Comparison of Antimicrobial Potency Assay of Common Antibiotic Prophylaxis Drugs Recommended in Dentistry for Preventing Infective Endocarditis - An Invitro Study from Chennai, India

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ABSTRACT

BACKGROUND

Infective endocarditis [IE] prophylaxis is recommended for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. The study intended to compare the antimicrobial potency of amoxicillin, cephalexin, and clindamycin against *Streptococcus mutans*, the common causative organism of dental infections. The objective was to assess the potency of recommended choice of antibiotics and its efficacy among each other in infective endocarditis prophylaxis during dental procedures.

METHODS

Saliva samples [N = 20] were collected from patients susceptible for IE and *Streptococcus mutans* was cultured in Infusion Agar. The principle used in this study was based on the Kirby - Bauer disc diffusion Antimicrobial Susceptibility Test [AST] Method and minimum inhibitory concentration [MIC]. In this method, the three HiMedia antibiotic discs of amoxicillin, cephalexin and clindamycin were loaded and assessed for measurable "zone of inhibition" against mutans.

RESULTS

One-way ANOVA was used to compare the means of zone of inhibition of each disc. The test was statistically significant with F value of 4.093 at P value 0.038. Post hoc analysis was conducted using Tukey's HSD test as one-way ANOVA was statistically significant. The mean difference of 13.16 mm between amoxicillin and cephalexin was found to be statistically significant at P value 0.041 with lower and upper bound at 0.527 and 25.806 respectively. The mean difference of 2.65 mm between amoxicillin and clindamycin and - 10.50 mm between cephalexin and clindamycin was not found to be statistically significant.

CONCLUSIONS

Amoxicillin showed to be more potent among the antibiotics chosen for this study. Clindamycin showed to be a better alternative to cephalexin and could be the first choice in case of patients allergic to penicillin group of drugs.

KEY WORDS

Antibiotic Prophylaxis, Infective Endocarditis, Antimicrobial Potency, Minimum Inhibitory Concentration [MIC], Antimicrobial Susceptibility Test [AST], Kirby Bauer Disk Diffusion Method

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BACKGROUND

Infective Endocarditis [IE] refers to the infection involving the endocardial surface, commonly involving heart valves, but it can also involve the endocardium or intracardiac devices.[1] Despite the existing advanced diagnostic aids, therapeutic antibacterial drugs available and preventive treatment strategies in place for anticipated complications, infective endocarditis persists to be the reason for considerable morbidity rate and mortality rate.[2,3,4] It had been well documented that mouth had been recognized as entry portal of the microbes in 14 - 20 % of patients with diagnosed IE.[5,6,7,8]

Streptococcus mutans, a member of the *Streptococcus viridans* group associated with dental caries, is commonly associated with endocarditis.[9,10] *S. mutans* DNA had been commonly detected in cardiovascular specimens, like heart valves and atheromatous plaque.[11] It had been isolated and characterized by the polymerase chain reaction [PCR] method with DNA sequencing from the samples collected from heart valves and in dental plaque of IE patients.[12]

Around 1955, The American Heart Association [AHA] established its primary protocol for IE prevention associated with treatment procedures done in a dental setting.[13] The indication for prophylaxis is of late restricted to patients with the increased risk of IE who are to undergo the highest risk of invasive dental treatment procedures.[14] The American Heart Association Antibiotic Regimens for Cardiac Prophylaxis recommends amoxicillin 2 g for adults and 50 mg / kg for children as a single dose 30 – 60 min prior to the dental procedure for IE. In case of allergy to the penicillin group of drugs, cephalexin 2 g for adults and 50 mg / kg for children or clindamycin 600 mg for adults and 20 mg / kg for children are recommended as alternatives.[15]

Although there is scientific proof of the amoxicillin effectiveness in the prevention of IE after dental procedures, yet the previous results documented in the literature had not confirmed the efficacy of other recommended prophylactic antibiotics.[16] The Antimicrobial susceptibility testing (AST) is a lab procedure conducted by clinical technician to discover which particular antimicrobial regimen is specifically effective for individual patients.[17] Minimum inhibitory concentrations (MICs) are defined as the lowest concentrations of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation.[18] Therefore, this in-vitro study was intended to compare the antimicrobial potency of amoxicillin, cephalexin and clindamycin against *Streptococcus mutans* using AST and MIC. The objective was to assess the potency of recommended choice of antibiotics and its efficacy among each other in infective endocarditis [IE] prophylaxis during invasive dental procedures.

