DOI: 10.7860/JCDR/2022/55107.16307

Original Article

Dentistry Section

Influence of CRP on Antibiotics Prescription Pattern for Dental Infections: A Prospective Interventional Study

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ABSTRACT

Introduction: Over the years, antibiotic prescription rates have increased dramatically for the treatment of dentoalveolar infections. A byproduct of this indiscriminate antibiotic prescription by dentists is the antibiotic resistance. Antibiotic resistant infections are a severe global health problem, putting the capacity to treat common diseases and perform complex medical procedures at risk.

Aim: To compare the amount of antibiotics prescribed for dental infections with and without analysing C-reactive Protein (CRP) value.

Materials and Methods: A prospective interventional study was conducted in Manipal University College Malaysia (MUCM), Melaka, Malaysia, dental clinic between October 2020 to March 2021 to record the antibiotic prescription by dentists. The study was divided into two phases where phase I had 28 subjects and phase II had 21 subjects and permission from Institutional Ethical Committee clearance was obtained for the study. The study was done to evaluate the effectiveness of C-reactive protein (CRP) to reduce antibiotic prescriptions in MUCM Dental Clinic. Data was summarised by computing frequency and percentages. The antibiotic prescription rate during phase I (n=28) (conventional method or routine pattern of prescribing antibiotics was done) and phase II (n=21) (CRP rapid test was done and the decision whether to prescribe antibiotics or not was done accordingly) was compared. The data was analysed by using Statistical Package for the Social Sciences (SPSS) software program, version 15.0 (South Asia, Bangalore) and compared applying the Chi-square test.

Results: There was no significant difference in the distribution of the presence of medical condition (p=0.201) and distribution of clinical features (p=0.804) of subjects included in phase I and phase II. The antibiotics prescription rate reduced significantly from 89.3% in phase I to 52.4% in phase II (p=0.0014), indicating that CRP rapid test helps in reducing antibiotics prescription.

Conclusion: The CRP rapid test aid in lowering antibiotic prescription in dental clinic settings. This may be useful to combat antibiotic resistance in general.

Keywords: Antibiotic misuse, Antibiotic resistance, C-reactive protein, Inappropriate prescription

INTRODUCTION

There has been a significant increase in incidents where antibiotics have been used to treat infections. Antibiotics have been known as life-saving drugs. Recently, the number of patients presenting to the Emergency Department (ED) with odontogenic infections has been increasing, likely due to many factors, including cost, fear, mental illness, substance abuse, health literacy and perceptions of oral disease as low importance [1]. Incidence of dentofacial infections may also cause severe, life-threatening conditions which require emergency treatment.

Dentofacial infections are commonly treated with antibiotics in general dental practices. However, antibiotic prescribing may be associated with unfavourable side effects ranging from gastrointestinal disturbances to fatal anaphylactic shock. Additionally, inappropriate, indiscriminate and irrational use of antibiotics has led to the development of antibiotic resistance. Scientific literature suggests that dentists prescribe around 7-11% of common antibiotics [2]. Evidence suggests that a large proportion of antibiotic prescribing in hospitals may be inappropriate. Optimising antibiotic prescribing and reducing the use of broad-spectrum agents has been shown to reduce the occurrence of Healthcare-associated Infections (HCAI) [3].

There has not been a clear justification for antibiotic prescribing practice in dental clinics. This may be due to several factors such as lack of knowledge and awareness of the development of antibiotic resistance, insufficient research done to standardise the prescription of antibiotics in general dental practice and lack of advancement or exposure to recent biotechnology in dental clinics concerning antibiotic prescription [4].

The CRP is a pentameric acute phase reactant discovered in 1930 in pneumococcal pneumonia patients. It is synthesised by the liver, and its production is controlled primarily by Interleukin 6 (IL-6). CRP is the most commonly measured circulating marker for subclinical inflammation, with widely available, stable and standardised assays for its measurement [5].

The serum levels of CRP rise with infection, making it a positive acute phase reactant with a very short half-life of five to seven hours. Thus, the advantage of having short half-lives makes serum CRP levels a sensitive indicator of infection. Serial CRP measurement can be used as a tool for early diagnosis of clinical infections, to monitor the effects of treatment, outcome, and early detection of relapse of the disease. Hence, it can be helpful in determining progression of a disease. Several studies have shown that CRP could be useful in infection diagnosis and monitoring the response to antibiotic therapy [5,6]. This is the first study in Malaysia evaluating the influence of CRP values on the antibiotic prescription percentage for dental infections.

