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Research Article

A Prospective, Observational and Comparative Study of *In-Vitro* Susceptibility of Isepamicin against Clinical Isolates from Various Clinical Sources (Triple I Study - Isepamicin in India)

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Abstract

Objectives: This study aims to investigate the *in-vitro* susceptibility of clinical isolates against Isepamicin and compared it with Gentamicin and Amikacin.

Patients and Methods: In this multicentre prospective study, clinical specimens of patients were collected from three different regions of India. Clinical isolates from urine, intra-abdominal, broncho-alveolar lavage, endotracheal secretion, and sterile blood were included. The E-test was used to quantify the minimal inhibitory concentration (MIC) for Isepamicin, Gentamicin, and Amikacin. The percentages of bacterial isolates were categorized as susceptible, intermediate, and resistant according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines as per Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM) recommendation.

Results: A total of 8 different bacterial isolates were collected from 150 clinical samples obtained from 50 patients. Respiratory (63 [42%]) and urine (44 [29.3%]) specimens were the most common sources for bacterial strains. The most identified bacterial isolates were *K. pneumoniae* (40 [26.6%]) and *P. aeruginosa* (38 [25%]). Isepamicin was found to be highly effective in urine samples and showed excellent sensitivity against *E. coli* (93.3%), followed by *P. aeruginosa* (57.9%) and *K. pneumoniae* (55.0%). Antimicrobial sensitivity was highest for Isepamicin (60/108 [56%]) at MIC≤1 mg/L and was most effective against Gram-negative bacterial isolates from the intensive care units (ICUs).

Conclusions: Isepamicin could treat *E. coli* infections and could be an effective therapy in the treatment of urinary tract infections (UTIs). Moreover, it could also be used as an alternative to Gentamicin and Amikacin against resistant cases.

Keywords: Aminoglycosides, Amikacin, *E. coli*, Gentamicin, Gram-negative bacteria, Isepamicin.

INTRODUCTION

The emerging antibiotic resistance represents a major concern nowadays. Several Gram-negative bacteria, which are a leading pathogen for a variety of infectious diseases, have developed resistance to a wide range of antibiotics, causing significant morbidity and mortality worldwide. Data from Indian hospitals has shown the prevalence of extended spectrum beta-lactamase (ESBL) producing Gram-negative bacteria in a range between 19% and 60%, and that of Carbapenem-resistant bacteria between 5.3% and 59%. Also, resistance to Gram-negative bacteria increases the financial burden of patients as measured by mortality, length of stay, and hospitalization cost [1].

The Enterobacteriaceae family, such as *Escherichia coli (E. coli), Klebsiella spp*., and *Enterobacter spp*., is the major cause of urinary tract infections (UTIs), of which the most common causative agent is *E. coli*, followed by *K. pneumoniae* [2, 3]. The treatment of UTIs is becoming more difficult due to the rapid spread of drug resistance, which is primarily related to the production of ESBLs, which leads to multidrug resistance (MDR) [4]. Hence, substantial effort should be put into developing new antibiotics against Gram-negative bacteria that reduce the suffering associated with UTIs.

Aminoglycosides have been widely used for the treatment of life-threatening infections, including UTIs, despite showing renal and auditory toxicities as major side effects. Isepamicin, a semisynthetic derivative of Gentamicin B, is one of the recently developed aminoglycosides that is prescribed in Asian and certain European countries for the treatment of infections caused by Gram-negative bacteria (*Enterobacteriaceae*). However, the emergence of resistance to aminoglycosides is mainly attributed to the aminoglycoside-

modifying enzymes such as type 1 6'- acetyltransferase produced by the pathogen, *Enterobacteriaceae*. Isepamicin has been shown to be more beneficial against strains that produce type 1 6′- acetyltransferase and one of the less toxic aminoglycosides [5, 6].

