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Gentamicin pharmacokinetics and pharmacodynamic correlation in pediatrics—A systematic review

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ABSTRACT

The primary objective of the review is to correlate the pharmacokinetics and pharmacodynamics data of gentamicin. A thorough literature search was carried out using the databases such as Scopus, PubMed, Google Scholar, and Cochrane. The different types of study designs included were observational (5), prospective (7), retrospective (9), cross-sectional (2), retrospective cross-sectional (1), and retrospective cohort (1). The data were extracted from these studies and it was reviewed by the authors. A total of 149 studies were identified through the database; after removing duplicates, 100 articles were screened, 31 articles were excluded from screening, and 69 articles were included. Out of 69 articles, 26 full-text articles were included and 43 full-text articles were excluded. The dosage recommendations under different disease conditions and their minimum inhibitory concentrations were reviewed. For sepsis condition, 5 mg/kg/day is the ideal dose of gentamicin and >2 mg/l shows minimum inhibitory concentration; for urinary tract infection, 4.5–7.5 mg/kg/day dose of gentamicin shows a minimum inhibitory concentration of >2 mg/l toward organism. For severe malnutrition, 7.5 mg/kg/day dose of gentamicin showed an inhibitory concentration of >2 mg/l. Pharmacokinetic and pharmacodynamic correlation model helps to identify the concentration of gentamicin showing sensitivity and resistance toward organisms at a targeted dosage range.

INTRODUCTION

When there is a seasonal change, the prevalence of respiratory infections is high in children. Gentamicin is a narrow therapeutic index drug belonging to the class of aminoglycosides which is effective against Gram-negative organisms such as *Escherichia coli*, *Klebsiella species*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Staphylococcus aureus*, and resistant against Enterobacteriaceae, Enterococci, and Staphylococci (Krause *et al*., 2016; Lundergan *et al*., 1999; MacDougall and Chambers, 2011). It is mainly indicated for the treatment of both upper and lower respiratory tract infections, urinary tract infections (UTI), meningitis, bacterial neonatal sepsis, peritonitis, bacterial septicemia, skin, bone, and soft tissue infections

(Pacifici, 2015). The mechanism action of gentamicin involves the inhibition of protein synthesis of bacteria by binding with 30S ribosomal subunits, causing the misreading of the mRNA, and facilitating the premature termination of translation (Hahn and Sarre, 1969; Kushner *et al*., 2016). The available dosage forms of gentamicin are ointment, injections, and drops (Bloomfield *et al*., 1978). The preferable route of gentamicin administration includes topical routes, intramuscular (IM), intravenous (IV), intrathecal, auricular, and ophthalmic drops (Bloomfield *et al*., 1978; Haddad *et al*.,1986). The recommended dose of gentamicin in pediatrics is 2–7.5 mg/kg every 8 hours; with an initial dose of 2–5 mg/kg/day and the maximum dose is 7.5 mg/kg/day. During maintenance dose therapy, dose adjustment may be required for renal failure patients (Taylor and Keane, 1976). The main adverse effects of gentamicin include nephrotoxicity and ototoxicity, wherein nephrotoxicity is reversible and ototoxicity is irreversible (Saleh *et al*., 2016). Gentamicin is contraindicated in myasthenia gravis, where neuromuscular transmission may be impaired (Garraghan and Fallon, 2015). Gentamicin interacts

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with penicillin or cephalosporin, cyclosporin, amphotericin B, and furosemide (Garraghan and Fallon, 2015; Noone and Pattison, 1971). Pharmacokinetic parameters of gentamicin include absorption: poorly absorbed orally; volume of distribution (V_d) in infants (0.4 ± 0.1 l/kg), neonates (0.45 ± 0.1 l/kg), and children (0.35 ± 0.15 l/kg); protein binding (0%–30%); half-life in neonates: if <1 week for 3–11.5 hours, 1 week to 1 month for 3–6 hour, infants 4 ± 1 hour, children 2 ± 1 hour, peak serum concentration for IM route within 30–90 minutes; and IV route within 30 minutes, which is excreted through the kidneys (Nocton and Gedeit, 2018). Gentamicin has an average trough concentration of <2 μg/ml and an average peak concentration of <12 μg/ml (Garraghan and Fallon, 2015).

