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ORIGINAL ARTICLE

Characteristics, treatment and outcome of bleeding after tooth extraction in patients on DOAC and phenprocoumon compared to non-anticoagulated patients—a retrospective study of emergency department consultations

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Abstract

Objectives Bleeding after tooth extraction range from minor bleeding to life-threating haemorrhagic shock and are among the leading complications in patients under oral anticoagulation with direct oral anticoagulants (DOACs) or phenprocoumon. Little is known about how anticoagulation in patients under DOAC or phenprocoumon alters the characteristics, treatment or outcome of bleeding events, in comparison to non-anticoagulated patients.

Methods Patients admitted to a tertiary ED in Bern, Switzerland, from June 1st 2012 to 31st May 2016 with bleeding related to tooth extraction under DOAC, phenprocoumon or without anticoagulation, were compared.

Results Out of 161,458 emergency consultations, 64 patients with bleeding from tooth extraction were included in our study. In anticoagulation groups, we found significantly more delayed bleeding events than in patients without anticoagulation (9 (81.3%) DOAC, 19 (86.4%) phenprocoumon, 8 (30.8%) no anticoagulation, $p < 0.001$). Anticoagulated patients had to stay longer in the ED than non-anticoagulated patients, with no significant difference between DOAC or phenprocoumon (hours: 4.8 (3.2–7.6 IQR) DOAC, 3.0 (2.0–5.5 IQR) phenprocoumon, $p = 0.133$; 2.7 (1.6–4.6) no anticoagulation; $p = 0.039$). More patients with anticoagulation therapy needed surgery than patients without anticoagulant therapy (11 (68.8%) DOAC, 12 (54.6%) VKA, $p = 0.506$; 7(26.9%) no anticoagulation; $p = 0.020$).

Conclusions Delayed bleeding occur more often in anticoagulated patients with both DOAC and phenprocoumon compared to patients without anticoagulation. Bleeding events in anticoagulated patients with DOAC and phenprocoumon equally need longer ED treatment and more frequent surgical intervention.

Clinical relevance Caution with delayed bleeding in anticoagulated patients with DOACs and phenprocoumon is necessary and treatment of bleeding is resource-demanding.

Keywords Apixaban · Anticoagulation · Direct oral anticoagulant · Phenprocoumon · Rivaroxaban · Tooth extraction bleeding

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Abbreviations

DOAC	Direct oral anticoagulant
ED	Emergency department
VKA	Vitamin K antagonist

Introduction

Bleeding events are one of the leading complications after tooth extraction, with an incidence of up to 25%. These range from frequent minor bleeding to rare life-threating

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haemorrhagic shock, even in healthy patients [1]. Previous studies have found no significant difference in bleeding incidence between patients on oral anticoagulant therapy with the vitamin K antagonist (VKA) warfarin than with patients without anticoagulant medication [2, 3]. In analogy to vitamin K antagonists, guidelines on the management of anticoagulants and tooth extraction therefore recommend that direct oral anticoagulant (DOAC) therapy should be continued in most dental procedures [4].

Most bleeding events from tooth extraction under anticoagulation may be stoppable within the outpatient setting. However, major bleeding complications can lead to admission to the emergency department (ED). This is becoming increasingly common with the growth in the use of DOACs [5]. While treatment guidelines about the perioperative management of rivaroxaban exist [3], a recent literature review of DOACs and tooth extraction found only limited evidence on the effects of DOACs on postoperative bleeding after extraction. A lack of evidence-based work on the management of bleeding events was identified [3].

The aim of the study was therefore to compare patient groups with oral anticoagulation with DOAC and phenprocoumon with patients without oral anticoagulation, with respect to the characteristics of bleeding, treatment and outcome.

Methods

The study population for this retrospective study included all admissions between June 1st 2012 and 31st May 2016 to the adult tertiary ED of Inselspital, Bern University Hospital. This department treats about 40,000 emergency patients per year and has a catchment area of about 2 million people in Canton Bern, Switzerland [6]. The study hospital provides a 24/7 service from the department of cranio-maxillofacial surgery and is the only cranio-maxillofacial centre in the catchment area.

All patients who consulted us with bleeding from tooth extraction, taking one of the approved anticoagulants, DOAC or phenprocoumon on arrival at our ED, were included. They were compared with patients who were not on oral anticoagulant therapy (see Fig. 1).

