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Susceptibility Profile of Novel Drug: Levonadifloxacin Against Multi-Drug Resistant MRSA (MDRSA) Isolates in a Tertiary Care Hospital, Mysore

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ABSTRACT

Background & Objectives: Antibiotics have become a significant concern due to the rising mortality rates from *Staphylococcus aureus* infections and the emergence of methicillin-resistant and other multidrug-resistant strains. Levonadifloxacin is a novel antibiotic belonging to the benzoquinolizine, subclass of quinolone formulated for intravenous and oral administration, approved for the treatment of acute bacterial skin and soft tissue infections, respiratory infections, and concurrent bacteremia. The objective of this study is to assess the susceptibility profile of Levonadifloxacin against multidrug resistant MRSA isolates in-vitro.
Methods: A total of 100 MRSA isolates were collected from July 2023 to March 2024. Susceptibility of Levonadifloxacin and other antibiotics were determined using the disk diffusion method as per recommendations of the Clinical and Laboratory Standards Institute.
Results: Against all MRSA isolates, the drug susceptibilities were Gentamicin (29%), Doxycycline (50%), Ciprofloxacin (8%), Levofloxacin (9%), Cotrimoxazole (54%), respectively while Levonadifloxacin showed 100% susceptibility. Linezolid showed 99% susceptibility.
Conclusion: Levonadifloxacin is a newer and safer treatment option for multi-drug resistant MRSA isolates.

Keywords: Levonadifloxacin, Multi-drug resistant MRSA, Antibiotic susceptibility, QRSA, Skin and soft tissue infections.

INTRODUCTION

Methicillin resistant *Staphylococcus aureus* (MRSA) is a significant public health concern and remains as a challenging pathogen because of its multi-drug resistance which leads to serious hospital-acquired and community acquired infections. According to the World Health Organisation bacterial pathogen priority list, MRSA is categorised as 'high priority' pathogen [2]. Global burden of antimicrobial resistance estimates that MRSA alone was

responsible for >100,000 deaths in 2019[3]. The mecA gene is the primary gene responsible for the resistance mechanisms in MRSA and the gene is part of the staphylococcal cassette chromosome mec (SCCmec), a mobile genetic element. The mecA gene encodes penicillin-binding protein 2a (PBP2a), which has a reduced affinity for beta-lactam antibiotics, including methicillin, rendering the bacteria resistant to these antibiotics. Multidrug-resistant MRSA (MDRSA) refers to strains of Methicillin-resistant *Staphylococcus aureus* that are resistant not only to methicillin but also to more than three other classes of antibiotics. The increased prevalence of MDRSA particularly makes clinicians challenging to treat [4]. The management of MDRSA infections relies on the availability of well-tolerated oral and IV antibiotics according to inpatient and outpatient requirements.

Currently, Vancomycin, Linezolid, Teicoplanin, Daptomycin are the antibiotics used to treat MDRSA infections. However, these drugs have several limitations which make restricted clinical use. Although Vancomycin remains gold standard for the treatment of MRSA infections, it has slow bactericidal activity, poor lung penetration, nephrotoxicity, risk of clinical failure due to MIC creep and ototoxicity [5]. Linezolid is easily administered orally but its prolonged use leads to myelosuppression and also it has weak bactericidal activity, therefore it is not indicated in patients with severe bacteremia. Teicoplanin and Daptomycin are used to a lesser extent as it is very expensive and causes significant side effects. Due to these various reasons, clinicians need improved access to antibiotics that are bactericidal, have adequate tissue penetration and relatively safer for long duration of treatment especially in case of skin and soft tissue infections.

Levonadifloxacin (intravenous formulation) and its prodrug, alalevonadifloxacin (oral formulation), are two newly approved antibiotics from the benzoquinolizine subclass of fluoroquinolones. Recently approved by the FDA, they are used to treat acute bacterial skin and soft tissue infections (ABSSIs), including diabetic foot infections and associated bacteremia. It is a broad-spectrum antibiotic with potent in vitro and in vivo bactericidal activity against resistant – *S. aureus* isolates, including MRSA, vancomycin-resistant *S. aureus* (VRSA), hetero-vancomycin-intermediate *S. aureus* and quinolone-resistant *S. aureus* (QRSA) isolates. It is believed that the presence of the chiral benzoquinolizine core in levonadifloxacin contributes to its strong affinity for DNA gyrase, while also retaining significant affinity for topoisomerase IV. Unlike other quinolones, such as ciprofloxacin and levofloxacin, which primarily inhibit DNA topoisomerase IV, levonadifloxacin exhibits a well-defined mechanism of action by strongly targeting both staphylococcal DNA gyrase and topoisomerase IV. By inhibiting DNA gyrase, levonadifloxacin effectively disrupts bacterial DNA replication and transcription, providing a valuable treatment option for infections caused by resistant bacterial strains. The intracellular activity of levonadifloxacin was found to be superior to that of other fluoroquinolones like ciprofloxacin. As the prevalence of multi-drug resistance against *S. aureus* is increasing, it is necessary for the clinicians to diagnose and treat the infections at the earliest. Hence this study is taken up to evaluate the in-vitro susceptibility profile of Levonadifloxacin against MDRSA isolates.

