

Cross-sectional, Observational Study to Assess Clinical Role of Oral and Injectable Linezolid in Post-operative Diabetic Foot Ulcers: COOLD Study

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Abstract

Background: Diabetic foot ulcers (DFUs) remain difficult to treat with likely incriminating risk factors involving Methicillin-resistant *Staphylococcus aureus* (MRSA). Linezolid offers complimentary consistent action against MSSA and MRSA pathogens making it an ideal choice for inpatient, switch or outpatient therapy for complicated skin and skin structure infections.

Objective: The objective of the study was to compare the efficacy of injectable versus oral linezolid in the management of post-operative DFUs.

Materials and Methods: Retrospective analyses of 100 cases receiving oral or injectable linezolid. A total of 100 subjects were enrolled in this study. Two groups were made of 50 patients each and labeled as Group A and Group B. In Group A, tablet linezolid was given in a dose of 600 mg BD for 7 days. In Group B, injectable linezolid was given in a dose of 600 mg intravenous (IV) BD for 7 days. Clinical and bacteriological improvement was documented. In both groups tablet cefuroxime, 500 mg BD was given for 7 days in conjunction with linezolid.

Results: We found 90–100% improvement in wound infections and in culture reports. Results in both the groups receiving oral or IV linezolid for post-operative DFU healing were comparable when administered for 7 days. Linezolid offered high therapeutic success rates (75–100%) against the incriminated pathogens of *S. aureus* with little action against *Acinetobacter* or *Pseudomonas aeruginosa*.

Conclusion: These results suggest that linezolid given empirically is highly effective in the treatment of DFUs. The equivocal clinical and microbiological eradication rates for oral and injectable formulations with 7 days therapy makes them less liable for resistance induction or development.

Key words: Linezolid, Diabetic foot ulcer, *Staphylococcus aureus*, Complicated skin and skin structure infections

INTRODUCTION

Diabetic foot infections remain a clinical enigma as a recurring or relapsing condition with undertreated or inappropriately treated infections.

Staphylococcus aureus remains the most common pathogen often represented by Methicillin-resistant *S. aureus* (MRSA) among the many organisms incriminated in such conditions.

Linezolid is effective for treatment of infections due to Gram-positive bacteria, including methicillin-, cephalosporin-, and vancomycin-resistant strains, but it has minimal activity against Gram-negative bacteria. It is available in both a parenteral and a highly bioavailable oral formulation, is administered twice per day, and achieves therapeutic concentrations in soft tissue and bone. Dosage adjustment is not necessary for patients with mild-to-moderate impaired renal function and liver diseases; furthermore, patients on hemodialysis should receive

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dose after dialysis session or a supplemental 200 mg dose of linezolid at the end of dialysis, the influence of severe hepatic impairment on the pharmacokinetic profile of linezolid has not been established.^[1-3]

At the same time the key advantage of linezolid as an orally administered formulation with complete bioavailability augers well for its rationale use as monocomponent or combination therapy especially in outpatient settings of India for cases with complicated skin and skin structure infections (cSSSTIs).

This study was conducted as a retrospective, case–control study to assess the comparative efficacy and safety of linezolid administered orally or intravenously for post-operative diabetic foot infections.

MATERIALS AND METHODS

A retrospective, case–control, and observational clinical study was conducted at the tertiary care center at Goa, India. The study documents including protocol were reviewed and approved by the Local Ethics Committee before initiation. The study was conducted as per the ICH good clinical practice principles and Declaration of Helsinki. The study inclusion criteria included consecutive cases of post-operative diabetic foot ulcers (DFUs) receiving linezolid as oral or intravenous (IV) formulations for at least 7 days. All of the cases with follow-up visit or data of less than a week were excluded including those patient records with overlapping drug schedules or formulations for Gram-positive pathogens including drug-sensitive or resistant *S. aureus*.

