

The effect of treated apical periodontitis before heart valve surgery on C-reactive protein levels

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Abstract

Objective: Dental infections produce significant increases in systemic inflammatory responses manifested by cytokines and acute-phase reactants. This study evaluated the postoperative C-reactive protein (CRP) levels according to patients having teeth treated or not treated for apical periodontitis (AP) before heart valve surgery.

Materials and Methods: Preoperative, postoperative third- and fifth-day CRP levels, and the previous dental data of 91 patients were investigated. Whether the patients had been treated for AP and whether they used antibiotic prophylaxis for this treatment were determined by examining the previous data. The analysis of covariance (ANCOVA) was used for statistical analysis.

Results: There were no statistically significant differences in the preoperative CRP levels and the third-day CRP levels between all patients treated and those not treated for AP ($p > .05$). The mean fifth-day CRP levels of the patients with teeth treated for AP were significantly lower than those of the patients with teeth not treated for AP ($p < .05$). Antibiotic prophylaxis had a significant effect on the fifth-day CRP levels.

Conclusion: The decrease in CRP levels after AP treatment may contribute to alleviating heart valve disease and maintaining cardiac health.

KEYWORDS

apical periodontitis, C-reactive protein, endodontics, oral inflammation

1 | INTRODUCTION

C-reactive protein (CRP) is a plasma protein that reflects the acute-phase response to inflammation and is one of the preferred indicators for monitoring the response to inflammation (Ramamoorthy, Nallasamy, Nallasamy, Reddy, Esther, & Maruthappan, 2012). It is regulated by cytokines, such as interleukin-6, interleukin-1 β , and tumor necrosis factor- α (Bennett & Plum, 1996; Ebersole & Cappelli, 2000). Measurements of serum concentrations are clinically used as a non-specific marker for inflammation. CRP is also the marker of inflammation most widely studied in patients with cardiovascular disease (CVD) and has thus become the marker of reference

for any other inflammatory-based disease (Myers et al., 2004). CRP synthesis begins 6 hr after stimuli and peaks at around 48 hr, with a half-life of 19 hr (Pepys, 1981). Table 1 displays the interpretation of CRP levels according to recent criteria (Nehring & Patel, 2018).

High CRP levels, especially after myocardial infarction, are associated with adverse outcomes, such as left ventricular failure (Suleiman et al., 2006) and increased rates of cardiac death and ventricular rupture (Pietila, Harmoinen, Jokiniitty, & Pasternack, 1996). Higher CRP levels have been related to an increased risk of acute cardiovascular events, and they are considered to be the only valid standardized biomarker for predicting CVD (Avan et al., 2018). A healthy lifestyle decreases CRP levels, whereas obesity, smoking,



and physical inactivity increase them (Palosuo, Husman, Koistinen, & Aho, 1986).

Dental infections cause increases in systemic inflammatory responses manifested by cytokines and acute-phase reactants (Ebersole & Cappelli, 2000). Oral diseases have been shown to increase the systemic levels of CRP (Mattila et al., 2002). CRP has been found in the serum of patients with some form of inflammatory oral disease. Chronic bacterial infections are one of the well-established risk factors for high CRP levels (Tüter, Kurtis, & Serdar, 2007). A positive correlation between CRP and periodontal disease severity was proved in many studies (Jayaprakash, Aghanashini, Chatterjee, Rosh, & Bharwani, 2014; Linden, McClean, Young, Evans, & Kee, 2008), and CRP levels were found to decrease after periodontal treatment (Marcaccini, Meschiari, & Sorgl, 2009). The highest incidence of positive CRP tests and the strongest CRP test reactions were observed in patients with acute alveolar abscesses (Boucher, Hanrahan, & Kihara, 1967). The formation of an apical lesion of endodontic origin, and the most frequent clinical presentation of which, is apical periodontitis (AP) (Gutmann, Baumgartner, Gluskin, Hartwell, & Walton, 2009). AP contributes to the systemic immune response, which is not confined to the localized lesion, and can potentially trigger an increase in systemic inflammation (Gomes et al., 2013). Recent studies have also revealed that AP could trigger a systemic immune response and affect the general health of patients. Although AP is accepted as an inflammatory disease, the use of inflammatory markers is restricted in its assessment (Sirin, Ozcelik, Uzun, Ersahan, & Yesilbas, 2019). Oral diseases causing increased CRP levels are also associated with the increased risk of CVD (Cotti & Mercurio, 2005). CRP levels can be used to evaluate systemic inflammation in patients with AP (Sirin et al., 2019).

