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Evaluating the Susceptibility Profile of Levonadifloxacin against MRSA and Fluoroquinolone-Resistant Staphylococcus Isolates in contrast to other prescribed antibiotics

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ABSTRACT

Introduction: According to the World Health Organization, the likelihood of mortality due to MRSA infections is estimated to be 64% higher compared to that caused by susceptible Staphylococcal isolates. In India, the prevalence of MRSA is considerable and varies across regions. Western India has reported a 25% MRSA prevalence, while Southern India has reported a higher rate of 50%.

Aims & Objectives: To find out the invitro susceptibility pattern of MRSA and the susceptibility of fluoroquinolone-resistant Staphylococcal isolates (including MRSA) against Levonadifloxacin along with other antibiotics within formulary.

Material & Methods: This was a prospective, descriptive study carried out in the Department of Microbiology, Central Laboratory School of Medical Science and Research (SMS&R), Sharda Hospital, Sharda University Greater Noida. For in-vitro susceptibility of MRSA, isolates positive for catalase and coagulase test (Staphylococcus aureus) were subjected for Antibiotic sensitivity testing along with cefoxitin disc and results were interpreted according to CLSI guidelines.

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Results: In the present study Gram positive isolates were found to be highly sensitive for Vancomycin (100%) followed by Linezolid (98%), Teicoplanin (92.8%), nitrofurantoin (83.14%) and Fosfomycin (88.37%) whereas, Cefipime was the least sensitive (1.2%) drug among all the antibiotics tested. MRSA was found to be highly sensitive for Vancomycin (100%) followed by Linezolid (96.8%), Teicoplanin (96.8%), Levonadiflocxacin (89.1%) and Gentamicin (67.4%) whereas, Cefoxitin was the least sensitive (0%) drug among all the antibiotics tested.

Conclusion: As the antibiotic resistance is on the rise nowadays, updating the strategies to overcome the growing antibiotic resistance like selection of narrow spectrum antibiotics with low resistance properties and antibiotic resistance surveillance is need of the hour.

Keywords: MRSA, Levonadifloxacin, Cefoxitin, Vancomycin, Antibiotic resistance.

INTRODUCTION

According to the World Health Organization, the likelihood of mortality due to MRSA infections is estimated to be 64% higher compared to that caused by susceptible Staphylococcal isolates. In India, the prevalence of MRSA is sizable and varies across regions. Western India has reported a 25% MRSA prevalence, while Southern India has reported a higher rate of 50% [1,2].

In the management of MRSA infections within large inpatient and outpatient healthcare settings, the availability of well-tolerated antibiotics is crucial. Currently, vancomycin and linezolid are the two most used antibiotics to combat MRSA infections. Teicoplanin and daptomycin are also employed to some extent for this purpose. Vancomycin has long been the preferred treatment for MRSA infections. However, it is considered suboptimal for critically ill patients due to its weak ability to kill bacteria, limited penetration into tissues like the lungs, potential kidney toxicity, and the risk of treatment failure due to minimum inhibitory concentration (MIC) creep. On the other hand, linezolid, while effective against MRSA is limited by its ability to only inhibit bacterial growth and is not recommended for bloodstream infections.

Levonadifloxacin and its prodrug alalevonadifloxacin are novel broad-spectrum anti-MRSA agents belonging to the benzoquinolizine subclass of quinolone, formulated for intravenous

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and oral administration, respectively. Various in vitro and in vivo studies have established their antimicrobial spectrum against clinically significant Gram-positive, Gram-negative, atypical, and anaerobic pathogens. The potent activity of levonadifloxacin against MRSA, quinolone-resistant *Staphylococcus aureus*, and hetero-vancomycin-intermediate strains is an outcome of its well-differentiated mechanism of action involving preferential targeting to DNA gyrase [3-5].