Nowadays, all antibiotics are susceptible to bacteria which lead to irrational use of antibiotics. Antibiotic sensitivity testing (AST) being a scientific tool will be helpful to identify the bacteria and will be helpful in rationalizing the antibiotic treatment.

AST is a test that determines the sensitivity of bacteria to an antibiotic. The two methods of AST are dilution method (broth dilution and agar dilution method) and diffusion method (Stokes' disk diffusion and Kirby–Bauer disk diffusion method).

The dilution method is used to find out the growth and identification of bacterial populations. Micro-dilution and macro-dilution are the two types of dilutions, wherein broth and agar are the commonly used media. In broth dilution, consecutive twofold dilutions (1, 2, 4, 8, and 12 μl) of antibiotics are made and in agar dilutions and antibiotics are diluted in agar medium (Khan et al., 2019). The disk diffusion method is the gold standard for confirming the susceptibility of bacteria. In this method, an isolated bacteria colony is selected, suspended into growth media, and standardized through a turbidity test (Graham et al., 1985).

Pharmacokinetics refers to the study of the time course of drug absorption, distribution, metabolism, and excretion. Pharmacodynamics refers to the relationship between drug concentration at the site of action and their effect (Tozer and Rowland, 2006).

The pharmacokinetic–pharmacodynamic modeling links the pharmacokinetics and pharmacodynamics to evaluate dose–concentration–response relationships and describe the effect of time courses resulting from a drug dose (Meibohm and Derendorf, 1997). Hence, this review focuses on the pharmacokinetic–pharmacodynamics modeling of gentamicin in pediatrics.

The objective of the study is to correlate pharmacokinetic and pharmacodynamic data of gentamicin for the pediatric population for different disease conditions.

MATERIALS AND METHODS

Types of participants

It includes pharmacokinetics, pharmacodynamics (sensitivity), and Pharmacokinetic- Pharmacodynamic (PK-PD) correlation of gentamicin studies that were carried out in the pediatric population for different disease conditions.

Types of interventions and outcome

Intervention—comparison of pharmacokinetic and pharmacodynamic data of gentamicin. Outcome—to understand

the concentration profile of gentamicin showing sensitivity against bacterial infections.

SEARCH METHODS

Electronic searches

A thorough literature search was conducted from the year 1998 to 2020, using the keywords aminoglycosides, gentamicin, population pharmacokinetics, pediatrics, pharmacokinetics and pharmacodynamics correlation, nonlinear mixed effects modeling, therapeutic drug monitoring, and antibiotic sensitivity test in the following database: Cochrane Library, PubMed, Scopus, and Google Scholar.

Data collection and analysis

The collected data was analyzed based on the inclusion and exclusion criteria. The pharmacokinetics and pharmacodynamics studies were categorized, followed by a comparison of the pharmacokinetic and pharmacodynamic profiles of gentamicin.

Data extraction and analysis

Three authors independently extracted all the studies. The following study characteristics were collected: author, study design, country of publication, age range of participants, year of publication, and dose and indication for gentamicin.

A total of 149 articles were identified through searching. 100 articles were screened after removing duplication; 31 articles were excluded from screening; and 69 articles were included. Out of 69 articles, 26 articles were included in the study and 43 articles were excluded. The Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) flow diagram describes the study as shown in Figure 1. All articles included in the review were conducted in pediatrics.

RESULTS AND DISCUSSION

Pharmacokinetic approach in different disease conditions

In Gram-negative bacterial infections, pediatric patients receiving a dose of 7.5 mg/kg/day of gentamicin as the drug of choice. Plasma samples were checked for the targeted trough concentration <2 μg/ml and peak concentration <10 μg/ml. The concentration was found to exceed the therapeutic range. The dose was adjusted to 3 mg/kg/day; their trough and peak concentrations were found to be 1–2 μg/ml and 6 μg/ml, respectively. The adjusted daily dose of gentamicin was 3–5 mg/kg/day which were found to be ideal for Gram-negative bacterial infections (Ismail et al., 1990).

For sepsis, meningitis, and neutropenic fever, neonates received a dose of 5 mg/kg/day of gentamicin every 24 hours as the drug of choice. Blood samples were collected to check for the targeted peak concentration of 8–10 mg/l and trough concentration <2 mg/l. The first dose of gentamicin appears to be more efficient in achieving the target serum concentrations than steady state which would be ideal for sepsis, meningitis, and neutropenic fever (Lim et al., 2020).