A review of 14 studies, comprising a total of 4901 isolates and examining Isepamicin against infections with Gram-negative bacteria, demonstrated comparable or higher *in-vitro* activity compared with Amikacin. Isepamicin also appeared to be superior to Amikacin in studies that included MDR bacteria [7]. Clinical studies have also shown no important difference in the effectiveness and safety profile of Isepamicin compared with those of Amikacin for the treatment of children with UTIs [8]. There is a lack of *in-vitro* data for Isepamicin against various pathogens from India, so the purpose of this study was to investigate the *in-vitro* susceptibility of clinical isolates obtained from patients admitted to tertiary care hospitals against Isepamicin and compare it with Gentamicin and Amikacin.

MATERIALS AND METHODS

Sample collection

The Gram-negative bacterial isolates evaluated in this study were isolated from clinical specimens of patients treated in three different centres (city hospitals), namely, Peerless Hospital, Kolkata (site A); Nanavati Max Super Speciality Hospital, Mumbai (site B); and Max Super Speciality Hospital, New Delhi (site C), located in the eastern, western, and northern regions of India, respectively.

The bacterial isolates [*Klebsiella pneumoniae* (*K. pneumoniae*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Acinetobacter baumannii* (*A. baumannii*), *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), *Enterobacter aerogenes* (*E. aerogenes*), *Serratia,* and *MRSA*] were collected from blood cultures, respiratory secretions, urine cultures, sterile body fluid cultures (bile), frank pus, and tissue culture of the microbiology laboratory. This study assessed the sensitivity of Isepamicin, Gentamicin, and Amikacin and their distributions as susceptible and resistant.

Inclusion Criteria

Both male and female patients, at least 18 years of age, visiting in-patient and out-patient departments and having clinical isolates from urine samples, intra-abdominal samples, broncho-alveolar lavage samples, endotracheal secretion samples, and sterile blood samples were included for sample collection.

Bacterial isolates and identification

After collection, clinical specimens were delivered to the laboratory, where processing and culture were done according to routine laboratory methods. Blood samples were collected in blood culture bottles, while other samples were streaked on MacConkey agar, sheep chocolate agar, and sheep blood agar medium using a calibrated loop (which can hold approximately 0.005 mL of the samples). Blood and chocolate agar were incubated in a Candle jar at 37°C for 24-48 hours. After incubation, the plates were observed for bacterial growth. The samples that showed significant bacterial growth were processed for the identification of the bacterial species using a VITEK 2 compact, fully automated system.

Determination of the sensitivity of bacterial Isolates

The E-test was used to quantify the minimal inhibitory concentration (MIC) for Isepamicin, Gentamicin, and Amikacin. This test was performed using a plastic strip containing a predefined antibiotic gradient, which was imprinted with the MIC reading scale in µg/mL. This strip was directly transferred to the agar matrix when applied to the inoculated agar plate. After incubation, a symmetrical elliptic inhibition zone was visible along the strip as bacterial growth was prevented. MIC was defined by the area of inhibition where the ellipse intersects the strip.

Antimicrobial susceptibility testing

Strain identification and MIC determination for the bacterial isolates were done using a VITEK 2 compact automated system (BioMerieux) against a set of antibiotics (Isepamicin, Amikacin, and Gentamicin), and the results were interpreted as per the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. The CLSI breakpoints (6a) were used for the interpretation of susceptibility to all antimicrobial agents except for Isepamicin. For Isepamicin, the breakpoints proposed in 2003 by the Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM) were used, and susceptibility was defined by an MIC ≤ 8 mg/L and resistance was defined by an MIC ≥16 mg/L.

The percentages of bacterial isolates were categorized as susceptible, intermediate, and resistant according to EUCAST guidelines (as per Comité de l'Antibiogramme de la Société Française de Microbiologie recommendation 2003).

RESULTS

Characteristics of the bacterial isolates

A total of 8 different bacterial isolates were prospectively collected from 150 clinical samples (male: 100, female: 50) at the microbiological laboratories of three centres during the year 2021. The samples were collected from 50 patients with a mean age range of 63 (18-96) years. The demographic characteristics of patients as per different sites are presented in Table 1.