In order to identify all patients admitted with bleeding from tooth extraction, a keyword search for “tooth”/“teeth” and “bleeding”/“hematoma” with different semantic combinations was performed in the medical records of all patients admitted in the study period. In our ED, diagnoses and procedures are documented in free text. Because ICD or OPCS codes in our department are generated only afterwards for billing purposes, free text reflects the medical conditions and necessities more closely and free of economic considerations. Patients without bleeding from tooth extraction were excluded by independent full-text assessment of the medical records by two researchers (MM and TS). Included patients were grouped by their anticoagulation status on arrival (DOAC, phrenprocoumon, no anticoagulation). All in Switzerland approved DOAC were included in our search [7]. Rivaroxaban is the most commonly prescribed of DOAC in Switzerland and our ED population [5]. Phenprocoumon is the most commonly used vitamin K antagonist, both in our patient population as well as in the rest of continental Europe and was therefore employed for comparison as a vitamin K antagonist [8].

To compare patient and bleeding characteristics, we extracted clinical and demographic data, including gender, age, the indication for anticoagulant therapy, as well as the time point of bleeding after extraction and the number and location of extracted teeth.

Furthermore, the impact and treatment of bleeding from tooth extraction was evaluated by extracting information on

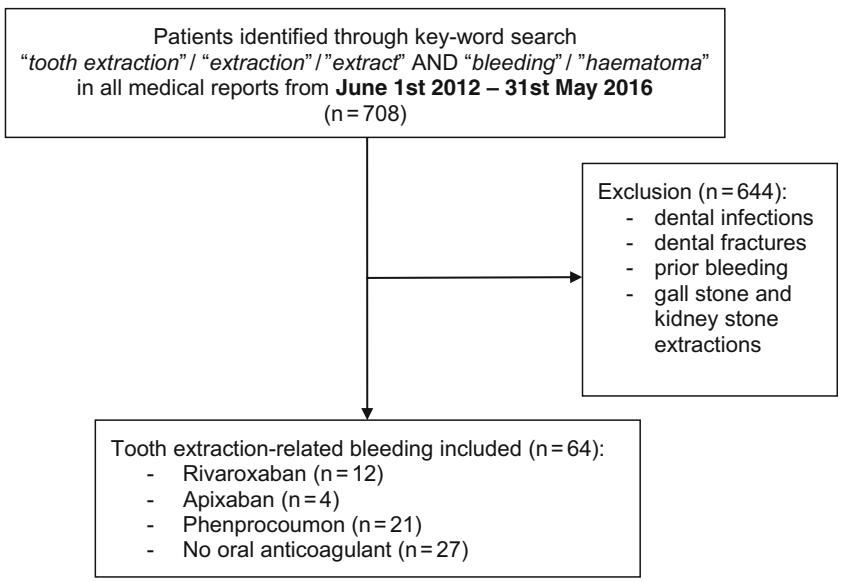

Fig. 1 Flowchart

the haemoglobin level on admission, the presence of anaemia (defined as less than 120 g/l for adult (> 15 years) non-pregnant woman and less than 130 g/l for adult men, according to the World Health Organisation [9], the need and extent of blood transfusion, the extent of local anaesthesia and the need for medical and surgical intervention. Bleeding in the first 24 h after tooth extraction was considered as early bleeding, > 24 h after extraction as delayed bleeding—as defined by Miclotte et al. [10].

The outcome of bleeding was assessed by the need for hospital admission as well as length of hospital and ED stay.

Statistics

We used Stata® 13.1 (StataCorp, The College Station, Texas, USA) for statistical analysis. The distribution of age, time spent on ED and length of hospital stay within the three different anticoagulation groups (DOAC, phenprocoumon and no anticoagulation) were presented as medians with 25th–75th interquartile ranges (IQR). The Mann-Whitney *U* test or the Kruskal-Wallis test were used to compare the distribution of these variables between patients taking DOAC vs. phenprocoumon and between all three anticoagulation groups. Categorical variables are presented as frequency (proportion). Fisher's exact test was performed to test for an association between a categorical variable, e.g. hospitalisation rate, and anticoagulation group over all three categories as well as only between the DOAC vs. phenprocoumon group. A p value of < 0.05 was considered significant.

Ethical considerations

This study was registered and approved by the Ethics Committee of the Canton of Bern, Switzerland (073/2015). Individual informed consent was waived because of the retrospective design and anonymised analysis of data.