METHODS

This in vitro study was conducted at the Department of Special Care Dentistry, a unit of Department of Oral Medicine and Radiology in collaboration with Department of Medical Microbiology in Saveetha dental college and hospital, Chennai. Duration was from October 2020 to November 2020 After getting informed consent, a total of twenty (N = 20) salivary samples based on convenience sampling obtained from both the genders (males = 10 and females = 10) of age range 18 - 74 years were collected from patients with a history of cardiac illness who had reported to the Department of Special Care Dentistry. As per the American Dental Association [ADA] guidelines, these patients may predispose to infective endocarditis and hence required IE antibiotic prophylaxis.[19,20]

Saliva Collection

The collection procedure of saliva was by spitting method.[21] In this method, the patients were advised to rinse their mouth in distilled water to remove existing food debris. The unstimulated saliva produced was allowed to pool in the floor of the mouth and the patient spat out into the sterile container for every 60 seconds till the required amount of 20 ml was attained. This unstimulated saliva was labelled and then transferred to the microbiology laboratory for further analysis by trained laboratory technician.

Antimicrobial Susceptibility Test [AST] and Minimum Inhibitory Concentration [MIC]

AST determines the concentration of an antimicrobial agent needed to inhibit the bacterial growth, for both bactericidal and bacteriostatic agents.[22,23] Kirby - Bauer Disk Diffusion Susceptibility Test[24] protocol established by American society for Microbiology had been followed. The principle behind this diffusion test is that the presence or absence of growth around the disks is an indirect measure of the ability of that compound to inhibit that organism.[25]

The saliva samples were plated in brain heart infusion [BHI] agar of Himedia (composition: 12.5 g / L HM infusion powder, 5g / L BHI powder, 10g / L Proteose peptone, 2 g / L Dextrose (Glucose), 5g / L Sodium chloride, 2.5 g / L Disodium hydrogen phosphate, 15 g / L Agar, Final pH (at 25°C) 7.4 ± 0.2) according to manufacturer instructions.[26] The cultural characteristics of *Streptococcus mutans* were noticed after an incubation at 35 - 37°C for 48 hours as white to grey coloured colonies of an average size of 1 mm in diameter.[27] Inoculum was prepared from each culture based on established protocols.[24,25]

AST was performed according to manufacturer's instructions for each patient. The antimicrobial sensitivity discs (SD) [Himedia] each 6 mm diameter and 30 mcg dosage of amoxicillin, cephalexin and clindamycin were introduced in *Streptococcus mutans* inoculum on BHI agar plate. The SD introduced were incubated at 37°C for 24 hours. Minimum inhibitory concentration [MIC] values characteristically represent the susceptibility of a particular bacterium to a particular antimicrobial. MIC were observed as a "zone of inhibition" surrounding the respective antibiotic discs which were then measured by placing a ruler under the petri plate. The obtained MIC values were compared to known standard values called "breakpoints" to deem the antibiotic sensitive[S] or resistant[R].

Statistical Analysis

The data was tabulated in an excel sheet of Microsoft office Professional Plus 2019, 64 - bit system and formatted. The data analysis was processed using IBM SPSS (statistical package for the social sciences) 23.0 software (SPSS Inc., Chicago, IL., USA). Post hoc analysis was performed using Tukey's HSD test as one-way ANOVA was significant.

RESULTS

The overall susceptibility interpretation was S (sensitive) to all three antibiotic discs. Table 1 and Figure 2 depicts the zone of inhibition (in mm) for the three groups of antibiotics. Regarding amoxicillin, the minimum inhibition zone was 19 mm and maximum was 39 mm. The mean was 32.33 ± 7.74 mm with lower and upper bound being 24.21 and 40.45 mm respectively. Regarding cephalexin, the minimum inhibition zone was zero mm and maximum was 34 mm. The mean was 19.17 ± 11.69 mm with lower and upper bound being 6.9 and 31.43 mm respectively and regarding clindamycin, the minimum inhibition zone was 25 mm and maximum was 36 mm. The mean was 29.67 ± 4.08 mm with lower and upper bound being 25.38 and 33.95 mm respectively.

