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ARAŞTIRMA / RESEARCH

Evaluation of spontaneous gingival bleeding and related drug withdrawal frequency in atrial fibrillation patients using oral anticoagulants: a case-controlled study

Oral antikoagülan kullanan atriyal fibrilasyon hastalarında spontan dişeti kanaması ve ilişkili ilaç bırakma sıklığının değerlendirilmesi: vaka kontrollü çalışma

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Abstract

Purpose: The aim of this study was to investigate the frequency of gingival bleeding (GB) and associated drug-withdrawal in atrial fibrillation (AF) patients using oral anti-coagulants (OAC).
Materials and Methods: 457 patients with AF receiving OAC were screened. The periodontal parameters and OAC drug-withdrawal of 32 patients with spontaneous GB were compared with 32 patients without bleeding who were matched for age, sex and OAC treatment protocol.
Results: GB was detected in 32 patients (7.0%) and 13 of these patients (40.6%) had OAC drug-withdrawal due to bleeding. The plaque index (PI), gingival index (GI) and probing pocket depths (PPD) were significantly higher in patients with GB. The GI scores independently determined the risk of OAC drug-withdrawal.
Conclusion: AF patients under OAC treatment may have significant rates of GB and subsequent OAC withdrawal due to pre-existing periodontal disease. The GI scores and GB can predict the risk of OAC drug-withdrawal. The periodontal examination and/or treatment of these patients should be performed before OAC treatment.

Keywords:. Atrial fibrillation, oral anti-coagulant therapy, periodontal disease, gingival bleeding

Öz

Amaç: Bu çalışmanın amacı, oral antikoagülan (OAK) kullanan atriyal fibrilasyon (AF) hastalarında spontan dişeti kanaması (SDK) ve buna bağlı ilaç bırakma sıklığının değerlendirilmesidir.
Gereç ve Yöntem: OAK ilaç kullanan 457 AF hastası taranarak spontan dişeti kanaması olan 32 hasta tespit edildi. Bu hastalar, spontan dişeti kanaması olmayan 32 AF hastası ile yaş, cinsiyet ve OAK tedavi protokolü açısından eşleştirilerek periodontal parametreleri karşılaştırıldı.
Bulgular: Çalışmaya dahil edilen total popülasyonda, 32 hastada (32/457; % 7.0) SDK saptandı ve bu hastaların 13'ünde (% 40.6) kanamaya bağlı OAK ilaç kullanımını bıraktığı tespit edildi. Plak indeksi (PI), gingival indeks (GI) ve cep derinlikleri (CD) SDK olan hastalarda anlamlı olarak daha yüksek bulundu. Gingival indeksin, hastaların OAK ilacı bırakma riskini bağımsız olarak etkilediği tespit edildi.
Sonuç: OAK tedavisi altındaki AF hastalarında, önceden var olan periodontal hastalık nedeniyle önemli oranda SDK ve buna bağlı hastanın OAK ilaç kullanımını bıraktığı gözlendi. Ayrıca gingival indeks skorları, SDK ve OAK ilacın bırakılmasında risk indikatörüdür. OAK tedavisinden önce hastaların periodontal muayenesi ve / veya tedavisi yapılması önerilir.

Anahtar kelimeler: Atriyal fibrilasyon, oral antikoagülan, periodontal hastalık, gingival kanama

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INTRODUCTION

Gingival bleeding is the sign of inflammatory gingival lesions and is considered the most sensitive indicator of early pathology[1, 2]. Gingival bleeding occurs due to frequent recurrent micro ulceration of the epithelium that covers the soft tissue wall of the periodontal pocket. Gingival bleeding can either be observed after mechanical stimulation of the gingival sulcus / periodontal pocket (eg, bleeding during tooth brushing, probing, or tooth cleaning)[3] or spontaneously. In addition, some medications affect vascular permeability, clotting or platelet function or number and can also cause gingival bleeding [4-6]. Gingival bleeding can often be a "serious" and rarely fatal drug side-effect that may require drug withdrawal in certain cases. The drugs that may potentially cause gingival bleeding are used to treat heart diseases such as atrial fibrillation (AF)[7].