Most previous studies focused on the relationship between CRP and periodontal diseases (Jayaprakash et al., 2014; Linden et al., 2008; Marcaccini et al., 2009). The positive association between CVD and AP remains controversial (Cotti, Dessi, Piras, & Mercurio, 2011). The principal hypothesis of the current study is that, although periodontal diseases are considered as risk factors for high CRP levels, endodontic diseases such as AP also cause elevated CRP levels. The present study aimed to evaluate the postoperative CRP

levels according to patients having teeth treated or not treated for AP before heart valve surgery (HVS).

2 | MATERIALS AND METHODS

All records of patients who underwent surgery in the cardiovascular surgery department of Bezmialem Dragos Hospital between August 2017 and August 2018 were collected. All HVSs were performed as open-heart surgeries by two cardiac surgeons (Table 2). The study protocol was approved by the ethics committee of Bezmialem Vakif University (Date: 21.01.2020; decision no. 54022451-050.05.04).

2.1 | Inclusion criteria

This study included patients who underwent HVS, completed dental and radiographic examinations before HVS, had at least one tooth with AP with a well-defined radiolucent area, did not smoke, had no systemic diseases (such as diabetes), did not need periodontal treatment, and had no immunological disorders such as oral lichen planus and Sjogren's syndrome or oral pathologies such as cancer. Examination of the patients' hospital dental records showed no disease requiring emergency dental treatment (such as symptomatic pulpitis or deep caries) other than AP. A total of 94 patients who met the criteria were initially included in the study.

2.2 | Laboratory methodology

Blood samples were collected from the patients preoperatively and on the third and fifth postoperative days. Within 30 min, the blood samples were centrifuged for 10 min at 1,372 g. The sera were then separated and stored at -80°C until analyzed. The laboratory CRP in the serums was determined through an immunoturbidimetric CRP assay (ARCHITECT c8000 Abbott). The serum CRP levels were recorded as milligrams per deciliter (mg/dL) in the hospital data system

TABLE 1 The interpretation of CRP levels (Nehring & Patel, 2018)

Less than 0.3 mg/dl	Normal (level seen in most healthy adults).
0.3–1.0 mg/dl	Normal or minor elevation (can be seen in obesity, pregnancy, depression, diabetes, common cold, gingivitis, periodontitis, sedentary lifestyle, cigarette smoking, and genetic polymorphisms).
1.0–10.0 mg/dl	Moderate elevation (systemic inflammation such as rheumatoid arthritis, systemic lupus erythematosus or other autoimmune diseases, malignancies, myocardial infarction, pancreatitis, bronchitis).
More than 10.0 mg/dl	Marked elevation (acute bacterial infections, viral infections, systemic vasculitis, major trauma).
More than 50.0 mg/dl	Severe elevation (acute bacterial infections).

TABLE 2 The types of HVS completed by 2 cardiac surgeons

	n
Aortic valve replacement	18
Mitral valve replacement + Tricuspid valve repair	17
Mitral valve repair	12
Mitral valve replacement	11
Mitral valve replacement + Aortic valve replacement	9
Mitral valve replacement + Tricuspid valve repair	8
Mitral valve repair + Tricuspid valve repair	7
Aortic valve replacement + Tricuspid valve repair	4
Mitral valve replacement + Aortic valve replacement + Tricuspid valve repair	3
Mitral valve replacement	2

(Bizmed). Intra- and inter-assay coefficients of variation for CRP were 21.7% and 29.6%, respectively.

2.3 | Investigation of hospital data

After the patients' hospital protocol numbers were retrieved, panoramic and periapical radiographies were retrospectively examined using Romexis Viewer (Planmeca), and CRP levels recorded in the hospital data system (Bizmed) were retrospectively investigated. Previous hospital data were also reviewed to determine whether the patients had been treated for AP and whether they had been administered prophylactic antibiotics. The intensive care periods of all patients were also examined. This study was conducted by two cardiac surgeons and an endodontist. To confirm the dental data in the hospital system, the patients were called by phone by the endodontist.