Clinical effectiveness was determined with the wound examination for closure or healing, clinical improvement, and bacteriological success rates at the end of 1 and 4 weeks, respectively. The analysis was made after administration of oral/injectable linezolid with improvement rating that was based on a daily assessment of wounds and assigned three ratings:

- Improvement: Where in wound showed signs of betterment post drug administration.
- Static: Where in wound did not show much changes following drug administration.
- Failure: Where in wound showed signs of worsening inspite of drug administration.

The improvement in patients receiving linezolid was graded as:

- Marked improvement: The wound showed 75–100% improvement.
- Moderate improvement: The wound showed 50–74.9% improvement.

- Mild improvement: The wound showed 25–49.9% improvement.

The safety profile of oral or IV linezolid formulations was determined as Treatment emergent adverse event of >1%. The adverse events documented on the prescription or follow-up records would be accessed for the safety analyses. Similarly, the serious adverse events (SAEs) reported to central drugs standard control organization on the suspect adverse drug reaction reporting form on pvpi@ipcindia.net would also be accessed for the analyses.

RESULTS

Consecutive 100 cases receiving oral or IV formulations of linezolid were analyzed. Two groups of patients of 50 cases each who received oral (Group A) or IV (Group B) formulations for 7 days were compared for bacteriological and clinical success rates. The dosage given in both groups was 600 mg twice a day. Concomitant medications included Cefuroxime axetil, analgesics, and/or anti-inflammatory drugs for resolution of local symptoms. Swab cultures taken from the wound before and after 7 days of therapy and reports were also analyzed.

Patients receiving oral steroids at least a week before surgery or debridement were excluded from the study analyses. In all of the cases, besides drug administration, daily desloughing of wounds was done with close monitoring of blood sugar or HbA1c levels.

The microorganisms encountered in cultures before drug administration were *S. aureus* (63%), *Acinetobacter* (18%), *Pseudomonas aeruginosa* (13%), and Mixed flora (6%).

Microbiological Efficacy

In both groups:

- All cultures with showed *S. aureus* became sterile at the end of 7 days.
- In patients whose cultures showed polymicrobial infections with *Acinetobacter*, 16% became sterile at the end of 1 week. 2% were given the drug for an extended period of 5 days more in addition to 1 week, at the end of which cultures were sterile.
- Similarly, in the above patients with concomitant *P. aeruginosa*, only one patient's culture was sterile at the end of 7 days. The remaining patients did not show any bacteriologic improvement with linezolid even after an extended period of 5 days in addition to 7 days of drug administration.

Clinical Efficacy

The clinical resolution of symptoms and slough was quick and significant at the end of 5 days of therapy [Table 1, Figure 1and 2].

Table 1: Comparison of slough covered area in both arms

Decrease in Slough	↓0–25%	↓25–50%	↓50–75%	↓75–100%
In group A				
Patients at end of 5 days (n)	-	2	7	41
Patients at end of 7 days (n)	-	1	3	46
In group B				
Patients at end of 5 days (n)	-	1	4	45
Patients at end of 7 days (n)	-	-	3	47

Table 2: Comparison of DFU lesions in both arms

Decrease in Ulcer lesion	Age group		
	30–45 years	45–60 years	60–75 years
In Group A			
Lesion size at the end of 5 days (cm)	↓0.55	↓0.35	↓0.3
Lesion size at the end of 7 days (cm)	↓0.7	↓0.45	↓0.35
In Group B			
Lesion size at the end of 5 days (cm)	↓0.65	↓0.5	↓0.3
Lesion size at the end of 7 days (cm)	↓0.7	↓0.55	↓0.35

DFU: Diabetic foot ulcer

Table 3: Comparison of lesion exudate in both arms

Linezolid therapy	% decrease in ulcer exudate or discharge			
	0–25%	25–50%	50–75%	75–100%
In Group A				
At the end of 5 days	-	-	5	45
At the end of 7 days	-	-	-	50
In Group B				
At the end of 5 days	-	-	4	46
At the end of 7 days	-	-	-	46

Clinical effectiveness as wound healing or closure [Figure 3 and 4] was considered clinically significant with 40–50% reduction or decrease in lesion diameter with similar assessment for a reduction in lesion exudate or discharge [Tables 2 and 3].