Table 1: Demographic characteristics of patients

Name of sites	Gender-wise sample collection		Age, mean (Age range) in years
	Male	Female	
Peerless Hospital, Kolkata (Site A)	28	22	64 (18-96)
Nanavati Max Super Speciality Hospital, Mumbai (Site B)	35	15	62 (20-87)
Max Super Speciality Hospital, New Delhi (Site C)	37	13	61 (23-86)
Total no. of samples (150)	100	50	63 (18-96)

*Data are presented as numbers and mean

The types of culture specimens from which bacterial strains were most frequently isolated included respiratory (63 [42%]) and urine (44 [29.3%]). The most identified bacterial isolates were *K. pneumoniae* (40 [26.6%]), followed by *P. aeruginosa* (38 [25%]), *E. coli* (30 isolates [20%]), and *A. baumannii* (33 [22%]), which accounted for nearly 94% (Table 2).

Table 2: Identification of bacterial isolates from the clinical specimens

Name of sites	Number of samples (N=150)					Number of bacterial isolates (N=150)							
	Resp	Urine	IA	Blood	CSF	*K. P*	*P. A*	*A. B*	*E.C*	*S. A*	*E. A*	*S*	*MRS A*
A (n=50)	13	12	16	9	-	14	11	12	13	-	-	-	-
B (n=50)	22	15	7	5	1	16	17	8	7	-	1	1	-
C (n=50)	28	17	-	5	-	10	10	13	10	5	1	-	1
Total, n (%)	63; 42%	44; 29%	23; 15%	19; 13%	1; 1%	40; 27%	38; 25%	33; 22%	30; 20%	5; 3%	2; 1%	1; 0.6%	1; 0.6%

*Abbreviations:
A. B, Acinetobacter baumannii; E. A, Enterobacter aurogenes; E.C, Escherichia coli; K. P, Klebsiella pneumoniae; P. A, Pseudomonas aeruginosa; S, Serratia; S.A, Staphylococcus aureus.
CSF, Cerebro-spinal fluid; IA, Intra-abdominal; Resp, Respiratory
Site A, Peerless Hospital, Kolkata; Site B, Nanavati Hospital, Mumbai; Site C, Max Super Specialty Hospital, New Delhi.

Antimicrobial sensitivity and resistant strain evaluation

Among the bacterial isolates which were most frequently isolated, *E. coli* was most sensitive to Isepamicin (93.3%), followed by *P. aeruginosa* (57.9%) and *K. pneumoniae* (55.0%) (Table 3). Sample-wise organism sensitivity data showed a similar trend, as *E. coli* was found to be sensitive to Isepamicin in ≥90% of samples obtained from respiratory, urine, intra-abdominal, blood, and CSF (Table 4).

Table 3: Combined sensitivity of Isepamicin against all clinical isolates

Bacterial strain	Resistant (R)	Sensitive (S)	Total	% of Susceptibility
K. pneumoniae	18	22	40	55.0
P. aeruginosa	16	22	38	57.9
baumannii	24	9	33	27.3
E. coli	2	28	30	93.3
S. aureus	-	5	5	100
E. aerogenes	-	2	2	100
Serratia	-	1	1	100
MRSA	1	-	1	0
Total	61	89	150	59.3%

**Isepamicin MIC values based on data published by French standards associated with EUCAST - Comite´ de l'Antibiogramme de la Socie´te´ Franc¸aise de Microbiologie Report, 2003*

