Postoperative Bleeding Following Dental Extractions in Patients Anticoagulated With Warfarin

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Purpose: The practicing dentist must frequently advise on the risks involved with dental extractions in the patient taking an anticoagulant. This study assessed the risk of bleeding in a large heterogeneous cohort of patients on warfarin treated by practitioners in training (dental students and junior staff in a teaching hospital).

Materials and Methods: This was a retrospective case-and-control study of 439 patients on warfarin (1,022 extractions) and 439 matched controls (1,049 extractions). Patients with an international normalized ratio (INR) lower than 2.2 had no specific measures, those with an INR 2.2 to 4 received suturing and tranexamic acid mouthwash, and those with an INR higher than 4 did not undergo extraction. Bayesian methods were used to estimate posterior probabilities of bleeding.

Results: Of cases, 63% were men, 25% were older than 80 years, 40% had an INR lower than 2.2, and 9% had an INR higher than 3. Nine cases bled 0 to 10 days postoperatively, with 1 requiring admission and transfusion. Significant predictors of bleeding were INR and number of extractions ($P < .001$ for the 2 comparisons). There were no events of bleeding in controls or cases with an INR lower than 2.2 (95% credible interval [CrI] for difference, −0.7 to 1.6). The posterior mean of bleeding was 1% (CrI, 0.1-2.6) for an INR lower than 2.2, 2.3% (CrI, 0.9-4.5) for an INR of 2.2 to 3, and 8.4% (CrI, 3.5-15) for an INR higher than 3.

Conclusion: Unselected patients taking an anticoagulant with an INR lower than 2.2 had a similar risk of bleeding as control patients. The risk was approximately 1 in 40 in those with an INR of 2.2 to 3, whereas the risk in patients with an INR higher than 3 was approximately 1 in 11.

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Warfarin is the most common anticoagulant used in Australia, with more than 2.6 million prescriptions filled in 2014.[1] Warfarin is used predominately for the prevention of life-threatening thromboembolic events, such as stroke and deep vein thrombosis, in at-risk patients.[2] The clinical indications for warfarin therapy recorded for patients in this study are presented in Table 1. It is a potent anticoagulant classed as a vitamin K antagonist that works by inhibiting vitamin K epoxide reductase, which in turn inhibits the recycling of vitamin K from its inactive to active form.[3] This in turn interferes with the formation of vitamin K–dependent clotting factors II, VII, IX, and X and antithrombotic factors protein C and protein S.

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Table 1. CLINICAL INDICATIONS FOR WARFARIN THERAPY

Clinical Indication	Patients, n	Patients, %
Atrial fibrillation	171	39.0
Venous thromboembolism	94	21.4
Prosthetic valve replacement	79	18.0
Myocardial infarction	61	13.9
Stroke	24	5.5
Valvulopathy	8	1.8
Not recorded	2	0.5
Total	439	100.0

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Suggestions on the approach to management of dental extractions in patients taking warfarin have varied considerably, from stopping the anticoagulant before extraction to continuing its use while using local hemostatic techniques. Ceasing warfarin with no bridging therapy has the risk of inducing a life-threatening thromboembolic event. Garcia et al[4] found that when withholding warfarin for even a short period in low- or moderate-risk patients, the risk of a thromboembolic event was as high as 0.7%. Because of this risk of thromboembolism and the low risk of perioperative and postoperative bleeding, it is well accepted that ceasing warfarin before dental extraction is not recommended.[5,6] However, in instances when the risk of bleeding remains a concern, the use of local hemostatic measures, such as tranexamic acid, fibrin glue, and oxidized cellulose, are indicated.[5-8]

The therapeutic effect of warfarin is measured as prothrombin time and communicated as the international normalized ratio (INR). Depending on the clinical indication for warfarin therapy, a different target INR range exists, with most patients targeting a value between 2 and 3. Consensus on what constitutes a safe upper limit for the INR when performing dental extractions remains controversial. Al-Mubarak et al[9] and Morimoto et al[10] found no statistical difference in postoperative bleeding in their respective cases for an INR no higher than 3. Bacci et al[5] reported safety with an INR no higher than 4, whereas Ferrieri et al[11] reported no statistical difference in bleeding between controls and cases with an INR no higher than 5.5. In a meta-analysis of patients on warfarin who were followed for spontaneous bleeding, the risk of bleeding was markedly increased at an INR higher than 3.[12] The difference in bleeding between those with an INR of 2 to 3 and an INR lower than 2 was not statistically meaningful, but there clearly was a biological effect.[12] Oake et al[12] also found a marked decrease in thromboembolic events in patients on warfarin with an INR of 2 to 3 compared with an INR lower than 2.