For neonatal sepsis and Gram-negative and Gram-positive infections, they received a dose of 4 mg/kg of gentamicin as the drug of choice. The trough concentration should not
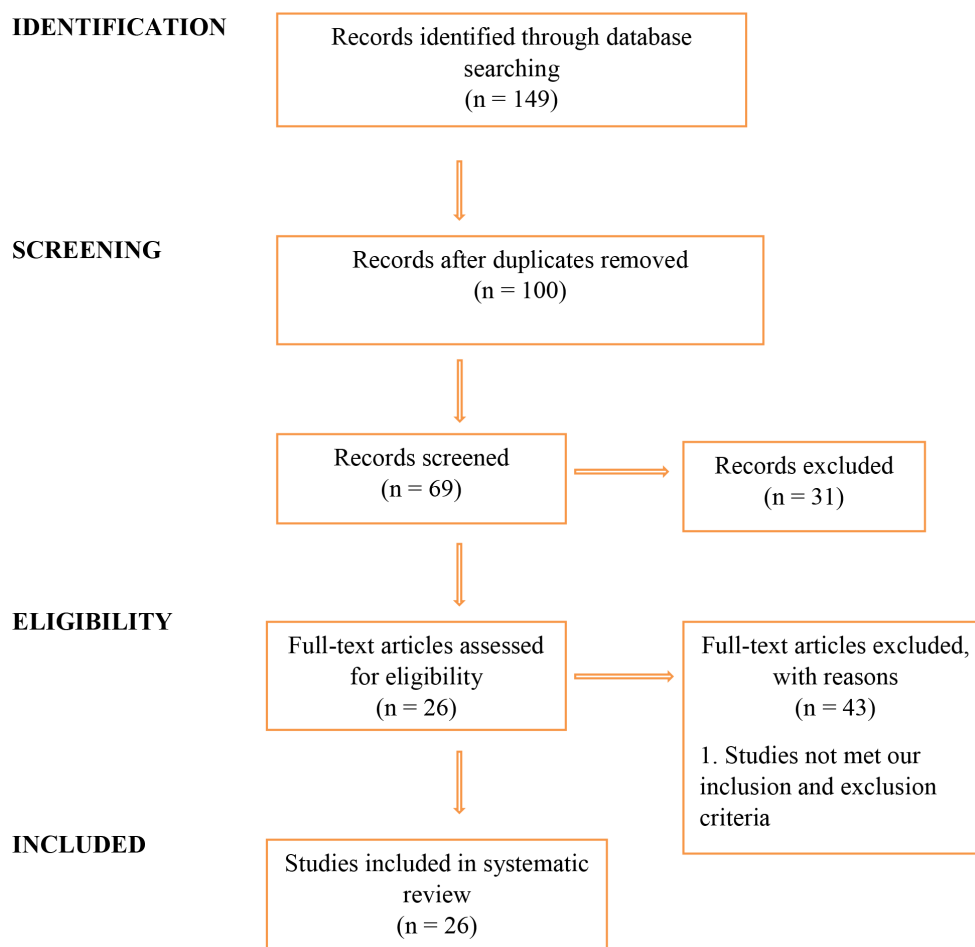
IDENTIFICATION

Records identified through database searching
(n = 149)

SCREENING

Records after duplicates removed
(n = 100)

Records screened
(n = 69)

Records excluded
(n = 31)

ELIGIBILITY

Full-text articles assessed
for eligibility
(n = 26)

Full-text articles excluded,
with reasons
(n = 43)

1. Studies not met our
inclusion and exclusion
criteria

INCLUDED

Studies included in systematic
review
(n = 26)

Figure 1. PRISMA flow diagram.

exceed more than 2 mg/l which can lead to toxicity. A dose 4 mg/kg of gentamicin was found to be sufficient to achieve a C_{max} concentration of 5 mg/l with a postnatal age. The dose needs to be increased to 7.5 mg/kg to achieve target peak concentrations of >10 mg/l; trough concentration <2 mg/l in neonates which were effective against sepsis, Gram-negative, and Gram-positive infections (van Donge *et al.*, 2018).