Atrial fibrillation is the most common type of supraventricular tachyarrhythmia[8]. The incidence of AF is 3%, and the thromboembolic events, the most serious complication [9]. For these reasons, oral anti-coagulant therapy (OAC) is indicated in this group of patients with a high stroke risk, especially in patients with thromboembolic risk score (Congestive heart failure, Hypertension, Age -CHA; Diabetes, previous Stroke/transient ischemic attack- DS; vascular disease, and sex category-VASc) $CHA_2DS_2VASc \geq 2$ points. In the last AF guidelines, it has been suggested that Dabigatran, Rivaroxaban, Apixaban and Edoxaban (new generation OACs) treatment should be used as priority compared to the vitamin K antagonist [9]. Patients with AF have increased inflammation and inflammation has an important role in AF physiopathology [9]. However, the frequency of gingival bleeding and related parameters are not clear in patients with AF. OAC treatment-related gingival bleeding is considered in the category of minor bleeding. The frequency of gingival bleeding due to the use of vitamin K antagonists is not clear, but was reported 5% in a study [10], but there is no clear information about the frequency of gingival bleeding with non-vitamin K antagonists in patients with AF. In patients under anti-coagulants treatment, this bleeding problem is resolved by withdrawal of the drug, but OAC treatment should not be stopped, especially in patients with AF and high CHA_2DS_2VASc score, and palliative dental and periodontal treatment is required in these patients. Therefore, it is vital to predict the occurrence of gingival bleeding in patients under OAC treatment, especially in patients with a high risk of stroke. The aims of this study were i) to investigate the frequency of gingival bleeding OAC withdrawal in AF patients and ii) to compare the periodontal parameters that may be related to gingival bleeding in these patients in a case-controlled design.

MATERIALS AND METHODS

The study was approved by the regional ethics committee of Cukurova University (decision date/number: 01-02-2019 / 85/44) and performed between March 2019 and July 2019 in Department of Cardiology, University of Health Sciences, Adana, Turkey.

Sample

In the first part of the study, 522 patients with a CHA_2DS_2VASc risk score ≥ 2 who were followed with a diagnosis of paroxysmal AF and therefore received OAC treatment were interviewed on the phone. The patients with critical valvular heart disease, malignancy, severe liver and kidney failure, active infection, acute coronary syndrome, thrombocytopenia, bleeding disease history in the last 6 months, using aspirin or other anti-platelet treatment, having less than 10 teeth and who did not accept to participate in the study were excluded. Thus, 65 patients were excluded due to these criteria. All other patients signed the patient consent form before the participation.

The patients were asked if they had spontaneous gingival bleeding (which included bleeding during eating). All patients' medical history was taken and their physical examination records were analyzed and cardiovascular risk factor determination of patients was performed. Risk factors such as hypertension (HT), diabetes mellitus (DM) and smoking were recorded. Body mass index (BMI) was calculated using weight and height. The OAC treatments used by all patients were noted. OAC withdrawal due to any reason was also recorded.

Nested case-controlled analysis

The patients who had self-reported spontaneous gingival bleeding were further evaluated clinically and compared with patients form the initial population with matched age, gender and OAC treatment protocol for AF who had no gingival bleeding.

Periodontal clinical examination

The parameters for the patients who were included for the clinical examination were as follows: Gingival inflammation as scored from 0 to 3 using the Gingival Index (GI) [11]; Plaque levels scored as plaque index (PI) [12] recorded from 0 to 3; The probing pocket depths of all present teeth were recorded at six sites of each tooth except third molars. All examinations were performed using periodontal probe. The diagnosis of the patients was made according to the criteria described by Armitage [13].

All clinical examinations were performed by two calibrated examiners (MO, MCH). Calibration of the examiners was conducted prior to the study to ensure the intra-examiner reproducibility of the clinical measurements. The examiners evaluated clinical parameters of six subjects who were not involved in the study on two occasions 24 h apart. The intra-class test was used to determine the intra-examiner reproducibility of all measurements. The examiners reached values of intra-class correlation of 0.86 and 0.84 respectively. In addition, Cohen kappa values that evaluate inter-observer variability were higher> 90% for all gingival bleeding parameters.