Table 4: Isepamicin susceptibility testing among the bacterial isolates

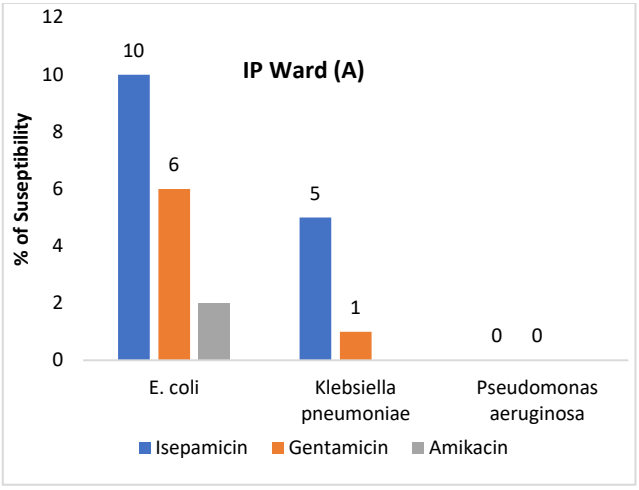
Bacterial isolates	CA-SFM Criteria for resistance (R) and susceptible (S) to Isepamicin (≥16 mg/L-R); (≤8 mg/L-S)											
	Respiratory			Urine			IA			Blood		
	(R)	(S)	(n) %S	(R)	(S)	(n)% S	(R)	(S)	(n)% S	(R)	(S)	(n)% S
K. pneumoniae	10	7	(17) 41	4	9	(13)69	3	5	(8)63	1	1	(2)50
E. coli	-	3	(3) 100	2	18	(20)90	-	4	(4)100	-	3	(3) 100
P. aeruginosa	7	10	(17) 58.82	7	3	(10) 30	1	7	(8)88	1	2	(3)67
A. baumannii	16	4	(20) 20	1	-	(1)0	2	1	(3)33	5	3	(8)38
S. aureus	0	3	(3)100							-	2	(2)100
E. aerogenes	-	1	(1)100							-	1	(1)100
Serratia	-	1	(1)100									
MRSA	1	-	(1)0									
Total	34	29	(63) 46	14	30	(44)68	6	17	(23)74	7	12	(19)63

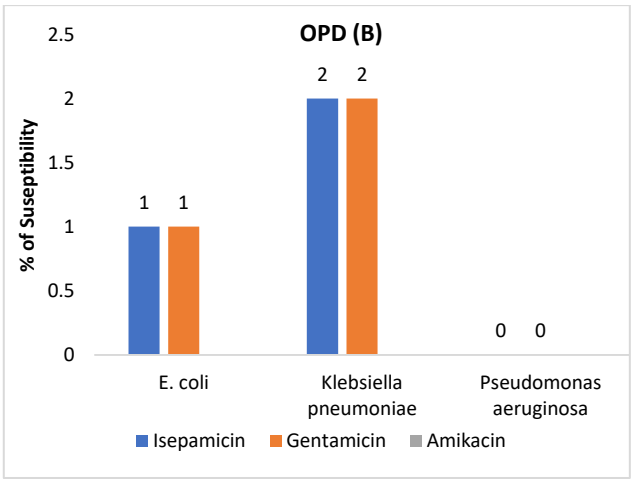
** R, Resistant strain; S, Sensitive strain to Isepamicin; n = number of bacterial isolates; %S = sensitivity in percentage. IA = Intra-abdominal sample*

Comparative evaluation of the susceptibility

In a comparative evaluation, antimicrobial sensitivity was found to be highest for Isepamicin (60/108 [56%]), followed by Gentamicin (23/108 [21%]) and Amikacin (4/108 [4%]) at MIC≤1 mg/L. However, Isepamicin, Gentamicin, and Amikacin showed 69%, 41%, and 52% susceptibility up to MIC ≤8 mg/L, respectively.

Isepamicin was found to be most effective against Gram-negative bacterial isolates from the ICUs of all three centres (Figure 1A, B, and C). Isepamicin was also found to be highly effective in urine samples, followed by respiratory samples, and showed higher susceptibility against *E. coli*, followed by *K. pneumoniae* and *P. aeruginosa* bacterial isolates comparable to Gentamicin and Amikacin (Figure 2A, B, C, and D).