The comparison of the "zone of inhibition" (in mm) between the three antimicrobial groups is shown in Table 2. One-way ANOVA was used to compare the means. The test was statistically significant with F value of 4.093 at P value 0.038. Post hoc analysis was performed using Tukey's HSD test as one-way ANOVA was statistically significant (Table 3). The mean difference of 13.16 mm between amoxicillin and cephalexin was found to be statistically significant at P value 0.041 with lower and upper bound at 0.527 and 25.806 respectively. The mean difference of 2.65 mm between amoxicillin and clindamycin and - 10.50 mm between cephalexin and clindamycin was not found to be statistically significant.

Antibiotic	Mean	Standard Deviation	95 % CI for Mean		Minimum	Maximum
			Lower Bound	Upper Bound		
Amoxicillin	32.33	7.74	24.21	40.45	19.0	39.0
Cephalexin	19.17	11.69	6.90	31.43	0.0	34.0
Clindamycin	29.67	4.08	25.38	33.95	25.0	36.0

Table 1. Zone of Inhibition (in mm) for the Three Groups of Antibiotics

Antibiotic	Mean	Standard Deviation	F Value	P Value
Amoxicillin	32.33	7.74	4.093	0.038
Cephalexin	19.17	11.69		
Clindamycin	29.67	4.08		

Table 2. Comparison of Zone of Inhibition (in mm) between the Groups. F Value and P Value Obtained from One Way ANOVA Test

P Value ≤ 0.05 is Statistically Significant

Groups		Mean Difference	P Value	95 % Confidence Interval	
				Lower Bound	Upper Bound
Amoxicillin	Cephalexin	13.16*	.041	.527	25.806
	Clindamycin	2.65	.849	- 9.973	15.306
Cephalexin	Clindamycin	- 10.50	.112	- 23.139	2.139