TABLE 3 Preoperative and postoperative CRP comparisons (mg/dL) among patients based on their ages (n: sample size, SD: standard deviation; $p < .05$)

	Age	Patients with untreated AP (n = 29) Mean ± SD	Patients with treated AP (n = 62) Mean ± SD	Patients with treated AP and who did not use antibiotic prophylaxis (n = 22) Mean ± SD	Patients with treated AP and who used antibiotic prophylaxis (n = 40) Mean ± SD
Pre-op CRP levels	20–42	0.91 ± 1.28	0.40 ± 0.37	0.31 ± 0.20	0.46 ± 0.45
	43–65	0.67 ± 0.96	0.45 ± 0.70	0.30 ± 0.18	0.53 ± 0.85
	66–89	0.93 ± 0.91	0.88 ± 1.43	0.26 ± 0.10	1.11 ± 1.64
	Total	0.79 ± 1.01	0.51 ± 0.82	0.30 ± 0.17	0.63 ± 0.99
3rd day CRP levels	20–42	11.35 ± 3.47	11.70 ± 4.11	12.17 ± 5.09	11.37 ± 3.53
	43–65	12.60 ± 3.76	13.30 ± 6.08	12.69 ± 4.80	13.63 ± 6.75
	66–89	12.37 ± 3.93	8.91 ± 5.18	11.88 ± 6.78	7.80 ± 4.47
	Total	12.16 ± 3.59	12.05 ± 5.61	12.41 ± 4.90	11.90 ± 6.02
5th day CRP levels	20–42	8.33 ± 2.03	5.96 ± 3.62	4.74 ± 3.17	4.35 ± 2.01
	43–65	7.32 ± 3.18	5.46 ± 2.83	5.96 ± 2.06	5.19 ± 3.19
	66–89	9.55 ± 4.69	4.45 ± 2.21	8.13 ± 3.24	4.44 ± 3.17
	Total	8.03 ± 3.32	5.42 ± 2.97	6.49 ± 2.77	4.84 ± 2.95

Among the patients, the three who did not respond were excluded from the study, so the reliability of the study would not be affected. The serum CRP levels of the 91 patients were compared in the preoperative and postoperative third and fifth days based on their age groups (Table 3).

2.4 | Statistical analysis

The homogeneity of variances was tested in SPSS (IBM SPSS for Windows, Ver. 24) using Levene's test of equality of error variances. CRP levels as dependent variables and patients' ages as covariates were analyzed. In order to compare CRP levels between groups, the ANCOVA test was used.

3 | RESULTS

This pilot study included 91 patients. A total of 62 patients with AP underwent endodontic procedures up to three days prior to HVS. The localizations of the teeth with AP are shown in Figure 1. The patients' ages ranged from 20 to 88 years (mean = 55.31 years), with 24 belonging to the age range 20–42, 50 to the age range 43–65, and 17 to the age range 66–89 (Table S1). With respect to gender, 58 (63.7%) patients were males, and 33 (36.3%) were females.

As per the preoperative recommendations of the cardiac surgeons and the endodontist, 40 patients were administered prophylactic antibiotics according to the recommendations of the American Heart Association (AHA; Wilson et al., 2007). According to their hospital records, 33 patients were administered 2 g of oral amoxicillin 60 min before the dental procedure, while 7 patients reportedly allergic to penicillin were administered 600 mg of clindamycin

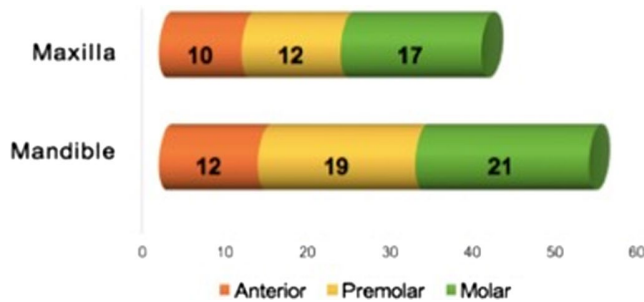


FIGURE 1 The number of teeth according to their localization [Colour figure can be viewed at wileyonlinelibrary.com]

intramuscularly 30 min before the dental procedure. Antibiotic prophylaxis was not required for 22 patients. Of the 29 untreated patients, 12 stated that they did not desire dental treatment because they had no complaints, and 17 reported having undergone an emergency valve operation.