Statistical analysis

The statistical tests were performed by the software SPSS 22.0 (SPSS for Windows 22.0, Chicago, IL, USA). Data are expressed as mean ± SD for continuous variables and as percentages for categorical variables. Student's t test was used for comparing continuous variables with normal distribution while Mann-Whitney U test was used for non-normally distributed samples. The chi-square ($\chi 2$) test was used for the comparison of categorical variables and frequencies. Multivariate, step-by-step forward conditional logistic regression analysis was used to find out the parameters that independently determine gingival bleeding and OAC drug withdrawal.

In the univariate analysis, main parameters associated with the presence of gingival bleeding and OAC drug withdrawal were selected in the multivariate model. In order to determine the gingival bleeding related periodontal examination findings, the kappa coefficient was used to examine the compatibility between observers in making the correct diagnosis with 2 different dentists. Receiver Operator Characteristic (ROC) curve analysis was performed for the importance of mean gingival index value did not determine the presence of gingival bleeding and OAC drug withdrawal and optimal cut-off points were determined for these parameters. The area under the curve was calculated for the accuracy of the test. Statistical significance p value was defined as <0.05 for all comparisons.

RESULTS

Overall 457 patients who underwent AF ablation due to paroxysmal AF were interviewed and spontaneous gingival bleeding was reported in 32 patients (7.0%). In 13 of these patients (2.8% for overall patients and 40.6% of the patients with GB), it was found that they had temporarily OAC drug withdrawal due to gingival bleeding.

Gingival bleeding was detected in 32 patients (17 female, 15 male and mean age 53.5 ± 9.8) These patients were further evaluated and compared with 32 matched patients form the initial population with similar age, gender and NOAC treatment protocol for AF (16 female, 16 male and mean age 50.7 ± 11.1) who had no gingival bleeding.

It was found that patients with gingival bleeding had a higher frequency of HT and DM. Although the smoking history was higher in patients with gingival bleeding, there was no statistically significant difference between the two groups (Table 1). The OAC medical treatment regimens of patients were similar in both groups while the OAC drug withdrawal rate was higher in patients with GB (Table 1). Mean PI, mean GI, mean probing pocket depth scores and the diagnosis of chronic periodontitis were found to be significantly higher in the patient group with gingival bleeding (Table 1). Tooth brushing frequency was lower in patients with gingival bleeding (Table1).

The parameters that were found in univariate analysis to be significantly different in patients with gingival bleeding and OAC drug withdrawal were further evaluated with multivariate logistic regression analysis to determine the parameter that independently determines the risk. Mean gingival index score independently determined the risk of both gingival bleeding and OAC drug withdrawal. According to this analysis, every 0.1 unit increase in the mean GI increased the risk of gingival bleeding by 60.5% and increased the risk of OAC drug withdrawal by 32.8% (Table 2).

Table 1. Comparison of characteristics of patients with and without spontaneous gingival bleeding

	Spontaneous gingival bleeding (-) *n*=32	**Spontaneous gingival bleeding (+) *n*=32**	**p**
Age (years)	50.7 ± 11.1	53.5 ± 9.8	0.301
Gender (Female / Male)	16/16	17/15	0.802
Body mass index (kg / m2)	28.4 ± 2.9	29.5 ± 4.1	0.208
Smoking, *n (%)*	5 (15.6%)	11 (34.4%)	0.086
Diabetes, *n (%)*	1 (3.1%)	7 (21.9%)	**0.026**
Hypertension, *n (%)*	5 (15.6%)	16 (50%)	**0.003**
INR	1.34 ± 0.5	1.65 ± 0.7	**0.046**
Mean plaque index	1.14 ± 0.45	1.53 ± 0.36	**<0.001**
Mean gingival index	1.06 ± 0.29	1.7 ± 0.39	**<0.001**
Mean probing pocket depth	3.12 ± 0.35	3.74 ± 0.74	**<0.001**
Frequency of brushing teeth (per / day)	1.39 ± 0.56	0.94 ± 0.5	**0.001**
Periodontal status: Gingivitis, *n (%)*	29 (90.6%)	11 (34.4%)	**<0.001**
Periodontitis, *n (%)*	3 (9.4%)	21 (65.6%)	
OAC treatment: Apixaban, *n (%)*	3 (9.4%)	3 (9.4%)	1.000
Dabigatran, *n (%)*	12 (37.5%)	12 (37.5%)	
Rivaroxaban, *n (%)*	5 (15.6%)	5 (15.6%)	
Warfarin, *n (%)*	12 (37.5%)	12 (37.5%)	
OAC drug withdrawals, *n (%)*	0 (0%)	13 (40.6%)	**<0.001**
Duration of drug use (month)	7.35 ± 7.5	11.90 ± 11.8	0.079