Table 3. Post Hoc Analysis. P Value Obtained from Tukey's HSD Post HOC Analysis

P Value ≤ 0.05 is Statistically Significant

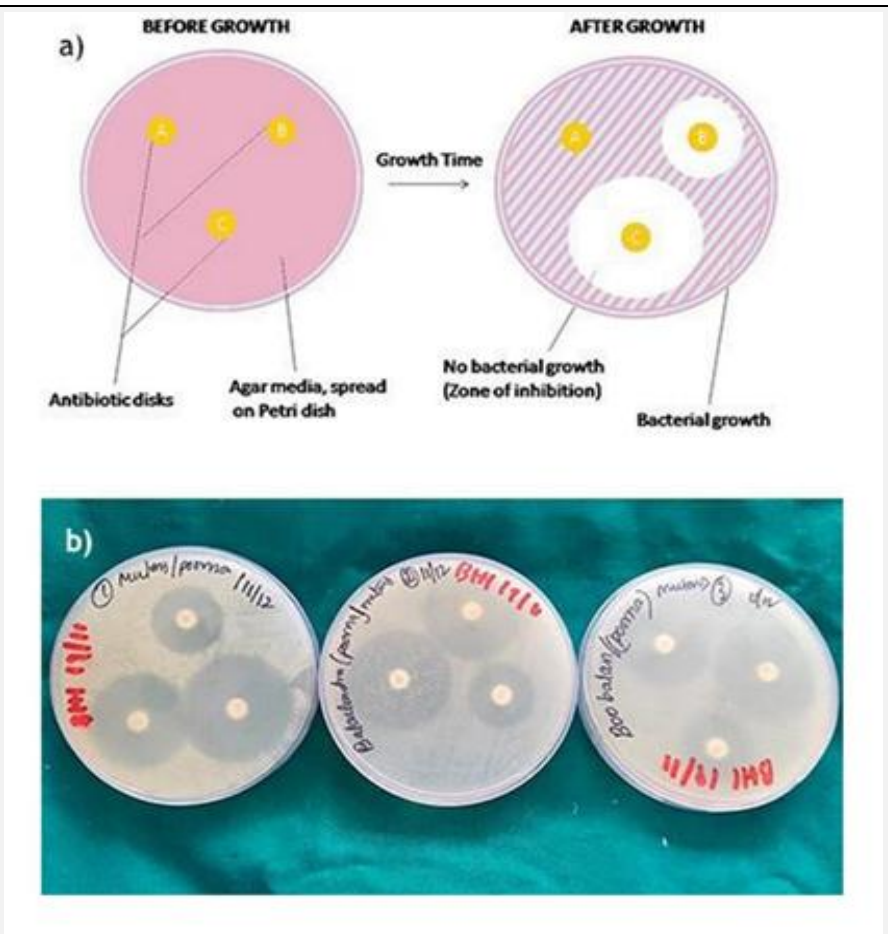

Figure 1: a) Graphical Representation of [MIC] Kirby - Bauer Disk Diffusion Agar Method. b) Image of Streptococcus mutans Cultured Saliva Samples Showing "Zone of Inhibition" around Each Antibiotic Disc

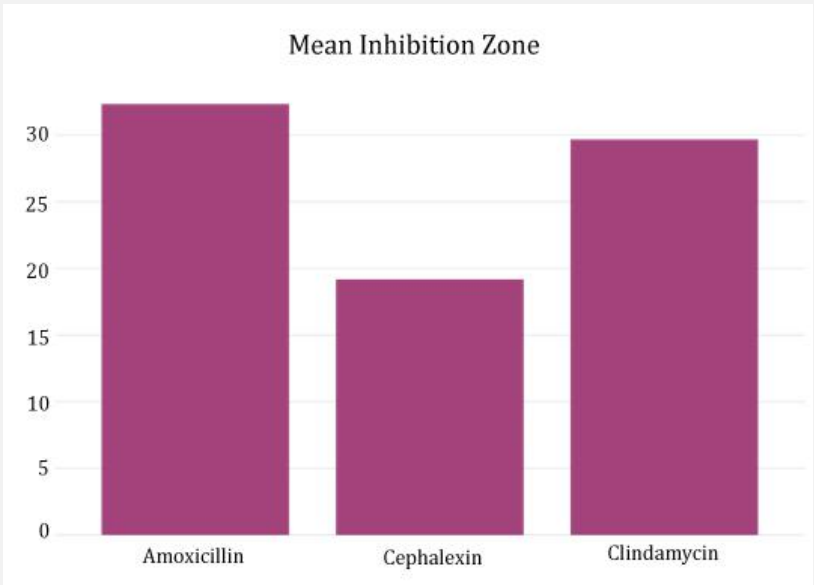

Figure 2. Graphical Representation of Mean Zone of Inhibition for Three Groups - Amoxicillin, Cephalexin and Clindamycin

DISCUSSION

Despite the disagreement about the risk of individuals developing infective endocarditis of oral cavity origin, various expert committees across the countries continue to publish prophylactic regimens for the prevention of infective endocarditis secondary to invasive dental procedures.[14] Antibiotics (means "against life") are "chemical compounds produced by microorganisms that inhibit the normal regulation of some essential bacterial structure or function with limiting effects on eukaryotic hosts".[28] Its efficacy is measured by AST and MIC tests using the Kirby Bauer method.

AST is crucially important; (i) to analyse the preclinical drug sample activity and allows the identification of main lead compound, (ii) to enable possible determination of drug resistance, (iii) to provide estimates in vivo and critically, clinical efficacy when testing compounds in biological matrices simulating infection focal sites,[29,30,31,32] MICs are used by diagnostic laboratories mainly to confirm resistance, but most commonly used as a research tool to determine the in-vitro activity of new antimicrobials, and data from such studies have been used to determine MIC breakpoints.[18] The susceptibility Test Interpretive Criteria (STIC), also called "breakpoints," are used to determine the optimal dose of antibacterials necessary for treating the underlying causative primary infection.[33] The utilization of the Kirby - Bauer disk diffusion susceptibility test is to determine the sensitivity and / or resistance of harmful aerobic bacteria and facultative anaerobes to numerous antimicrobial compounds for the purpose of aiding a diagnostician in choosing better possible treatment options for their patients.[25]