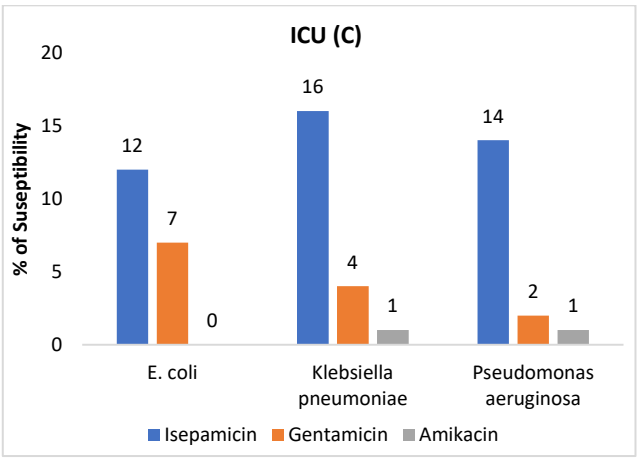
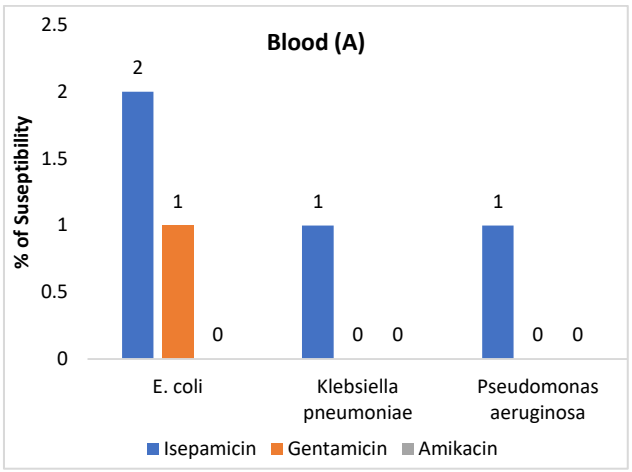
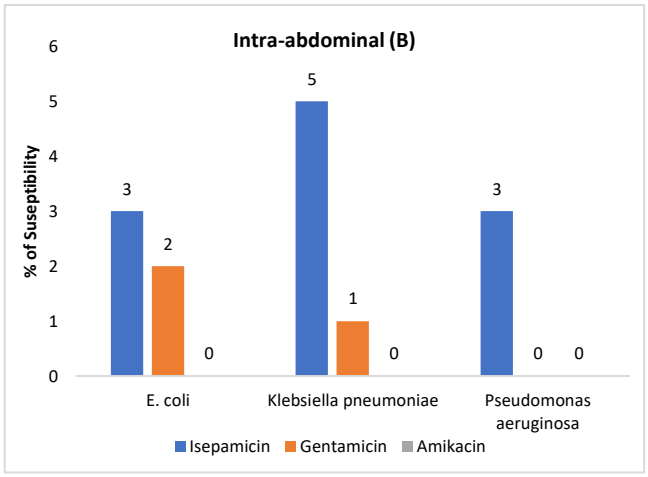
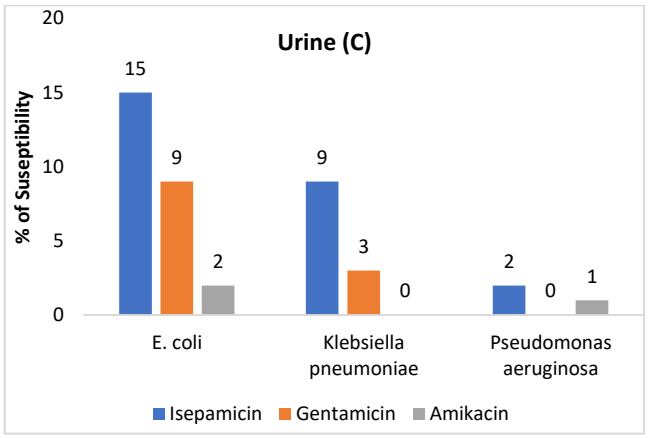