MATERIALS & METHODS

Sample collection & Processing:

From July 2023 to March 2024, specimens were collected from inpatients of Cardiology, Medicine, Gynaecology, Surgery and Orthopaedic wards and Intensive Care units at Mysore Medical College Hospital and Research Institute, Mysore. Patients above 18 years of age were included in the study. Clinical specimens collected were blood, urine, sputum, and pus and transported to the laboratory within

2 hours of sample collection. Blood samples collected in BHI bottles and incubated at 37°C for 24 hours and were inoculated into MacConkey agar and Chocolate agar. Urine, sputum, and pus samples collected in a sterile container were inoculated in MacConkey agar and Chocolate agar and incubated for 18 hours at 37°C.

Organism identification:

By conventional methods, *Staphylococcus aureus* was identified using biochemical reactions like catalase and coagulase tests. Antibiotic susceptibility testing was done using Kirby-Bauer disk diffusion method. Antibiotic discs were procured from HiMedia Laboratories Ltd commercially and used. The antibiotic panel of drugs used include the following discs Cefoxitin(30mcg), Gentamicin(10mcg), Doxycycline(30mcg), Ciprofloxacin(5mcg), Levofloxacin(5mcg), Cotrimoxazole(25mcg), Linezolid(30mcg), and Levonadifloxacin (10mcg). MRSA was determined by the susceptibility pattern toward Cefoxitin disc with zone size <21mm according to CLSI guidelines M100 33rd edition, 2023. Antibiotic susceptibility for levonadifloxacin was taken susceptible as ≥17mm, intermediate as 14-16mm, and resistant as ≤13 mm as per CLSI M100 26th edition.

STATISTICAL ANALYSIS

Following data collection, all questionnaires underwent thorough examination to ensure completeness, accuracy and internal consistency, thereby eliminating any instances of missing or inconsistent data, which were subsequently discarded. Corrected data were entered into the Statistical Package for Social Sciences (SPSS) statistical software version 25 for the analysis. Quantitative variables were summarized by calculating their mean and standard deviation. On the other hand, qualitative variables were summarized by percentage.

RESULTS

A total of 100 multi-drug resistant MRSA isolates were taken for the study. Patients of more than 18 years of age were taken up for the study.

Table1: Sample distribution

Specimen	No. of samples
Pus	60 (60%)
Blood	35 (35%)
Urine	4 (4%)
Sputum	1 (1%)
Total	100

Among all the clinical specimens, majority were pus samples (60%), followed by blood (35%) (Table 1).

Table 2: Ward distribution

WARD NAME	TOTAL
ICU (MICU, SICU, RICU, SARI ICU)	22
Medicine	14
Surgery & orthopaedics	31
OBG	21
Others (EYE, ENT, SKIN)	12

MRSA isolates were more predominant from surgery and orthopaedics ward (31%) followed by various ICUs (Table 2).

Table 3: Antibiotic profile of MRSA isolates

ANTIBIOTIC DISC	SENSITIVE	RESISTANT
Cefoxitin(30mcg)	nil	100
Gentamicin(10mcg)	29	71
Doxycycline(30mcg)	50	50
Ciprofloxacin(5mcg)	8	92
Levofloxacin(5mcg)	9	91
Cotrimoxazole(25mcg)	54	46
Linezolid(30mcg)	99	1
Levonadifloxacin(10mcg)	100	nil

The antimicrobial susceptibility of MRSA isolates was tested by using Gentamicin, Doxycycline, Ciprofloxacin, Levofloxacin, Cotrimoxazole, Linezolid including Levonadifloxacin. Levonadifloxacin showed 100% susceptibility against all the isolates. Among other antibiotics, Linezolid showed maximum susceptibility of 99% whereas Quinolone group of antibiotics such as Ciprofloxacin (8%) and Levofloxacin (9%) showed poor activity against these isolates.