Moreover, the development of adverse side effects such as bone marrow suppression leading to thrombocytopenia requires linezolid to be used for shorter duration and necessitates concomitant monitoring of safety parameters. Due to these reasons, clinicians need access to improved antibiotics that are bactericidal, have adequate tissue penetration and is safe especially for the longer duration of treatment to treat MRSA infection [2].

Levonadifloxacin is a novel antibiotic belonging to the benzoquinolizine subclass of fluoroquinolones with potent activity against MRSA and quinolone-resistant *S. aureus* (QRSA). Intravenous levonadifloxacin and its oral formulation, alalevonadifloxacin, have recently been approved in India for the treatment of acute bacterial skin and skin structure infections with concurrent bacteraemia and diabetic foot infections. It has shown excellent activity against Gram-positive organisms like *S. aureus* (including methicillin-resistant and quinolone-resistant isolates), *Streptococcus pyogenes*, and *Enterococcus faecalis* (including vancomycin-resistant isolates), and *Streptococcus dysgalactiae* spp. *Dysgalactiae*. Its potent activity is attributed to the unique mechanism of action that primarily inhibits DNA gyrase.[2] In another report, the clinical, pharmacological and antimicrobial profile of levonadifloxacin has been elaborated in comparison with other anti-MRSA antibiotics [4].

The literature is still scanty regarding Levonadifloxacin activity in Gram positive bacteria, thus the present study was aimed to evaluate the in-vitro activity of levonadifloxacin against clinical isolates of *Staphylococcus aureus* collected from a tertiary care teaching hospital in India.

MATERIAL AND METHODS

This was a prospective, descriptive study conducted in the Department of Microbiology, Central Laboratory School of Medical Science and Research (SMS&R), Sharda Hospital, Sharda University Greater Noida for the period of one year during which total 250 samples were taken. Pathogenic Gram Positive cocci isolates from all the samples received for culture and sensitivity in the bacteriology section, Central laboratory, Sharda Hospital were included.

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For in-vitro susceptibility of MRSA, isolates positive for catalase and coagulase test (Staphylococcus aureus) were subjected for Antibiotic sensitivity testing along with cefoxitin disc (surrogate marker for methicillin sensitivity).

For susceptibility of fluoroquinolone-resistant Staphylococcal isolates (including MRSA) against Levonadifloxacin, detection of fluoroquinolone resistance would be confirmed by zone size less than 15mm against ciprofloxacin. The susceptibility pattern of these isolates was compared and plotted against the susceptibility against levonadifloxacin.

Aim & Objectives – To study the Antibiogram profiling of gram positive cocci , test the in vitro susceptibility pattern of MRSA with special reference to Susceptibility of fluoroquinolone-resistant Staphylococcal isolates (including MRSA) against Levonadifloxacin

RESULTS

In the current study a total number of 250 Gram Positive Cocci isolates were included in the study. All the samples were processed for routine microscopy following culture & sensitivity test as per CLSI guidelines to know their resistance pattern.

The age-wise distribution of the bacterial isolates among different age groups shows that the maximum number of isolates belongs to the age group 21-40 (38.4%) followed by 41-60 (28.8%) and age less than 20 yrs (18.8) whereas the least number of isolates belong to the age group 61-8- (14%). In the present study, out of 250 samples, the maximum samples were of females 133 (53.2%) and the least were of males 117 (46.8%).

Out of a total of 250 samples, the majority of samples were received from IPD 243 (97.2%) while the rest were from OPD 7 (2.8%). Out of 250 samples, Pus was received as major specimen i.e. 46.8%, then Urine (35.6%) and rest i.e. 17.4% were Sputum, Swab, HVS, ETT, Blood, BAL, Throat swab, TS and Tissue.