For sepsis, neonates received a dose of 5 mg/kg/day of gentamicin, with a target maximum concentration of 20 mg/l. Low serum levels are achieved with a dosing range of 5–8 mg/kg/day. A once-daily dose is expected to induce a high C_{max}/Minimal Inhibitory Concentration (MIC) level. Micro-organism activity with MICs was as high as 2 mg/l for gentamicin. A lower maximum concentration is achieved by dividing dose and maximum concentration/minimum inhibitory concentration above 8–10 mg/l would be difficult to reach, particularly for Multi-drug Resistance (MDR) *P. aeruginosa* (Mareville *et al.*, 2012).

For hypoxic ischemic encephalopathy with hyperthermia, neonates received a dose of 5 mg/kg/day of gentamicin every 24 hours. Blood samples were collected and their targeted trough concentration >2 mg/l and peak concentration <6 mg/l were not obtained among the neonates with 24-hour dosing intervals. At 5 mg/kg/day every 36 hours of dosing intervals, the targeted trough

concentration <2 mg/l was obtained in neonates which would be effective against hypoxic-ischemic encephalopathy (Frymoyer *et al.*, 2013). The pharmacokinetic studies' characteristics included in this review are shown in Table 1.

Wound infection

Wound infections are common conditions in pediatrics which occur mainly in the skin for which gentamicin sulfate cream is used as the drug of choice. A wound swab was collected to check for susceptibility. The Gram-negative bacteria such as *E. coli (*48.3%), *Proteus* species (74%), *K. pneumonia* (36%), and *P. aeruginosa* (86%) show sensitivity toward gentamicin, whereas Gram-positive organism shows resistance against gentamicin (Kibret and Abera, 2011; Mama *et al.*, 2014).

Urinary tract infections

UTI are the most common bacterial infections in neonates and gentamicin is commonly prescribed for the same. The urine samples were collected to check for sensitivity and the following organism such as *E. coli*, *Klebsiella* spp., *Proteus mirabilis*, and *P. aeruginosa* was identified. *Escherichia coli* shows a resistance of about 30%–75% for amikacin, gentamicin. *Klebsiella* (50%), *P. mirabilis* (52.2%), and *P. aeruginosa* (100%) are sensitive toward

gentamicin (Abuhandan *et al.*, 2013; Garoy *et al.*, 2019; Kibret and Abera, 2011; Rezaee and Abdinia, 2015; Wang *et al.*, 2014).

     Community-acquired and persistent nosocomial infections commonly occur in neonates in hospital settings. Gentamicin is mainly used to treat community-acquired infections in neonates. The swab samples for pus, urine, and sputum were checked for susceptibility. The organisms identified were *P. aeruginosa*, *K. pneumonia*, and *S. aureus*. *Pseudomonas aeruginosa* (83.5%), *K. pneumoniae* (100%), and *S. aureus* (92.4%) were sensitive toward gentamicin (Ali *et al.*, 2014; Nwankwo and Nasiru, 2011; Shilpa *et al.*, 2016; Sivanmaliappan and Sevanan, 2011; Yadav *et al.*, 2017).

Typhoid fever

     Typhoid fever commonly occurs in pediatrics and is caused by contaminated food and water. Gentamicin is effective against *Salmonella typhi* mainly in pediatrics. The blood samples were collected for sensitivity and *S. typhi* was identified; it is susceptible to Ceftriaxone (100%), Cefixime, Gentamicin (99.4%), and Ciprofloxacin (98.6%) (Ali and Sultana, 2016). Probiotics are live micro-organisms that help to provide immunity and prevent the infections in neonates. The swab and sputum samples were checked for sensitivity. Bacteria such as *Lactobacillus acidophilus* was identified and it is sensitive against gentamicin (Zhou *et al.*, 2005).

Pneumonia

     Pneumonia is the second most commonly occurring bacterial infection in children and gentamicin is a commonly used drug in pneumonia. The sputum was collected and Gram-negative organisms, *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Serratia marcescens*, and *Acinetobacter* spp. were identified. *Escherichia coli* (87%), *Klebsiella* spp. (93%), *Enterobacter* spp. (93.9%), *S. marcescens* (95.8%), *Acinetobacter* spp. (41%) are sensitive toward gentamicin (Sader *et al.*, 2014).