Results

The database comprised 161,458 consultations in the ED of Bern University Hospital, Switzerland, from June 1st 2012 to 31st May 2016. The keyword search for "tooth" /"teeth" AND "bleeding"/"hematoma" identified 708 patients. Of these patients, 644 were excluded as they exhibited dental pathologies that were unrelated to extraction, prior bleeding events or other non-dental extractions. In total, 64 patients were included with bleeding events related to tooth extraction. For further group comparison, 16 patients with DOAC (12 patients with rivaroxaban and 4 with apixaban), 21 patients with phenprocoumon and 27 patients without oral anticoagulant medication were included (Fig. 1).

An overview of baseline characteristics of patient groups with DOAC, phenprocoumon and without anticoagulant medication is presented in Table 1. All three patient groups were comparable with respect to gender (male: 7 (43.8%) DOAC vs. 13 (59.1%) VKA vs. 15 (57.7%) no anticoagulation; $p = 0.657$) as well as in the number of teeth extracted (single tooth: 15 (93.8%) DOAC vs. 19 (86.4%) VKA vs. 20 (76.9%) no anticoagulation; $p = 0.343$) and region of extraction. For details about the region of bleeding, see Table 1. In seven patients, the documented underlying procedure of the bleeding was an osteotomy (DOAC $n = 1$ vs. phenprocoumon $n = 1$ vs. no anticoagulation $n = 5$, $p = 0.351$). In all other patients, only tooth extractions were documented. Twelve (50.0%) patients without anticoagulant medication had third molar removal in contrast to no patients on rivaroxaban and two (10.0%) patients on vitamin K antagonist with third molar removal ($p < 0.001$). There was no significant difference in age between the DOAC and phenprocoumon group (76 years (IQR 73–83) vs. 76 years (IQR 67–82); $p = 0.478$); however, the patient groups on anticoagulation were significantly older than the patients without anticoagulation (77 vs. 44 years).

The time point of the bleeding events was examined and no difference between the phenprocoumon and DOAC groups was found with respect to the incidence of delayed bleeding (9 (81.3%) vs. 19 (86.4%), respectively; $p = 0.624$). In contrast to this, both these treatment groups exhibited significantly more delayed bleeding events than the group without anticoagulation (no anticoagulation: 8 (30.8%) delayed bleeding; $p < 0.001$). All characteristics of bleeding events for the different groups are summarised in Table 1.

We found no significant differences between the groups with respect to the impact of the bleeding events (anaemia on admission (7 (43.8%) DOAC, 6 (28.6%) VKA, 4 (15.4%) no anticoagulation; $p = 0.375$), the need for blood transfusion (1 (6.3%) DOAC, 0 VKA, 1 (3.9%) no anticoagulation; $p = 0.716$).

Regarding outcome of the bleeding events, it was found that patients on either therapy with DOAC or phenprocoumon had to stay longer in the ED than non-anticoagulated patients, with no significant difference between DOAC or phenprocoumon (hours: 4.8 (3.2–7.6 IQR) DOAC, 3.0 (2.0–5.5 IQR) VKA, 2.7 (1.6–4.6) no anticoagulation; $p = 0.039$, Table 2). There were no significant differences (8 patients (50%) DOAC, 9 patients (40.9%) VKA, 7 (26.9%) no anticoagulation; $p = 0.310$)) in the length of hospital stay (days: 1 (1–2 IQR) for DOAC and VKA vs. 3 (1–6 IQR) no anticoagulation; $p = 0.370$) (Table 2).

In regard to the therapeutic management of the bleeding events, significantly more patients with anticoagulation therapy needed surgery than did patients without anticoagulant

Table 1 Comparison of study characteristics between teeth extraction related bleeding in patients taking DOAC ($n = 16$; rivaroxaban, $n = 12$ and abixaban, $n = 4$), phenprocoumon ($n = 22$), and no anticoagulation ($n = 26$), Mann-Whitney *U* test, Kruskal-Wallis test or Fisher's exact test, as applicable