INR: International normalized ratio, OAC: oral anti-coagulant

Table 2. Multivariate regression analysis for the prediction of spontaneous gingival bleeding and OAC withdrawal

Spontaneous gingival bleeding	**Odds Ratio**	**95% Confidence Interval**	**p**
Median gingival index (each 0.1)	1.605	1.293 – 1.991	<0.001
OAC drug withdrawal	Odds Ratio	95% Confidence Interval	p
Median gingival index (each 0.1)	1.328	1.108 – 1.592	0.002

OAC: Oral anti-coagulant

When ROC analysis was performed to detect patients with gingival bleeding with mean GI score, the area under the ROC curve was found to be 0.894 and statistically significant (p <0.001, Table 3, Figure 1). When the mean GI limit value was taken as 1.40, the probability of being patient with OAC drug withdrawal was found with 81.3% sensitivity and 83.9% specificity (Table 3).

Table 3 ROC curve analysis for the prediction of gingival bleeding and OAC withdrawal

Variable	**AUROC Curve**	**P**	**Cut-off**	**Sensitivity**	**Specificity**
For Spontaneous gingival bleeding					
Median gingival index	0.894 (0.816–0.971)	<0.001	1.40	81.3%	83.9%
For OAC drug withdrawal					
Median gingival index	0.806 (0.684–0.928)	0.001	1.65	84.6%	80.0%

OAC: Oral anti-coagulant

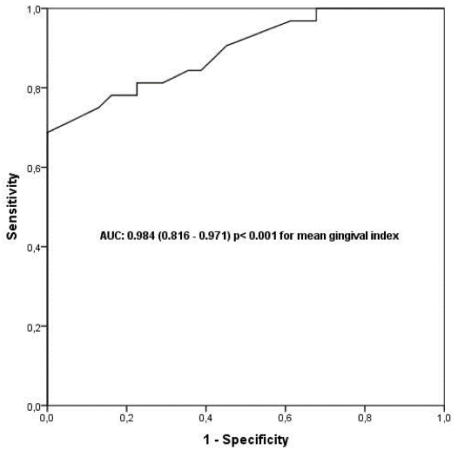

Figure 1.Receiver operating characteristic curves for mean gingival index in the prediction of the group with spontaneous gingival bleeding.

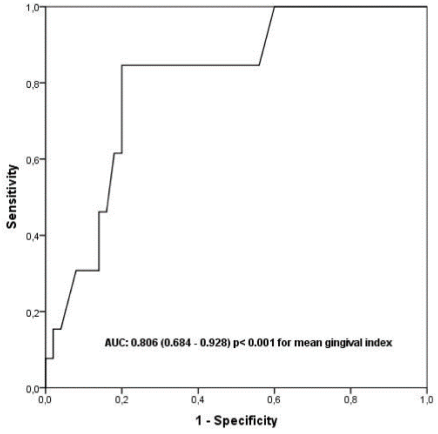

Figure 2.Receiver operating characteristic curves for mean gingival index in the prediction of the group with OAC drug withdrawal.

Similarly, when ROC analysis was performed with mean GI score to determine patients with OAC drug withdrawal, the area under the ROC curve was found to be 0.806 and statistically significant (p = 0.001, Table 3, Figure 2). When the mean GI limit value was taken as 1.65, the probability of being patient with OAC drug withdrawal was found with 84.6% sensitivity and 80.0% specificity (Table 3).