Severe acute malnutrition (SAM)

     SAM is more common in children mainly with pneumonia and UTI conditions. A susceptibility test was carried out with urine and sputum samples. Organisms such as *E. coli* and nontyphoidal *Salmonellae* were identified and it shows 100% sensitivity toward gentamicin (Okomo *et al.*, 2011).

Sepsis

     Sepsis is more common in neonates; gentamicin is the drug of choice for sepsis. The blood samples were checked for sensitivity and Gram-positive and Gram-negative organisms were identified. Methicillin-resistant *S. aureus* (MRSA) was sensitive toward gentamicin and *Klebsiella* and *E. coli* showed high resistance to Cefotaxime (90.5%), Gentamicin (75%), and Ciprofloxacin (76.2%) (Mokuolu *et al.*, 2002; Pokhrel *et al.*, 2018).

Community-acquired Gram-negative uropathogen infections

     Escherichia coli and *K. pneumonia* were isolated and showed high sensitivity to Ciprofloxacin (95.3%), Amikacin (93.9%), Nalidixic acid (92.2%), Gentamicin (89.2%), and Nitrofurantoin (83.8%) (Mohamed *et al.*, 2012).

     The organisms were identified from different diseases and their percentages of sensitivity toward gentamicin are shown in Table 2 and their respective characteristics for pharmacodynamics are shown in Table 3.

Pharmacokinetic–Pharmacodynamic Correlation

     The PK-PD model was developed by using *in vitro* time-kill curve experiments; it is classified into two types: static time-kill curve experiments and dynamic time-kill curve experiments.

Table 1. Gentamicin doses concerning the achieved concentration.

Source	Disease	Dose	Concentration
Ismail *et al.* (1990)	Gram-negative bacterial infection	7.5 mg/kg/day	Trough concentration <2 µg/ml
			Peak concentration <10 µg/ml
Lim *et al.* (2020)	Sepsis and meningitis	5 mg/kg/day	Trough concentration <2 mg/l
			Peak concentration 8–10 mg/l
van Donge *et al.* (2018)	Neonatal sepsis and Gram-negative and positive infection	4 mg/kg	C_{max} 5 mg/l
Mareville *et al.* (2012)	Sepsis	5 mg/kg/day	Target C_{max} 20 mg/l
Frymoyer *et al.* (2013)	Hypoxic ischemic encephalopathy with hyperthermia	5 mg/kg/day	Trough concentration <2 mg/l

Table 2. Organisms identified from different disease conditions and its percentage of sensitivity towards gentamicin.

Disease condition	Micro-organism and sensitivity
Wound infection	*E. coli* (48.3%), *Proteus species* (74%), *K. pneumoniae* (36%), *P. aeruginosa* (86%).
UTI	*Klebsiella* (50%) and *P. aeruginosa* (100%)
Community-acquired, persistent nosocomial	*P. aeruginosa* (83.5%), *K. pneumoniae* (100%), *S. aureus* (92.4%)
Typhoid fever	*S. typhi* (99.4%)
UTI, wound and ear infections	*E. coli* (79.4%)
Gram-negative organism in Intensive Care Unit (ICU)	*E. coli* (87%), *Klebsiella* spp. (93%), *Enterobacter* spp. (93.9%), *S. marcescens* (95.8%), *Acinetobacter* spp. (41%).
SAM	*E. coli* (100%), non-typhoidal *Salmonellae* (NTS) (100%)
Neonatal sepsis	MRSA (70%)

Table 3. Pharmacodynamic study.