	DOAC		Phenprocoumon		*p* (*D.* vs. *P.*)	No anticoagulation		*p* (all)
Age, (median (IQR))	76	(73–83)	76	(67–82)	0.478	44	(23–59)	< 0.001
Male, (*n* (%))	7	(43.8)	13	(59.1)	0.512	15	(57.7)	0. 657
Indication anticoagulation, (*n* (%))								
Atrial fibrillation (AF)	9	(56.3)	9	(40.9)				
Pulmonary embolism (PE)	1	(6.3)	0	(0)				
AF + PE	4	(25.0)	0	(0)				
Valve/vascular replacement	0	(0)	7	(31.8)				
Not specified	2	(12.5)	6	(27.3)	0.004			
Recurrent bleeding, (*n* (%))	2	(12.5)	3	(13.6)	1.000	0	(0.0)	0.105
Extracted teeth, (*n* (%))								
Single	15	(93.8)	19	(86.4)		20	(76.9)	
Multi	1	(6.3)	3	(13.6)	0. 624	6	(23.1)	0.343
Region*, (*n* (%))								
Lower jaw	2	(16.7)	10	(47.6)		10	(41.7)	
Upper jaw	10	(83.3)	11	(52.4)		10	(41.7)	
Both	0	(0.0)	0	(0)	0.133	4	(16.7)	0.052
Third molar extraction, (*n* (%))	0	(0.0)	2	(10.0)	0.508	12	(50.0)	<0.001
Time after extraction, (*n* (%))								
Early bleeding	3	(18.8)	3	(13.6)		16	(61.5)	
Delayed bleeding	9	(81.3)	19	(86.4)		8	(30.8)	
Not specified	0	(0.0)	0	(0)	0.682	2	(7.7)	<0.001

*If specified. *AF* atrial fibrillation, *D.* DOAC, *P.* phenprocoumon, *PE* pulmonary embolism

therapy (11 (68.8%) DOAC, 12 (54.6%) VKA, 7 (26.9%) no anticoagulation; $p = 0.020$). These patients also tended to spend more time in the ED. No difference could be demonstrated between the DOAC and VKA groups. There was no significant difference between the groups with respect to the options for conservative treatment (see Table 2).

Discussion

In summary, patients on anticoagulant therapy had more delayed bleeding events and were more likely to require surgery than patients not on anticoagulants and had to spend more time in the ED. No differences were found between different anticoagulants.

Table 2 The impact of tooth extraction related bleeding in different patient groups taking DOAC ($n = 16$; rivaroxaban, $n = 12$ and abixaban, $n = 4$), phenprocoumon ($n = 22$), and no anticoagulant medication ($n = 26$), Mann-Whitney *U* test, Kruskal-Wallis test or Fisher's exact test, as applicable

	DOAC		Phenprocoumon		*p* (*D.* vs. *P.*)	No anticoagulant		*p* (all)
Anaemia, (*n* (%))	7	(43.8)	6	(28.6)		4	(15.4)	
Not specified	5	(31.3)	7	(31.8)	0.508	10	(38.5)	0.375
Blood transfusion, (*n* (%))	1	(6.25)	0	(0.0)	0.421	1	(3.9)	0.716
Surgery, (*n* (%))	11	(68.8)	12	(54.6)	0.506	7	(26.9)	0.020
Conservative, (*n* (%))								
No therapy needed	3	(60.0)	3	(30.0)		7	(36.8)	
Gauze packing (GP)	2	(40.0)	5	(50.0)		10	(52.6)	
Cauterisation + GP	0	(0.0)	2	(20.0)	0.615	2	(10.5)	0.806
ED stay, hour (median (IQR))	4.8	(3.2–7.6)	3.0	(2.0–5.5)	0. 133	2.7	(1.6–4.6)	0.039
Hospital admissions, (*n* (%))	8	(50.0)	9	(40.9)	0. 743	7	(26.9)	0.310
Length of hospital stay, days (median (IQR))	1	(1–2)	1	(1–2)	1.000	3	(1–6)	0.370

The anticoagulant groups and non-anticoagulant group in our study are comparable with respect to gender and number as well as region of teeth extracted. The greater age of patients with anticoagulant medication in comparison to patients without anticoagulation may very well be explained by the greater prevalence of atrial fibrillation in older patients [11]. This greater age may warrant more caution in this patient group, as fatal complications have been documented previously, particularly in the elderly [12]. As third molar removal is typically performed in young patients, the observed greater number of third molar removal in patients without anticoagulation compared to patients on any anticoagulation likely reflects the higher age of patients on anticoagulant medication. With our retrospective data, we cannot make a statement about the general prevalence of third molar removal in our populations. This should be topic of further research to better understand the mechanisms of bleeding.