The meta analysis of conducted prior trials indicate that though prophylactic antibiotic coverage is effective in reducing bacteraemia, yet case–control studies conclude that this may not necessarily translate into a significant benefit for low-risk category of patients.[14] In IE prevention, interdisciplinary interaction of specialists (cardiologists, cardiac surgeons, dentists, etc.) is important, as well as informing high-risk patients about the need for antibiotic prophylaxis during invasive procedures.[34] Regarding the efficacy of amoxicillin in the prevention of infective endocarditis, 80 % reduction of post-extraction bacteraemia was reported.[35] Among children, 50 mg / kg of body weight of amoxicillin significantly reduced bacteraemia secondary to the tooth restoration procedures and oral hygiene measures (from 20 % to 6 %), and tooth extractions (from 76 % to 15 %).[36]

Interestingly, The National Institute for Health and Care Excellence [NICE] guidelines have stated "Antibiotic prophylaxis against infective endocarditis is not recommended routinely for people undergoing dental procedures".[37] This however encourages the use of antibiotic prophylaxis based on clinical judgment in appropriate individual cases though not for all cases based on the recommendation by the patient's cardiologist.

In our study, the mean difference of 13.16 mm between amoxicillin and cephalexin was found to be statistically significant at P value 0.041 with lower and upper bound at 0.527 and 25.806 respectively. The mean difference of 2.65 mm between amoxicillin and clindamycin and - 10.50 mm between cephalexin and clindamycin was not found to be statistically significant. The overall susceptibility interpretation of amoxicillin, cephalexin and clindamycin was S (sensitive / susceptible) to all three antibiotic discs. This finding is similar to the findings of Chun et al.[38] and Dhotre et al.[39] Amoxicillin still continues to be the antibiotic of choice for the prevention of IE according to our study. This result is similar to the findings of Diz Dios et al.[40] where the study concluded that among 68 regimens scrutinized for 24 common bacterial infections in India, the costliest drug regimen was for infective endocarditis, with INR 3912 for generic and INR 11823.84 for median branded prescription and also amoxicillin was the cost effective antibiotic available.[41] This might also be an additional reason for its common prescription in IE prevention.

Our study also shows better potency of clindamycin similar to amoxicillin than cephalexin. Clindamycin is the prophylactic antibiotic of choice for patients with a penicillin

allergy.[42,43] Previous studies have demonstrated that amoxicillin and clindamycin taken by oral route of absorption provide high serum concentrations in the first and second hours after ingestion (15 and 25 mg / L, and 4.5 and 4.8 mg / L, respectively), with high levels at 4 - 6 hrs (5 mg / L and 2 mg / L, respectively), and detectable levels still present after 9 - 10 hrs (0.7 mg / L and 0.2 mg / L, respectively).[44] considering the fact that the bacterial growth in the vegetation commences significantly at around 4 hours after the infection onset, it has been postulated that the extended presence of amoxicillin and clindamycin in the bloodstream probably ends with activation of other host defense immunity mechanisms.[45,46]

The advantage of our study was its reproducibility as it had been demonstrated under standard settings by standard protocols.

CONCLUSIONS

Our study had produced results similar to previous studies that amoxicillin places itself as an indispensable gold standard antibiotic in prophylaxis against IE. And in case of patients who are allergic to penicillin group of drugs, Clindamycin should be the first choice of alternative antibiotic among others.

Limitations

Though the result of our study conforms with previous studies, there exists limitations such that it was an in-vitro study and could not completely simulate clinical conditions. Larger clinical trials are needed to arrive at definitive conclusions. Future studies should incorporate complete simulation of complex oral microbiome and the influence of other microbes in performance of antibiotics. This will enable us to assess if this complexity turns as an added advantage or disadvantage in attaining expected prophylaxis against IE.

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