on the skin to cross this protective barrier and cause infections.[10] Patient-related risk factors include known colonization, immunosuppression, diabetes, open chronic wounds, and increased illness severity. Treatment-related factors include previous antibiotic use, intravascular catheterization, and prolonged hospitalization. MRSA infections are associated with an increased incidence of bacteremia, septic shock, amputation, and mortality.[11-14] Additionally, infections due to MRSA can significantly prolong hospitalization, which can more than double hospital stay and treatment costs.[15,16]

Gram-positive bacteria are important pathogens among patients with skin and soft tissue infections. Historically, oxacillin has been a drug of choice for many gram-positive skin and soft tissue infections.[17] However, the emergence of multidrugresistant gram-positive species, particularly MRSA, is an increasing concern; in recent surveys in the United States and Europe, methicillin resistance has been observed in 22 to 25% of *S. aureus* isolates from patients with skin and soft tissue infections.[18,19] Although patients with MRSA were excluded from this study, the increasing prevalence of resistant gram-positive pathogens suggests that many patients will require treatment with an antimicrobial that has activity against these resistant strains. Linezolid may substantially impact the approach to treatment of skin and soft tissue infections caused by many gram positive species because it has a unique mechanism of action, possesses significant activity against gram-positive pathogens (including MRSA), and has excellent clinical efficacy as demonstrated in this and other studies.[20,21] Thus, it is a promising empiric treatment for either community-acquired or nosocomial skin and soft tissue infections. Linezolid's efficacy in treating skin and soft tissue infections may be due, in part, to the high concentrations achieved in the skin (K. M. Donaldson, P. Blood., T. J. Parker, P. T. Daly-Yates, and J. D. Harry, unpublished data) and its ability to inhibit bacterial virulence factor and toxin production in *S. aureus* and *S. pyogenes* at concentrations well below the MICs (C. G. Gemmell and C. W. Ford, Abstr. 39th Intersci Conf. Antimicrob. Agents Chemother., abstr. 1537, 1994). It has been suggested that antimicrobials that have both antibacterial properties as well as the ability to inhibit the synthesis of bacterial toxins may provide greater efficacy and improved outcomes in these gram-positive bacterial toxin-mediated diseases.[22-24] Unlike other antibiotics, the oral formulation of linezolid is 100% bioequivalent to the intravenous formulation, ensuring that patients receive adequate serum and tissue concentrations of drug upon switch to oral therapy. This will allow physicians to switch to the oral formulation earlier in hospitalized patients and may result in earlier discharge.[25] Further studies evaluating the use of oral linezolid alone in the treatment of complicated skin and soft tissue infections are needed.

In the present study, linezolid proved to be safe and well tolerated regardless of the site of infection. The majority of adverse events reported were mild or moderate in intensity. No serious drug-related adverse events were reported in the linezolid group. Complicated skin and soft tissue infections are a significant cause of morbidity and mortality in hospitalized patients. The emergence of resistant pathogens has created the need for newer, more effective antimicrobial therapies, which can be given parenterally or p.o. In conclusion, linezolid is well tolerated and as effective as ciprofloxacin - metronidazole for complicated skin and soft tissue infections, with the added advantages of convenient twice-daily dosing administered either i.v.(intravenous) or p.o.(per oral).

The results indicate that the two drugs are equivalent for the intent to treat population, with linezolid superior to the comparative regimen in the per-protocol analysis and to combination of ciprofloxacin and metronidazole in the MRSA and other organisms like *Klebseilla, Pseudomonas, Proteusmirabblius, E. Coli, Streptococcus species,* subset. The difference between linezolid and ciprofloxacin and metronidazole results was most dramatic in patients with abscesses and surgical-site infections caused by MRSA and other organisms. The superior results in the MRSA patient

group compared to the trend for better outcome noted in the Methicillin Sensitive Staphycoccus aurerus (MSSA) group may be explained by the more-severe infections in the MRSA group, thus allowing easier differentiation of clinical responses. In addition, the MSSA group was smaller, making statistical significance more difficult to achieve. The better outcomes among MRSA-infected patients also could be related to the enhanced skin and tissue penetration of linezolid.[26-29]

The 100% oral bioavailability of linezolid also allowed some investigators to avoid the i.v. route for linezolid. Comparing the patients treated only with oral linezolid to the patients treated with i.v. ciprofloxacin and metronidazole revealed no difference in outcomes despite the different routes of administration. Patients with MRSA infections who are treated with linezolid have shorter i.v. treatment times and an increased chance of being discharged from the hospital in 1 week.[30,31] Other advantages of oral over i.v. therapy include no need for i.v. access, no risk of catheter-related infection, and decreased pharmacy and nursing time to administer the drug while the patient is hospitalized.[32-34]

The emergence of community-acquired MRSA SSTIs poses a new dilemma for practicing physicians, and epidemiologic studies are needed to determine the prevalence of MRSA SSTIs in communities.[35] However, selection of patients at high risk for hospital-acquired MRSA infection is possible based on clinical risk factors.[36] It seems prudent to prescribe an agent effective against MRSA to patients with risk factors for hospital-acquired MRSA or to patients who have presumed staphylococcal infections where the prevalence of MRSA is known to be 20% in the hospital or if the infection is severe. The results of this study demonstrate that linezolid therapy is safe, well tolerated, and superior to ciprofloxacin-metronidazole in the treatment of Complicated SSTIs due to MRSA.

CONCLUSION

Linezolid shows more therapeutic efficacy than combination of Ciprofloxacin and Metronidazole. A Significant difference (P<0.01) was observed in test group (Linezolid) compared to the control group in diabetic foot infections. Use of creative routes of antibiotic administration and new antibiotics are help in improving in the treatment more effectively and to minimize the physical, and emotional aspects that results from diabetic foot infections.

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