DISCUSSION

In the current study, two important findings related to gingival bleeding were detected in patients with paroxysmal AF under OAC treatment. First, the frequency of gingival bleeding related to OAC treatment was 7% which is low compared to previous epidemiological studies[14, 15] probably related to self-reporting of the bleeding status. Spontaneous gingival bleeding had forced drug withdrawal in 40.6% of the patients with GB. This is a relatively high percentage as both conventional and new generation OACs are safe drugs in terms of bleeding [16]. The second is that the mean gingival index score independently determined both the gingival bleeding and the associated OAC withdrawal. These findings suggest that a pre-existing gingival inflammation is strongly associated with drug withdrawal.

There are no other studies examining gingival bleeding and its associated periodontal parameters in patients with AF under OAC treatment in the literature. Oral infections that are reported to be potentially associated with AF include dental infections (such as caries, endodontic lesions, dental abscesses) and periodontal diseases (such as gingivitis and periodontitis) [17].

OACs and anti-platelet agents cause gingival bleeding with changes in vascular permeability. However, gingival bleeding requires accompanying gum disease and increased inflammation. Although the frequency of gingival bleeding due to the use of vitamin K antagonists has been shown to be 5% (Wu et al., 2015), there is no clear information about the frequency of gingival bleeding with non-vitamin K antagonists in patients with AF. In the studies of Dabigatran, Rivaroxaban, Apixaban and Edoxaban for the treatment of AF, no information was given about the frequency of gingival bleeding due to these drugs and patients who had OAC withdrawal [18-21]. In a recent study, gingival bleeding occurred in 1.7% of patients after a short 3-month follow-up of 110 mg Dabigatran treatment [22]. However, in this study, the follow-up period was short and low-dose Dabigatran treatment was used.

Current AF guidelines do not provide a specific recommendation for gingival bleeding due to the anticoagulant treatment [9]. This important and frequent complication, which is not mentioned even in multicenter studies, is an important problem related to OAC in patients with AF. In previous studies, the OAC treatment withdrawal temporarily

increases the frequency of thromboembolic events and especially stroke and this frequency is between 1-2.6% [23]. The reason for the high rate of treatment withdrawal in our study may be due to the lack of information about gingival bleeding and not having a dental examination before treatment.

Previous studies have shown that there is a relationship between male gender, obesity, presence of DM, smoking and HT, and gingival bleeding [24-27]. It has been reported that gingival bleeding in these diseases is often associated with an increased inflammatory process [1, 2, 26]. In the current study; smoking, DM and HT were found to be higher in patients with gingival bleeding while BMI value was similar in patients with and without gingival bleeding.

Gingival bleeding is an important problem and a symptomatic condition. Therefore, all cardiology patients to receive OAC treatment must have a prior dental examination, and dental/periodontal prophylaxis and/or treatment when needed. Besides gingival bleeding; bacteremia and endocarditis/ pericarditis caused by endodontitis- and periodontitis-related bacteria [28, 29] may also be prevented by this protocol. The results of this study strongly suggest that there should be close communication between the cardiologist and the dentist due to the frequent gingival bleeding in patients with a mean gingival index > 1.40 in patients who will receive OAC or NOAC treatment.

This study has some important limitations. The first is that the study was designed retrospectively and single-centered. The initial AF population was only interviewed on the phone and the spontaneous bleeding was self-reported. The most important reason for this is that it is difficult to have very large patient groups to be followed up clinically and to have these patients under the control of a dentist. Another limitation was that the study was conducted only in patients with paroxysmal AF who were regularly followed in a single outpatient clinic. Especially, it should be evaluated in other group of patients under OAC treatment.

Within the limitations of this study, the results showed that 7% patients with paroxysmal AF under OAC treatment had spontaneous GB and 40.6% of these patients had OAC drug withdrawal due to GB. Dental examination and the determination of the mean gingival index prior to the onset of OAC treatment of these patients may predict the risk of gingival bleeding and OAC drug withdrawal. OAC-induced gingival bleeding can cause symptomatic discomfort as well as severe bleeding. It may also lead to an increase in stroke frequency, especially in those with a high CHA_2DS_2VASc risk score, if the withdrawal of OAC treatment occurs due to the gingival bleeding. Therefore, dental and periodontal examination and treatment before OAC treatment can decrease the risk of gingival bleeding and OAC drug withdrawal. These present findings should be supported by prospective, multicenter and randomized studies.

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