Source	Study design	Disease	*Organism*	Sensitivity or resistance to gentamicin
Mama *et al.* (2014)	Cross-sectional	Wound infection	*E. coli* (48.3%), *Proteus species* (74%), *K. pneumoniae* (36%), *P. aeruginosa* (86%).	Sensitivity
Kibret and Abera (2011)	Retrospective	Wound infection, UTI, ear infection	*E. coli* (79.6%)	Sensitivity
Rezaee and Abdinia (2015)	Prospective	UTI	*E. coli* (32%)	Resistance
			Klebsiella spp.	Sensitivity
Garoy *et al.* (2019)	Cross-sectional study	Skin and soft tissue infection	MRSA (77%)	Sensitivity
Abuhandan *et al.* (2013)	Prospective study	UTI	*E. coli*, *Klebsiella* spp.	Sensitivity
Wang *et al.* (2014)	Observational study	General infection	*P. Mirabilis* (57.7%)	Sensitivity
Yadav *et al.* (2017)	Prospective study	Community-acquired infection	*P. aeruginosa* (53%)	Sensitivity
Shilpa *et al.* (2016)	Observational study	Community and hospital-acquired infection	*K. pneumonia* (37.50%)	Resistance
			K. pneumonia (62.50%)	
				Sensitivity
Onwubiko *et al.* (2015)	Prospective study	Nosocomial infection	*S. aureus* (63%)	Sensitivity
Sivanmaliappan *et al.* (2011)	Prospective study	Soft tissue infection	*P. aeruginosa* (66.6%)	Resistance
Ali *et al.* (2014)	Observational study	Community-acquired infection Gram-negative uropathogens	*E. coli and K. pneumonia* (89%)	Sensitivity
Ali *et al.* (2014)	Prospective study	Typhoid fever	*S. typhi* (99.4%)	Sensitivity
Zhou *et al.* (2005)	Observational study	New probiotics	*L. acidophilus*	Sensitivity
Sader *et al.* (2014)	Retrospective study	Gram-negative infections	*P. aeruginosa* (87%)	Sensitivity
			Klebsiella spp. (91%)	
			E. coli (84.2%)	
			Enterobacter spp. (94.8%)	
			Acinetobacter spp. (29.5%)	
			Serratia spp. (97.7%)	
Okomo *et al.* (2011)	Retrospective study	SAM	*E. coli* (100%), NTS (100%)	Sensitivity
Pokhrel *et al.* (2018)	Retrospective cross-sectional study	Neonatal sepsis	*Klebsiella* (75.5%)	Resistance
Mokuolu *et al.* (2002)	Retrospective study	Sepsis	*S. aureus* (62.5%)	Sensitivity

The correlation was carried out by the semi-mechanistic PK-PD model which describes the time course of the drug concentration and the bacterial growth and killing after antibacterial treatment. For an extremely preterm new-born infant, the highest possible dose is 6 mg/kg for a 36-hour interval, while a dose of 7 mg/kg with a 36-hour interval in the typical term newborn infant. Dosing intervals should longer than 24 hours for extremely preterm infants to reach trough levels of <2 mg/l, unless the dose is reduced to less than 4 mg/kg. To achieve concentrations of <1 mg/l in typical newborn infants, doses of 4 and 5 mg/kg with a 36-hour interval is recommended (Carapetis *et al.*, 2001; Nielsen *et al.*, 2011).

In sepsis conditions, 5 mg/kg/day of gentamicin shows a minimum inhibitory concentration of >2 mg/l toward *E. coli*, *P. aeruginosa*, *Staphylococcus epidermidis*, *Enterobacter* spp., Streptococci, *S. aureus, K. pneumoniae*, and *Citrobacter diversus*. For MDR *P. aeruginosa*, the minimum inhibitory concentration in the range of 8–10 mg/l is not shown (Frymoyer *et al.*, 2013).

In urinary tract infection, 4.5–7.5 mg/kg/day of gentamicin shows minimum inhibitory concentration >2 mg/l toward Gram-negative bacilli, Enterococci, and *Staphylococcus* spp. (Carapetis *et al.*, 2001). In severe malnutrition, 7.5 mg/kg/day of gentamicin shows a minimum inhibitory concentration of >2 mg/l toward *Plasmodium falciparum* and *E. coli* (Seaton *et al.*, 2007).

CONCLUSION

This review focuses on gentamicin correlating the pharmacokinetics and pharmacodynamics data by using the semi-mechanistic PK-PD model. This review guides us about how to correlate the pharmacokinetic and pharmacodynamic data. It will help us find out at what concentration gentamicin shows resistance and sensitivity toward bacteria, especially in pediatric population.

AUTHORS' CONTRIBUTION

Keerthana Chandrasekar and K. P. Arun formulated the hypothesis. B. Vahini, V. Vijay, and R. Shalini carried out the data collection and analysis. All the authors read and accepted the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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None.

ETHICAL APPROVAL

Not applicable.

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