The null hypothesis of the study was that there was no significant difference in the antibiotic prescription (percentage) for dental infections with or without analysing the CRP value. Thus, the aim of the study was to compare the antibiotics prescription percentage for dental infections with and without analysing CRP value.

MATERIALS AND METHODS

A prospective interventional study was conducted in Manipal University College Malaysia Dental Clinic, Melaka, Malaysia, between October 2020 to March 2021 to evaluate the effectiveness of CRP to reduce antibiotic prescriptions.

Ethical approval was obtained from the Institutional Ethical Committee of MUCM (MUCM/FOD/AR/B8/E C-2020 (12)). Before the study, a patient information sheet was prepared and distributed to the subjects. Informed consent was obtained from all the patients. All the data and information were kept confidential.

The reference population for this study was the outpatient attending to MUCM dental clinic who required antibiotics by conventional method (where antibiotics are required conventionally prior to the management of conditions mentioned in the inclusion criteria).

Inclusion criteria: Patients requiring antibiotics in MUCM (Conventional method) who visited the Department of Oral Surgery, Periodontology, Oral Medicine and Conservative Dentistry and Endodontics for the following reasons were included in the study: Prophylaxis, prior to the management of dentoalveolar conditions such as symptomatic or asymptomatic periapical abscess, pericoronitis, bone grafting, flap surgeries, aggressive or chronic periodontitis, draining sinus, dry socket, infections, cellulitis, and fever.

Exclusion criteria: All systemic medical conditions requiring hospitalisation and antibiotic therapy, patients undergoing antibiotic therapy for other conditions, patients on contraceptives, patients undergoing psychiatric treatment, and pedodontics patients were excluded from the study.

Sample size calculation: The following formula was used to compute sample size to compare two independent groups with binary outcomes (antibiotics prescription) [7].

$$n=\frac{K(P_1(1-P_1)+P_2(1-P_2)}{(P_1-P_2)^2}$$

Significance level (α)=0.05

Power of the test (1-β)=80%

K=(1.96+0.84)2=7.84

P1=0.85, Expected proportion of antibiotic prescription in phase I (no CRP test)

P2=0.5, Expected proportion of antibiotic prescription in phase II (CRP test criteria)

The required sample size calculated was n=24 per group.

Study Procedure

About 617 subjects in phase 1 and 1235 subjects in phase II were screened for antibiotic requirement as per the conventional method. In phase I, 28 cases and in phase II, 21 patients were indicated for antibiotic prescription by the conventional method. Of the 28 cases in phase I, three of the patients were not prescribed antibiotics based on the clinician's judgement. The final decision regarding the prescription of antibiotics in both phases were left to the discretion of the clinicians. For comparison purposes, equal duration was recorded for phase I and phase II, summing up to a total of six months. Intention to treat analysis was carried out in this study.

Phase I: For phase I (October to December 2020), a study focusing on the antibiotic prescription in all patients was done by going through the GLOCO system and the individual patient's documented folder. A thorough history of the patients was recorded as well as the clinical findings which leads to the diagnosis by the clinician. This study also recorded the reasons in which dentists in MUCM decided to prescribe the antibiotics.

Following phase I of the study, an academic seminar was held to introduce the usage of CRP among dental staff and students as well as specialists in MUCM.

Phase II: For phase II, (January to March 2021) patients with conditions requiring antibiotics were sent to the Oral Surgery Department to undergo the CRP rapid test to evaluate their CRP level. The decision whether to prescribe antibiotics or not was done accordingly. The CRP rapid test was done only in phase II, while the conventional method or routine pattern of prescribing antibiotics was done in phase I. Patients with conditions requiring antibiotics by conventional method in phase II was sent to the Oral Surgery Department to undergo the test (before any treatment was given), to aid the dentist's decision in prescribing antibiotics and to examine whether CRP rapid test helps in reducing antibiotics prescription.

MultiCare™ Analyser by Medicity was the equipment used for CRP rapid test. It was decided to consider the cut-off point for serum CRP level to be at 5.0 mg/L, since it is the generally acceptable range for CRP, which is internationally adopted for inflammation. Normal range: less than or equal to 5 mg/L; Elevated range: more than 5 mg/L [8].

STATISTICAL ANALYSIS

The data were analysed using SPSS software program, version 15.0. South Asia, Bangalore. Data was summarised by computing frequency and percentages. The antibiotic prescription rate during phase I and phase II were compared by applying the Chi-square test. The level of significance was considered <0.05.