The practicing dentist in the public and private setting must frequently provide treatment, including dental extractions, to patients on warfarin therapy. The dentist should include a discussion of the risks of postoperative bleeding as part of routine preoperative consent. The literature reports a rate of bleeding after dental extraction of approximately 2 to 8%.[5,13,14] However, it is important to note that these figures come from clinical trials or specialist centers usually with highly skilled operators. The protocol used in the authors' institution was developed after extensive trials with experienced staff to determine the optimum management routine for patients on warfarin.[7,8] This case-and-control study aimed to *1)* assess the risk of bleeding in patients on warfarin after dental extraction when treated by junior practitioners according to the authors' standardized protocol and *2)* quantify risk by different INR levels and number of extractions.

Materials and Methods

The database of patients attending the extraction clinic of Adelaide Dental Hospital (Adelaide, Australia) from July 2010 to June 2014 was searched to establish all patients who had a documented INR. In total, 439 patients taking warfarin and having had at least 1 dental extraction were identified after a review of the records. A matrix with the following variables was constructed: age; gender; INR; clinical indication for anticoagulant therapy; procedure, including site and number of teeth extracted; and any documented complications. A matched control group of 439 patients who were not taking an anticoagulant with similar age, gender, and medical comorbidity mix were recruited over a 3-month period in late 2012.

All patients underwent medical, clinical, and radiographic assessment before extractions. In addition, an INR, preferably on the same day of the procedure or within 24 hours, was required. Patients were appropriately prescribed and provided with antibiotics, if indicated, to lower the risk of endocarditis in at-risk patient groups. Extractions were performed in accordance with the recommendations set out by the Oral and Dental Therapeutic Guidelines, which were based on the authors' research.[7,8,15] Patients with an INR lower than 2.2 were treated with no additional precautions similar to those who were not taking an anticoagulant. For those patients with an INR of 2.2 to 4.0, further management after extractions was implemented. This included irrigation of the socket with a 4.8% solution of tranexamic acid, placement of an oxidized cellulose absorbable hemostatic agent (Surgicel; Ethicon, Somerville, NJ) within the socket, and closure by suturing. Then, patients were required to bite on gauze soaked in tranexamic acid for 30 minutes. In addition, patients were advised to rinse with the same solution 4 times per day for

2 days. Patients with an INR higher than 4 were referred to their prescribing clinician to ensure therapy was within the therapeutic range and were rebooked for extraction on a later date.[7,8] All dental extractions for the anticoagulated and control groups were performed by junior dentists or senior dental students supervised by junior house officers. The Royal Adelaide Hospital human research ethics committee approved this study.

Statistical analysis was undertaken using R 3.2.[16] The reported probability of bleeding with anticoagulation was estimated from the literature and used to estimate a prior.[5,13,14,17] The authors used 2% and 8% to represent 1 standard deviation above and below the mean to provide a relatively broad prior. A tighter prior with 2% and 8% representing 2 standard deviations above and below the mean also was used for comparative purposes. The posterior probability was estimated using standard Bayesian methods. Bayesian methods were chosen as a way of integrating the prior knowledge to generate an interval the practicing dentist could use for counseling patients. Although the treatment protocol subdivided patients into INRs lower and higher than 2.2, in view of the meta-analysis, the authors also analyzed bleeding in 3 cohorts: INR lower than 2, INR of 2 to 3, and INR higher than 3. Logistic regression and model comparison were performed with the R package MCMCpac.[18]

Results

Of the 439 patients taking an anticoagulant (278 men and 161 women), 9 patients (2.1%) returned with postoperative bleeding 0 to 10 days postoperatively (mean, 2.56 days). Their mean age was 69.5 years (>65 yr old, 68.3%; >80 yr old, 26.7%). Table 2 lists the demographics and features of patients separated into groups determined by the INR.