Figure 1: Comparative antimicrobial susceptibility ward wise (A-IP Ward; B-OPD; C-ICU)







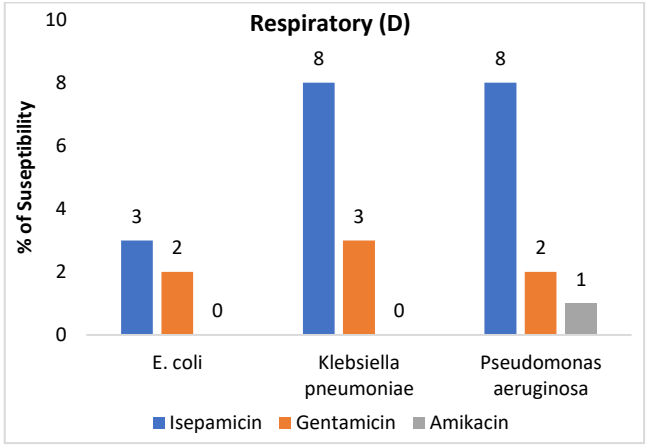


Figure 2: Comparative evaluation of the susceptibility of Isepamicin, Gentamicin, and Amikacin in different collected samples (A-Blood; B-Intra abdominal; C-Urine; D-Respiratory)

The most susceptible antibiotic to *E. coli* is Isepamicin (MIC≤1 mg/L), followed by Gentamicin and Amikacin (Table 5). In the urine sample, only 10% of *E. coli* was found to be Isepamicin-resistant.

Table 5: Comparative susceptibility evaluation of Isepamicin, Amikacin, and Gentamicin on highly sensitive bacterial isolates

	Sensitivity of Isepamicin				**Sensitivity of Gentamicin**				**Sensitivity of Amikacin**			
Lab Diagnosis	**MIC (≤1)**	**MIC (≤8)**	**MIC (≥8)**	**Grand Total**	**MIC (≤1)**	**MIC (≤8)**	**MIC (≥8)**	**Grand Total**	**MIC (≤1)**	**MIC (≤8)**	**MIC(≥8)**	**Grand Total**
E. coli	23	5	2	30	14	8	8	30	2	23	5	30
K. pneumoniae	23	1	16	40	7	5	28	40	1	17	22	40
P. aeruginosa	14	8	16	38	2	8	28	38	1	12	25	38
Grand Total	**60**	**14**	**34**	**108**	**23**	**21**	**64**	**108**	**4**	**52**	**52**	**108**
Overall Sensitivity												
Highly Sensitive	56%				21%				4%			
Sensitive	69%				41%				52%			
* MIC: Minimum inhibitory concentration (mg/L); Data are presented as number and percentage												

DISCUSSION

The infections caused by gram-negative bacilli are important to treat to avoid complications and reduce morbidity and mortality, as they show high resistance to antibiotics. In this TRIPLE I Study, we evaluated the *in-vitro* activity of Isepamicin against 8 different bacterial isolates from 150 different clinical samples, prospectively collected from patients with different ailments and from 3 participating centres in India [9].

In our study, Isepamicin exhibited very high *in-vitro* activity against Gram-negative pathogens, including *E. coli, K. pneumoniae,* and *P. aeruginosa*, collected from different specimens of unique patients. Also, Isepamicin was the most susceptible *in-vitro* agent against all isolates among all the antibiotics tested. High susceptibility to Isepamicin was also observed for the isolates collected from patients hospitalized in the ICU [10].