RESULTS

Distribution of characteristics of the subjects included in phase I and phase II of the study is shown in [Table/Fig-1].

Variable	Phase I n (%)	Phase II n (%)
Gender		
Female	14 (50.0%)	21 (100%)
Male	14 (50.0%)	-
Age (in years)		
Range	25-73	22-54
Mean (SD)	43.8 (9.6)	28.6 (6.4)
Reason for arrival		
Dental emergency	10 (35.7%)	-
Infection	3 (10.7%)	3 (14.3%)
Oral prophylaxis	15 (53.6%)	18 (85.7%)

[Table/Fig-1]: Distribution of characteristics of the subjects included in phase I and phase II of the study.
Phase I, n=28; Phase II, n=21

There was no significant difference in the distribution of the presence of medical condition (p=0.201) and distribution of clinical features (p=0.804) of subjects included in phase I and phase II. The antibiotics prescription rate reduced significantly from 89.3% in phase I to 52.4% in phase II (p=0.0014), indicating that CRP rapid test helps in reducing antibiotics prescription [Table/Fig-2].

Characteristic	Phase I n (%)	Phase II n (%)	Chi-square value	p-value
Medical condition				
Present	10 (35.7)	4 (19.1)	1.63	0.201
Absent	18 (64.3)	17 (81.0)		
Clinical features				
Present	13 (46.4)	9 (42.9)	0.062	0.804
Absent	15 (53.6)	12 (57.1)		
Antibiotics prescription				
Not prescribed	3 (10.7)	10 (47.6)	10.208	0.0014
Prescribed	25 (89.3)	11 (52.4)		

[Table/Fig-2]: Comparison of patient characteristic and antibiotic prescription rate in phase I and phase II

A significantly higher antibiotics prescription rate was found associated with the presence of clinical features (p=0.013). The association between the presence of medical condition and antibiotic prescription rate was not significant [Table/Fig-3]. There was no significant difference in the distribution of medical conditions and distribution of clinical features in phases I and II in the present study.

Modifiers		Antibiotics prescription (%)		Chi-square value	p-value
Clinical features	Present	Prescribed	20 (91)	6.23	0.013
		Not prescribed	2 (9)		
	Absent	Prescribed	16 (59)		
		Not prescribed	11 (41)		
Medical conditions	Present	Prescribed	13 (93)	3.78	0.052
		Not prescribed	1 (7)		
	Absent	Prescribed	23 (66)		
		Not prescribed	12 (34)		

[Table/Fig-3]: Association between patient characteristic and antibiotic prescription rate.

DISCUSSION

Testing of CRP in general dental practice in MUCM helped reduce the antibiotic prescription for the patients. Based on the present study, antibiotics were more likely to be prescribed to patients if they presented with clinical features indicating the presence of infection. Besides that, after the intervention or introducing CRP levels, the dental practitioners in MUCM prescribed antibiotics only if the CRP levels were high in the patients, indicated for antibiotics based on the signs and symptoms or medical conditions they had. An essential reason for performing the CRP rapid test is to avoid prescribing unnecessary antibiotics to patients with a dental infection. The CRP rapid test was the factor that exerted the most significant influence on whether a patient with dental disease was prescribed antibiotics. While practicing it, the test result had a substantial impact on the prescribing rate. The patients who tested CRP levels within a normal range were not prescribed any antibiotics in phase II. This is similar to the finding of Bjerrum et al., in which practices using CRP measurement had a lower prescription rate of antibiotics. The difference found might be due to different attitudes to antibiotic prescription for dental infection irrespective of the access to CRP tests [9].

Prophylactic antibiotics are prioritised for medically compromised patients where the risk of secondary infections is high. Simon Murray S et al., suggested that general practitioners were influenced by four clinical features (runny nose, fever, sore throat, and cough) to prescribe antibiotics for respiratory tract infections [10]. This coincides with the findings of the present study that the presence of clinical features increases the chances of antibiotic prescription. However, the study also concluded that a more extensive study with the best evidence from literature could confirm the association between these two variables. Clinicians should be encouraged to use their clinical skills coupled with relevant laboratory investigations to diagnose infections and consult with the infection specialists [3].

The present study did not observe significant association between antibiotic prescription and medical conditions (p=0.052). Since, this is the secondary outcome and the sample size was determined according to the primary outcome, the mentioned insignificant association between antibiotic prescription and medical conditions may be due to inadequate sample size. The role of prophylactic antibiotics has a significant impact on dentistry. To avoid any complications in medically compromised patients, antibiotics have become a common practice. Antibiotics must only be used as additive therapy in patients with systemic manifestations. In addition, prophylactic measure is observed in immunocompromised patients or predisposing patients conditions such as endocarditis. In the absence of the reasons mentioned above, the administration of antibiotics has no evidence of therapeutic benefit [11].