Safety Profile

There were no clinically significant adverse events reported during the course of the observation including anemia or optic neuritis and peripheral neuropathy. Similarly, there were no SAEs reported including thrombocytopenia.

DISCUSSION

The lifetime risk of DFU may be as high as 25%.^[4,5] They are a major cause of morbidity and mortality, accounting for approximately two-thirds of all non-traumatic amputations performed worldwide. Infected or ischemic DFUs account for approximately 25% of all hospital stays

**Figure 1: Before intravenous drug administration****Figure 2: After intravenous drug administration**



Figure 3: Before oral drug administration



Figure 4: After oral drug administration

for patients with diabetes.^[6] This underlines the significance and importance of prompt and appropriate treatment with local wound care, use of mechanical offloading or debridement before the treatment of infection with definitive or empiric therapy.^[7,8]

The choice of anti-infective therapy is often driven by the local surveillance patterns for likely involving Gram-positive pathogens including methicillin-sensitive or resistant *S. aureus*.

The incidence of infection caused by antibiotic-resistant bacteria, particularly MRSA, is increasing worldwide.^[9,10]

In patients with diabetic foot infections, isolation of MRSA is associated with previous antibiotic therapy and leads to worse clinical outcomes.^[11,12] Thus, agents with extended activity against MRSA are needed for patients at risk. Whether an empirical antibiotic regimen for diabetic foot infection must also be effective against Gram-negative bacilli and anaerobes are not clear. Several studies have suggested that therapy with oral antimicrobial agents is effective, but few studies have compared the outcomes of oral and parenteral regimens especially in real-world settings of India involving mono- or poly-microbial infections.

The current study addresses the above scientific need-gap with results commensurating the potential of linezolid in the management of cSSSTIs especially as post-operative wound lesions or DFUs. This retrospective, case-control analyses highlighted significant improvement of 75–100% in both groups in the local condition of the wound within 5 days of therapy with up to 90–100% in the 7 days therapy group. A 7 days course of linezolid also had the added advantage of a decrease in ulcer size by 0.2–0.3 cm as compared to a 5 days course. The effects of oral and injectable linezolid were comparable, thus proving that bioavailability was 100% for oral linezolid. Linezolid in a dose of 600 mg BD IV or oral is equally effective. Linezolid is effective against most Gram-positive organisms including polymicrobial infections involving *Acinetobacter* with little action on *Pseudomonas*. Linezolid given IV or as oral formulation was found to be a safe drug in patients with deranged renal function tests.

MRSA infection is on the rise with likely contributors being prior or prolonged antibiotic course, bacterial contamination, or load with inappropriate therapy in most cases due to lack of diagnostic tests or investigations for definitive therapy initiation with daptomycin or vancomycin. Again the omnipresent use of these anti-infective agents is limited by the PK-PD dyssynergy in cases with concomitant CKD.

The results of current study compliment the findings by Lipsky *et al.*^[13] while offering equivocal results for oral or IV formulations in post-operative DFU cases when administered for 7 days including for patients with deranged renal function

Study Limitations

These analyses were limited by the retrospective nature of study design with likely markers for variable use of oral or injectable formulations being likely to be missed. Similarly, the baseline demographics and underlying conditions were not matched as case-control analyses. However, the results are exploratory while offering a real-world perspective on the likely use of injectable formulations in cSSSTIs especially in patients with extensive lesions.

CONCLUSION

Linezolid is a highly effective antimicrobial in the treatment of DFUs with equivocal efficacy of injectable and oral formulations in lesions with predominantly Gram-positive pathogens.

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