DISCUSSION

MRSA has spread worldwide and pose a significant threat, affecting both hospital settings and the community. Recently, MDRSA is emerging and particularly in healthcare settings, where they can cause severe infections, including bloodstream infections, pneumonia, surgical site infections, and also associated with higher morbidity and mortality due to limited treatment options. The available treatment options for MDRSA strains are Vancomycin, Teicoplanin, Linezolid, Daptomycin and some beta-lactam antibiotics such as Ceftaroline and Ceftabiprole. In India, Levonadifloxacin is used for the treatment of bloodstream infections, respiratory tract infections, acute bacterial skin and soft tissue infections including diabetic foot infections caused by Gram-positive organisms.

In our study, majority of MRSA isolates were from pus samples (60%) followed by blood. A similar observation was reported by *Mehta* et al., his study showed 71.4% MRSA isolated from pus and wound swabs [18]. In another study by *Rajaduraipandi* et al., MRSA was isolated highest in sputum samples (35.7%) followed by pus (33.6%) [19]. Many studies have reported a higher incidence of MRSA isolation in ICUs; however, our study found the highest incidence in surgical and orthopaedic wards (31%), followed by ICUs and medical wards.

Among the 100 MRSA isolates in our study, Levonadifloxacin exhibited 100% in-vitro susceptibility by the disk diffusion method. This was similar to the study done by Qureshi *et al.*, where all MRSA isolates (100%) were found susceptible to levonadifloxacin. Also, in another study done by Baliga *et al*., highlights the efficacy of levonadifloxacin against Gram-positive isolates collected from various Indian hospitals, demonstrating 100% susceptibility when tested using the disk-diffusion method [5]. Study by Appalaraju *et al*., exhibited Levonadifloxacin potent activity against 390 *S. aureus* isolates (98.7% susceptibility) collected from 15 tertiary hospitals, located in different parts of India [6].

The next maximum susceptibility was shown by Linezolid with 99% susceptibility in our study. According to WHO, Linezolid is a reserve drug, as such it should be taken as a last resort of treatment option when all other alternate treatment options have failed or are not suitable for MRSA isolates. This is because it is a potential alternative drug of choice in treatment of MDR-TB and XDR-TB. A study conducted by Lakshmi S. Kakhandki *et al*., reported an 87.71% susceptibility to Linezolid, which was analyzed in relation to clinical outcomes [17]. Also, Linezolid possesses major side effects like bone marrow suppression due to prolonged use, peripheral neuropathy, serotonin syndrome, lactic acidosis and Antibiotic-associated diarrhoea and colitis.

Quinolone antibiotics are commonly prescribed for treating a wide range of bacterial infections in both hospital and outpatient settings. Quinolone resistant *Staphylococcus aureus* (QRSA) has been reported worldwide with varying prevalence rates. QRSA is emerging due to mutations in genes encoding DNA gyrase like gyrA and gyrB, mutation in topoisomerase IV and plasmid mediated resistance. In this study, we observed maximum resistance to Quinolones with 92% and 91% for Ciprofloxacin and Levofloxacin respectively. These findings are consistent with a study by Shalit *et al.*, which reported 90% resistance to quinolones [21].

Among other tested antibiotics, Cotrimoxazole showed 54% susceptibility compared to another study by Gurung *et al*., which showed 56.8%. Doxycycline showed only 50% susceptibility in this study when compared to a study by Huda H *et al*., which showed 70.5% susceptibility against various clinical specimens [22]. Cotrimoxazole and doxycycline are cost effective but has limited data for its use against bacteremia and skin and soft tissue infections. Gentamicin, even though it is susceptible in 29% isolates, it should be used only in combination with other active agents that are susceptible. Vancomycin use is nowadays restricted due to the emergence of vancomycin resistant *S. aureus*, weak bactericidal activity, hypersensitivity reactions and the accompanying therapeutic failure [4].

Thus, Levonadifloxacin has more clinical advantages like safe to use in patients with renal and liver impairment without dose adjustments, available in both IV and oral formulations to treat severe infections and makes it easy to switch over from IV to oral therapy, devoid of side effects like bone marrow suppression, phototoxicity and prolonged QT interval. Levonadifloxacin and alalevonadifloxacin have been used post approval to treat >47,000 patients, and the prescription monitoring database revealed that pneumonia, ABSSSI, septicemia, DFIs, bone and joint infections, catheter-related bloodstream infections, and febrile neutropenia were the common conditions for which these novel antibiotics were used [5,6].

CONCLUSION

This study concludes that Levonadifloxacin, a novel drug shows excellent in-vitro activity against MDRSA. Also, Levonadifloxacin (IV and oral) is a very effective and safe antibiotic that can be used in patients with skin and soft tissue infections and also safe in patients with co-morbidities such as renal and hepatic failure. The present study also emphasizes the need for continuous monitoring of MDRSA, their antibiogram and its preventive measures in both tertiary care settings and peripheral hospitals.

Declaration by Authors
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