E. coli was found to be 90-100% sensitive to Isepamicin in all collected specimens. Likewise, 67-88% of *P. aeruginosa* were sensitive to Isepamicin in intra-abdominal and blood specimens, and 59-63% of *K. pneumoniae* were sensitive to Isepamicin in urine and intra-abdominal samples. In line with the present study, Maraki et al. also reported superior Isepamicin susceptibility (96.9%) when given with Colistin, with *E. coli* (99.9%) and *K. pneumoniae* (95.3%) being the most susceptible isolates [7]. They further found Carbapenem-nonsusceptible isolates (89.6%) to be susceptible to Isepamicin. In another study, Tsai et al. reported that Isepamicin and other aminoglycosides (Gentamicin, Amikacin, and Tobramycin) were found effective against 95% of bacterial isolates [11]. Karakullukçu et al. also reported that Isepamicin was effective against 95.1% of Carbapenem-resistant enterobacterales [12].

Overall, Isepamicin susceptibility was found to be highest, i.e., 69% at MIC values of ≤1mg/l, amongst *E. coli, K. pneumoniae,* and *P. aeruginosa*, comparable to Gentamicin (21%), and Amikacin (4%). Isepamicin was also found to be highly effective in urine samples and showed higher sensitivity against *E. coli*, indicating its potential clinical use in the treatment of severe UTIs.

Moreover, Isepamicin can also be used as an adjuvant therapy for the treatment of intra-abdominal and blood infections that occur due to Gram-negative bacilli. These findings are further supported by two multicentre studies [13], in which *E. coli* (97%) and *Enterobacteriaceae* (93.6%) were found susceptible to Isepamicin in clinical samples. However, for *P. aeruginosa* isolates, Isepamicin has shown low susceptibility (36%), and other aminoglycosides tested in this study (Gentamicin and Amikacin) also have not shown any potential antimicrobial effect against *P. aeruginosa.*

The high susceptibility and more effective *in-vitro* potential of Isepamicin against gram- negative bacterial isolates, as compared with other aminoglycosides, could be attributed to the lower impact of 1 6'-N-acetyltransferase enzyme on Isepamicin [14]. This enzyme is the most common aminoglycoside-modifying enzyme present in these pathogens and causes resistance to aminoglycosides. However, *K. pneumoniae* and *P. aeruginosa* bacterial isolates were found to be resistant in urine (69% and 70%, respectively) and respiratory (58% and 46%, respectively) clinical samples against Isepamicin. This resistance to Isepamicin could result from the combination of more than one aminoglycoside-modifying enzyme or decreased permeability or efflux mechanisms accompanying such an enzyme [15, 16]. However, these mechanisms should be explored in future studies. Despite the beneficial role of Isepamicin in our *in vitro* study, the clinical effectiveness of Isepamicin in patients is difficult to interpret because it was used in combination with other agents in a few studies, and thus the outcome cannot be attributed to Isepamicin per se.

Isepamicin could be used as an alternative to Amikacin and Gentamicin based on historical data, as the sensitivity pattern has not significantly changed much compared to older data. Also, there is a need to emphasize a local antibiogram with sensitivity to Isepamicin while deciding about empirical therapy. Though aminoglycosides can cause nephrotoxicity, vestibular toxicity, and ototoxicity, Isepamicin is one of the less toxic aminoglycosides. Nevertheless, the current data support the use of Isepamicin over other aminoglycosides in patients with drug resistant Gram-negative bacterial infections.

CONCLUSION

We found that Isepamicin has the potential to treat infections caused by *E. coli* and could be an effective therapy in the treatment of UTIs. It is further found to be moderately sensitive to *Klebsiella* and *Pseudomonas*. Moreover, it could be

used as an alternative to Gentamicin and Amikacin and against resistant cases. To validate these findings, future research is warranted to explore Isepamicin's potential in adequately designed clinical studies.

Conflicts of Interest

There are no conflicts of interest.

Author contributions

This work was carried out in collaboration among all authors. Dr. Ami Varaiya, Dr. Bansidhar Tarai, and Dr. Bhaskar Narayan Chaudhuri participated in study design, study execution, data collection, data analysis, and manuscript development. Dr. Abdul Ansari and Dr. Niraj Tyagi supervised the study. All the authors read and approved the final version of the manuscript.

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