Infections or other causes of tissue injury result in a complex set of systemic and metabolic reactions associated with alterations in the hepatic synthesis and serum levels of some proteins, including CRP [12]. In this study, 11 (52.4%) patients presented with high CRP levels, in which all were prescribed with antibiotics. Meanwhile, 10 patients (47.6%) showed relatively lower CRP levels, and antibiotics prescription was not given. This is in contrast to a Swedish study where CRP pretesting did not significantly affect the prescription of antibiotics or admittance to a hospital [13]. This study also examines the awareness and acceptance of the dentists in MUCM to the changes in the conventional antibiotic prescribing guidelines. It was found out that dentists of MUCM did adhere to the recommended value of CRP and the adjunct in prescribing antibiotics. This result was different from a study done in the Netherlands whereby 40% of changes in antibiotic prescribing decisions were not according to guideline recommendations [14].

Compared to phase II, the mean age of phase I was higher (43.8 years), which may also contribute to the higher prescription rates. This is also true for the medical condition (35.7%) and the clinical features (46.4%), both of which have relatively higher percentages in subjects of phase I. There may also be a correlation between the antibiotic prescribing rate in phase I and the reason the antibiotic prescription was made, since, in this study a higher percentage of patients arrived with a dental emergency (35.7%) in phase I as compared to zero percent in phase II.

A minimum of 10 days gap is imposed before any dental treatment as a safety measure to prevent asymptomatic transmission. This practice may contribute to a higher antibiotic prescription in phase I. This occurs due to the public's growing concern towards their general health during the pandemic, which causes the demand to grow explosively [15].

Extensive studies on the response of CRP to antibiotic therapy in infections are lacking. Diagnostic tests, though available, were not routinely used to rationalise antibiotic prescribing [16]. Evidence suggests that antibiotic therapy should be considered only after the conventional therapies have not been successful [17]. Some studies supports the routine prophylactic use of antibiotics so as to reduce the postoperative complications after third molar surgery [18,19]. However, several studies have revealed an insignificant gain in the patient's postoperative condition after antibiotics use [20,21].

In the fight against antibiotic resistance, it's also crucial to avoid unnecessary antibiotic prescriptions in order to prevent dentoalveolar infections that might harm patients, which is why the rapid test was created. However, since this study does not include a follow-up of the patients after prescribing antibiotics, there may be unreported secondary infections due to this practice. There may also be false-negative findings that may appear harmful for the patients. A meta-analysis study done by Adamina et al., found that in the absence of postoperative infectious complications, CRP levels were lower in non invasive procedures than open and invasive procedures [22]. The results of the present study does not support the null hypothesis and prove that there exists a statistically significant difference in antibiotic prescription for dental infection with or without analysing CRP value.

Limitation(s)

The study was limited by a small sample size. Another factor that limits the study is the Coronavirus Disease-2019 (COVID-19) pandemic which reduced the total number of patients attending the clinic. Other medical conditions also affect the CRP levels and hence rapid test may not be suitable in an outpatient clinical settings as CRP levels may be influenced by other factors due to medical conditions. Since, this study does not include follow-up of the patients, there are chances that patients may develop secondary infections did not report directly to the clinic and opt for another clinic to get other treatment, prescription or consultation. The study also did not evaluate the anticipation of the dentists in MUCM towards this new practice nor their satisfaction with the new adjunct of antibiotic prescription. This may display as a shortfall in the application of the CRP rapid test.

CONCLUSION(S)

The CRP rapid test does help in lowering antibiotic prescription in dental clinic settings. This may be useful to combat antibiotic resistance in general. This study also found out that antibiotic prescription is associated with signs and symptoms of the patient. It is essential to carefully assess and evaluate patient's health prior to prescribing antibiotics. A high CRP level is associated with more antibiotic prescriptions. Clinician awareness and knowledge of the significant CRP level is important for the proper antibiotic prescription routine in general private dental settings to reduce antibiotic resistance.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Jan 22, 2022
- Manual Googling: Mar 21, 2022
- iThenticate Software: Apr 14, 2022 (19%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 21, 2022**
Date of Peer Review: **Feb 02, 2022**
Date of Acceptance: **Apr 15, 2022**
Date of Publishing: **May 01, 2022**