Although the preoperative and the fifth-day CRP levels had sufficient homogeneity (Table 4), the homogeneity assumption could not be provided for the third-day CRP level ($p = .026$). When the patients' ages were considered as the covariate, a statistically significant difference was found between the fifth-day CRP levels between all patients with teeth treated and those with teeth not treated for AP before HSV ($p = .001$). When the CRP levels of patients who used and who did not use antibiotic prophylaxis were compared, the homogeneity assumption could not be provided only for the preoperative CRP levels ($p = .008$). No statistically significant differences were found in the preoperative CRP levels ($p = .153$) and third-day CRP levels ($p = .763$) between the patients who used antibiotic prophylaxis and those who did not. However, a statistically significant

TABLE 4 The results of Levene's test of equality of error variances ($p < .05$)

	Dependent Variable CRP Levels	F	df1	df2	p
Patients with treated and untreated AP	Pre-op CRP levels	2.220	1	89	.140
	3rd day CRP levels	5.152	1	88	.026*
	5th day CRP levels	0.161	1	89	.689
Patients who used and did not use antibiotic prophylaxis	Pre-op CRP levels	7.493	1	60	.008*
	3rd day CRP levels	0.416	1	60	.522
	5th day CRP levels	0.619	1	60	.435

* Indicates significant differences.

TABLE 5 Preoperative and postoperative CRP comparisons according to the ANCOVA analysis ($p < .05$)

	Dependent Variable CRP Levels	Sum of Squares	df	Mean Square	F	p
Patients with treated and untreated AP	Pre-op CRP levels	1.347	1	1.347	1.733	.191
	3rd day CRP levels	0.565	1	0.565	0.022	.883
	5th day CRP levels	136.084	1	136.084	14.236	.001*
Patients who used and did not use antibiotic prophylaxis	Pre-op CRP levels	1.366	1	1.366	2.100	.153
	3rd day CRP levels	2.979	1	2.979	0.092	.763
	5th day CRP levels	35.133	1	35.133	4.220	.044*

* Indicates significant differences.

difference was found in the fifth-day CRP levels of the patients who used and who did not use antibiotic prophylaxis ($p = .044$). It was determined that antibiotic prophylaxis has a significant effect on the fifth-day CRP levels (Table 5). Additionally, the mean fifth-day CRP levels of the patients with electively treated were significantly lower than the mean fifth-day CRP levels of the patients undergoing an emergency HSV ($p = .027$). When the intensive care periods of the patients were compared, no statistically significant difference was found ($p = .789$).

4 | DISCUSSION

Heart valve diseases are an important cause of morbidity among elderly people all over the world. Heart valve disorders comprise a series of congenital and acquired conditions, the underlying causes of which have varied over the last decades (Alfieri & Vahanian, 2017). All heart valves can suffer alterations due to different etiologies, such as myxomatous mitral valve disease or senile calcified aortic valve stenosis (Toro, Mangas, & Gómez, 2011). Less frequent presentations include severe tricuspid valve regurgitation secondary to pacemaker implantation (Gallego Galiana et al., 2015). As heart valve diseases are common and an important condition for dental treatment, patients with heart valve disease were included in this study.

AP and periodontal diseases with different etiologies and pathogenesis have been reported to contain similar pathogens of anaerobic gram-negative bacteria. Both types of infection are associated with complex microflora (Bender, 1982). Moreover, inflammatory responses that accompany periodontal disease and AP are similar (Silva, Garlet, Fukada, Silva, & Cunha, 2007). The anatomic proximity

of endodontic and periodontal infections to the bloodstream can cause bacteremia during treatment and daily activities (Tomas, Diz, Tobias, Scully, & Donos, 2012). Therefore, only AP was evaluated in this study, and patients with periodontal problems were not included.

In the preoperative period of cardiovascular surgery, patients should be screened for the possible existence of odontogenic infections caused by dental caries or periodontitis. In this regard, patients who have not received preoperative dental treatment may be at increased risk in the postoperative period (Wu, Manzon, Badovinac, & Woo, 2008). The management of oral diseases before cardiac valvular surgery should be adapted to the timing of the intervention. Restorative dentistry and endodontic and periodontal therapy can be performed before elective valvular intervention and during the follow-up of patients at high risk of endocarditis (Sung et al., 2014). Periodontal treatment is important to eliminate the local etiological factors and gingival inflammation (Kumar, Shah, Budhiraja, Desai, & Shah, 2013). Although the relationship between chronic periodontitis and CRP levels has already been shown in some studies (Buhlin, Gustafsson, Pockley, Frostegard, & Klinge, 2003), research examining the relationship between the treatment of AP and CRP remains limited. In the present study, the fifth-day CRP levels of patients older than 43 years with teeth not treated for AP were higher than those of patients with teeth treated for AP (Figure S1). These results show that untreated AP with aging can potentially trigger an increase in systemic inflammation and CRP. Therefore, a detailed dental examination may be recommended for the prognosis of patients who are scheduled for HVS.