Among the 250 bacterial isolates, *MRSA* 92 (36.80%) was the most frequently isolated organism followed by *MRCONS.* 58 (23.2%), *Enterococcus spp.* 54(21.6%), *MSSA* 17 (6.8%), *MSCONS* 17 (6.8%) respectively. whereas, *Group A Beta HS.* 12(4.80%) was the least isolated organism. Among the 92 bacterial isolates of *MRSA*, highest number of samples sent from

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General surgery i.e. 38.04% followed by *ICU* 18.48% , *Ortho 15.2*1% , *OPD* 6.52%, General medicine and PVT 4.35% , Dermatology, Respiratory medicine and pediatrics 3.26% *ENT* 2.17% respectively. whereas, *Obstetrics and gynaecology*. 1.09% was the last.

Gram positive isolates were found to be highly sensitive for Vancomycin (100%) followed by Linezolid (98%), Teicoplanin (92.8%), nitrofurantoin (83.14%) and Fosfomycin (88.37%) whereas, Cefipime was the least sensitive (1.2%) drug among all the antibiotics tested.

Table 1: Antibiogram for Gram Positive isolates

Antibiotics	Frequency (N)	Percentage
Vancomycin	**250**	**100%**
Linezolid	**245**	**98.0%**
Teicoplanin	**232**	**92.8%**
Levonadifloxacin	**145**	**78.37%**
Gentamicin	**132**	**52.80%**
Nitrofurantoin *	**74**	**83.14%**
Cotrimaxazole	**94**	**37.60%**
Clindamycin	**88**	**35.20%**
Azithromycin	**85**	**34.00%**
Erythromycin	**81**	**32.4%**
Levofloxacin	**70**	**28.0%**
Penicillin	**65**	**26.0%**
Ciprofloxacin	**63**	**25.2%**
Fosfomycin**	**38/43**	**88.37%**
High level streptomycin	**37**	**14.8%**
High level gentamycin	**34**	**13.6%**
Cefoxitin	**34**	**13.6%**
Ampicillin	**28**	**11.2%**
Cefipime	**3**	**1.20%**

*Sensitivity Analysed in urine Samples only N=89

** Sensitivity Analysed in urine Samples (Enterococcus spp.) N=38

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MRSA was found to be highly sensitive for Vancomycin (100%) followed by Linezolid (96.8%), Teicoplanin (96.8%), Levonadiflocxacin (89.1%) and Gentamicin (67.4%) whereas, Cefoxitin was the least sensitive (0%) drug among all the antibiotics tested.

Table 2: Antibiotic Susceptibility Pattern of ***MRSA***

Antibiotics	**Frequency (N=92)**	**Percentage**
Levonadifloxacin	**82**	**89.1%**
Vancomycin	**92**	**100%**
Linezolid	**89**	**96.8%**
Teicoplanin	**89**	**96.8%**
Gentamicin	**62**	**67.4%**
Clindamycin	**44**	**47.8%**
Cotrimoxazole	**43**	**46.7%**
Azithromycin	**41**	**44.6%**
Erythromycin	**25**	**27.2%**
Levofloxacin	**15**	**16.3%**
Ciprofloxacin	**11**	**12.0%**
Penicillin	**9**	**9.8%**
Cefoxitin	**0**	**0.0%**

Fluroquinolone Resistant MRSA were found to be highly sensitive for Vancomycin (100%) followed by Linezolid (96.2%), Teicoplanin (96.2%), whereas, Levonadifloxacin was the least sensitive (87.6%) drug among all the antibiotics tested. Ciprofloxacin sensitive MRSA isolates showed susceptibility of 11.96% for levonadifloxacin while Ciprofloxacin resistant MRSA isolates showed susceptibility of 77.17% for levonadifloxacin.