It is unclear whether there is an underlying pathophysiological mechanism that explains the greater number of delayed bleeding events in the two anticoagulant groups compared to patients without anticoagulation. According to current guidelines, it is not recommended that DOAC should be interrupted for minor dental interventions [4]. Although the time point of last dose of medication is not routinely documented in our medical database, it is possible that the delayed bleeding may be connected with restarting anticoagulant therapy. Unfortunately, for DOAC patients, concentrations of anticoagulant drugs, that may provide insights into the mechanisms of bleeding events, were not routinely measured in our retrospective data. It might therefore be desirable to measure DOAC levels in specific high-risk populations in the future. This finding of increased delayed bleeding events may as well prompt the dentist or treating ED clinician to be cautious with follow-up appointments in anticoagulated patients. It is important that all physicians treating anticoagulated patients are well informed about bleeding complications and risk stratification of individual patients.

A recent systematic review attempted to identify evidence-based interventions for treating post-extraction bleeding in patients without anticoagulants. The authors concluded that, due the lack of "reliable evidence on this topic, clinicians must use their clinical experience to determine the most appropriate means of treating this condition" [1]. Therefore, our standard procedure for postoperative bleeding is mostly related to management recommendations for invasive dental treatment in patients using oral antithrombotic medication [3, 10]. In patients with coagulopathies, bleeding management is even more challenging, as the clinical experience in treating such complications is smaller [13, 14]. This more difficult treatment of anticoagulant related bleeding is reflected in our data with an increased number of patients taken to theatre with anticoagulant related tooth extraction bleeding compared to patients without anticoagulation. This is similar for DOAC and classical anticoagulant therapy with phenprocoumon and makes therapy in these patient groups more expensive and demands more resources. This may develop into an important issue with the increasing number of anticoagulated patients, especially with DOACs [5]. Both DOAC and phenprocoumon patients tended to stay for longer periods in the ED than non-anticoagulated patients. This contributes to the issue of costs and may make greater demands on the patient-flow organisation at the treating ED. As regards outcome parameters, there were no differences between the group with respect to the number of hospital admissions and length of hospitalisation. Real-life data, also including economical considerations in connection with bleeding events, are emerging on anticoagulation and the newer DOACs [15]. Those studies may influence the choice of a specific anticoagulant medication. However, based on the literature and our data, it is not yet possible to make recommendations for a specific anticoagulant therapy for dental bleeding.

Limitations

A limitation of this study is the selective design, with the inclusion of ED patients presenting with a condition that is often treated out of hospital. Nevertheless, we included major bleeding related to tooth extraction that would have been potentially harmful to the patient if not treated adequately. The treatment of minor bleeding in the outpatient setting may explain the low number of cases admitted to our hospital. As the sample is small, despite over 160,000 screened ED consultations, it is not possible to exclude that our study is underpowered to detect a difference between the different anticoagulant groups. The influence of the surgical technique on the impact and outcome of bleeding was not analysed in this study. The bleeding risk may be lower in the case of primary closure of the extraction socket. As with all retrospective data, no guarantee can be given for the completeness of the medical documentation, as this was performed by the responsible treating physician. In addition to this, the risk of missing patients in retrospective database research can only be minimised, but not excluded, as we did with two independent raters responsible for the inclusion of patients and full-text database screening.

Conclusion

Our study suggests that delayed bleeding events after tooth extraction occur more often in anticoagulated patients than in patients without oral anticoagulant therapy, but no difference between DOAC and phenprocoumon could be demonstrated. In addition to this, bleeding in patients on anticoagulants required surgery more often and more protracted ED treatment was necessary compared to patients without anticoagulation. Due to the low incidence, future research is recommended to confirm our findings in larger populations and find possible differences between different types of oral anticoagulation.

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Compliance with ethical standards

Conflict of interest MM, BS and FS declare that they have not conflicts of interest. MN has reviewed research grants or lecture fees from Bayer, CSL Boehringer, Roche diagnostics, and Instrumentation Laboratory. AKE is member of the advisory boards of all registered DOACs. TCS has received research grants or lecture fees from Bayer, Boehringer Ingelheim, Daiichi-Sankyo and the Gottfried und Julia Bangerter-Rhyner-Foundation.

Ethical approval This study was registered and approved by the Ethics Committee of the Canton of Bern, Switzerland (073/2015).

Informed consent Individual informed consent was waived by the Ethics Committee of the Canton of Bern, Switzerland, because of the retrospective design and anonymised analysis of data.

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