The recommendations by the American Heart Association (AHA) for the prevention of infective endocarditis (IE) were updated. It was stated that antibiotic prophylaxis administered in association with a dental procedure could be important for patients with cardiac conditions that carry a lifetime risk of acquisition of IE, such as mitral valve prolapse (Wilson et al., 2007). Regular tooth brushing almost certainly presents a greater risk of IE than a single dental procedure because of repetitive exposure to bacteremia with oral flora. Although there are many studies about antibiotic prophylaxis in the literature, the clinical effectiveness of antibiotic prophylaxis has not been proved (Wray, Ruiz, Richey, & Stokes, 2008). CRP levels in circulation are attenuated by antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (El-Sharawy, El-Hakim, & Sameeh, 2006). In the present study, patients who used and did not use antibiotic prophylaxis were evaluated separately. A statistically significant difference was found in the fifth-day CRP levels of the patients who used and who did not use antibiotic prophylaxis ($p = .044$). It was determined that antibiotic prophylaxis has a significant effect on the fifth-day CRP levels. Therefore, prophylaxis may be considered by consulting each patient's doctor in these patient groups.

In a previous study, 89.2% of cardiac specialists stated that endodontic treatment should be performed prior to cardiovascular surgery (Alim, Gunecer, & Dincer, 2020). How long before dental procedures should be completed before cardiovascular surgery in

the literature is not clear. Therefore, patients whose dental treatment was completed up to the last three days before HVS were included in this study.

CRP levels may increase with age (Reuben, Judd-Hamilton, Harris, & Seeman, 2003). In the present study, it was found that in particular, the fifth-day CRP levels in patients within the 66–89 age range with untreated AP were higher than in the other age groups. Notably, for elderly patients, if any cardiac operation is planned, the treatment of existing infections may contribute to reducing postoperative CRP levels. Moreover, positive associations between smoking (Wannamethee et al., 2005), body mass index (BMI; Heilbronn, Noakes, & Clifton, 2001; Mendall, Patel, Ballam, Strachan, & Northfield, 1996), and CRP levels have been consistently reported. Moreover, adipose tissue has been suggested to play a role in the regulation of circulating CRP levels via IL-6 production (Bastard et al., 1999). Weight loss has been demonstrated to reduce CRP (Heilbronn et al., 2001; Tchernoff, Nolan, Sites, Ades, & Poehlman, 2002). To interpret the CRP levels, it may be necessary to determine a patient's weight status. CRP is also positively associated with systolic blood pressure, pulse pressure, and hypertension (Sung et al., 2003). The Turkish Adult Risk Factor Study, which analyzed CRP gene polymorphisms, found that high CRP levels were associated with hypertension in both men and women (Komurcu-Bayrak et al., 2009).

Smokers were excluded from this study to ensure the reliability of the results, while BMI and hypertension were not taken into account because the study was retrospective. This is one of the most important limitations of this study. Moreover, the patients' dental conditions were evaluated according to radiographic data and hospital records only, and their oral hygiene habits were unknown. As previously mentioned, this study was designed to detect changes in CRP levels only. Further research on this matter is needed.

5 | CONCLUSION

This study evaluated the postoperative CRP levels according to patients with teeth treated or not treated for AP before HVS. CRP levels are an important indicator in the evaluation of CVDs and can be used as an additional test when investigating systemic inflammation in AP patients. The decrease in CRP levels after the treatment of AP may contribute to alleviating the risk of heart valve disease and maintaining cardiac health.

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AUTHOR CONTRIBUTIONS

Betul Aycan ALIM: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualization; Writing-original draft; Writing-review & editing. **Emir CANTURK:**



Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Visualization; Writing-original draft; Writing-review & editing. **Cengiz KOKSAL:** Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing-original draft; Writing-review & editing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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