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Discussion

Treating resistant staphylococcal isolates is challenging, especially in intensive care units. Vancomycin and linezolid (teicoplanin and daptomycin to some extent) are currently the two most commonly used antibiotics to treat methicillin-resistant staphylococcal infections; however, both medications have drawbacks. For example, vancomycin is thought to be a less-than-ideal option in critically ill patients because of its weak bactericidal activity, poor penetration into tissues (such as the lung), renal toxicity, and risk of clinical failure due to Minimum Inhibitory Concentration (MIC) creep [6–8]. Linezolid is a bacteriostatic agent and therefore, not recommended to be used in Blood Stream Infections (BSI). Adverse side effects of linezolid like bone marrow suppression leading to thrombocytopenia requires its usage in shorter duration along with monitoring of safety parameters [9]. Thus, for treatment of methicillin resistant staphylococcal infections, clinicians require improved antibiotics that are bactericidal, having good tissue penetration and are safe especially for the longer duration use. Levonadifloxacin is a novel antibiotic belonging to the benzoquinolizine subclass of fluoroquinolone with potent activity against MRSA and QRSA. Both intravenous levonadifloxacin and its oral formulation, alalevonadifloxacin, have recently been approved in India to treat acute bacterial infections in skin [10]. Its approval is based on a successfully conducted Phase three clinical study comparing levonadifloxacin with linezolid

Among the clinical samples, most of the isolates of MRSA were from pus samples (67.39 %). The predominance in pus could be due to exposure of wound to microorganism in the environment and *S. aureus* present on skin as commensal makes wound more prone for infection. Similar findings were reported by Mallick and Basak in Maharashtra (61.4%) 119 and Patel FV et al. (60%) [11]. Most of isolates of MRSA were from Intensive care unit patients(18.48%) and surgical patients(38.04%). This could be attributed to the possibility of invasion of MRSA colonization of skin during invasive procedures in Surgery Speciality and indwelling devices in ICU. Similar results were observed in previous studies in literature . Additionally, this study also focuses on understanding the trends in the susceptibility pattern of the Gram-positive isolates. Among the isolates of MRSA n=92, the most sensitive drug turned out to be Vancomycin 92(100%) followed by linezolid 89(96.8%) and Teicoplanin 89(96.7%) while the least sensitive drug was Penicillin Nitrofurantoin 9 (9.8%). Similar results was seen by study by Krishnakumar S et al [12]. In this study,89.13%MRSA isolates were found to be susceptible to Levonadifloxacin while among fluoroquinolone resistnt isolates

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susceptibility was observerd as 87.6% which appears as promising. These findings were consistent with a previous study done in Vellore, Tamilnadu by Bakthavatchalam et al, where all the 793 S.aureus isolates collected were found to be susceptible to levonadifloxacin [13] . In a study by Appalaraju B et al, Levonadifloxacin showed highly effective activity against 98.7% of the S.aureus isolates collected among 15 tertiary care hospitals from various regions of India [14].

Additionally, it could also be used as an empirical therapy. In spite of vancomycin and linezolid showing similar high susceptibility rates, vancomycin use is often associated with nephrotoxicity and longer duration use of linezolid leads to myelosuppression [15]. Contrary to vancomycin, levonadifloxacin can be administered to patient with renal or liver impairment without the need for dose adjustments. Moreover, the availability of oral formulation of levonadifloxacin with comparable pharmacokinetics feature allows easy intravenous to oral switch [16-18].

Conclusion –

In this study Levonadifloxacin has elicited potent activity against MRSA isolates . Among MRSA Levonadifloxacin was found to be having a reasonably good susceptibility (89.1%). It can thus safely be assumed that Levonadifloxacin is a promising therapeutic agent against MRSA and also other fluroquinolones resistance gram positive isolates.

This study supports the therapeutic utility of Levonadifloxacin for treating MRSA infections and could be better option for the management of resistant Gram positive bacterial infections. Further studies, with greater sample size, would be needed for authentication and utility of Levonadifloxacin as a therapeutic agent among MRSA isolates.

As the antibiotic resistance is on the rise nowadays, updating the strategies to overcome the growing antibiotic resistance like selection of narrow spectrum antibiotics with low resistance properties and antibiotic resistance surveillance is need of the hour.

Declarations:

Conflicts of interest: There is no any conflict of interest associated with this study

Consent to participate: We have consent to participate.

Consent for publication: We have consent for the publication of this paper.

Authors' contributions: All the authors equally contributed the work.

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