Table 2. CHARACTERISTICS OF STUDY POPULATION

	Controls	Cases	Cases With INR <2.2	Cases With INR 2.2-4
n	439	439	178	261
INR, mean	N/A	2.29	1.72	2.68
Age (yr), mean	65.19	69.53	68.58	70.16
Men	234	278	108	170
Women	205	161	70	91
Number of extractions	1,049	1,022	393	629
Single extraction	281	249	103	146
Multiple extractions	158	190	75	115
Bleeding cases	0	9	0	9

Abbreviations: INR, international normalized ratio; N/A, not applicable.

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Bleeding occurred in patients who had single extraction (3 cases) and multiple extractions (6 cases) for caries, periodontal disease, or caries and periodontal disease. Bleeding occurred in 6 of the 9 cases within 1 day of extraction. There were 5 reported instances of bleeding in the posterior maxilla, 1 in the anterior mandible, and the remaining generalized as ooze. All but 1 case were managed with local hemostatic measures by irrigating the socket with tranexamic acid, placing oxidized cellulose within the socket, resuturing, and then biting on gauze soaked in tranexamic acid. Patients also were advised to continue the tranexamic acid mouth rinse for 2 days. One patient required hospital admission with transfusion of blood products when he presented with bleeding 10 days postoperatively and an INR higher than 5. This patient had multiple severe medical comorbidities and he was awaiting cardiac transplantation. He had a single dose of prophylactic antibiotic and none subsequently. However, he was on multiple other medications for his cardiovascular state and other medical comorbidities. His records showed wide fluctuation in his INR despite a constant dose of warfarin. In the preceding month, this varied from lower than 2 to 3.2 at the time of extraction to higher than 5 10 days later. Table 3 presents the characteristics of patients with postoperative bleeding.

There were no cases of bleeding in the control group of an equal number of 439 patients not taking warfarin. This group had a similar total number of extractions performed (1,049 vs 1,022 in anticoagulated group).

On logistic regression analysis, INR and number of extractions were meaningfully associated with risk of bleeding after extraction. Given the small number of events, credible intervals were wide. For every increase in INR by 1, the odds of bleeding increased by approximately 13 (95% credible interval, 3.3-68.8). For every extra extraction, the odds of bleeding increased by 1.28 (95% credible interval, 1.088-1.48). Age and gender had no predictive value in determining bleeding risk. When considering the various predictive models, the model using only the INR as a predictive factor had the greatest strength.

There were no bleeding events in the 151 patients with an INR no higher than 2 or in the 27 patients with an INR of 2 to 2.2. Because the authors' current treatment algorithm changes at an INR of 2.2, this was used as the cutoff to compare with patients not taking an anticoagulant. Credible intervals were calculated using uninformative priors. The credible intervals strongly overlapped (difference in 95% credible intervals, −0.71 to 1.5). Thus, the difference in

Table 3. CHARACTERISTICS OF BLEEDING CASES

Case	Gender	Age (yr)	INR	Teeth Extracted	Indication for Extraction	Mode of Extraction	Days of Bleed	Bleeding Site	Severity of Bleed
1	M	80	2.3	16	Caries	Simple	1	16	Small ooze
2	F	61	2.4	15, 18, 21-24, 31-35, 37, 41-43	Caries, periodontal disease	Simple	0	generalized	Small ooze
3	M	62	2.6	17	Caries, periodontal disease	Simple	6	17	Small ooze
4	F	75	2.8	26, 27, 28	Caries, periodontal disease	Simple	1	26-28	Small ooze
5	M	54	3.2	12, 13, 15, 21-23, 27, 36, 37, 46-48	Periodontal disease	Surgical	10	left maxilla	Persistent ooze
6	M	56	3.3	23, 31, 37, 41-44	Caries	Simple	1	43	Small ooze
7	M	70	3.3	26	Periodontal disease	Simple	0	26	Small ooze
8	F	49	3.4	26-28, 37, 38	Periodontal disease	Simple	3	Generalized	Small ooze
9	F	40	3.9	27, 28, 34, 36-38, 44-46	Caries, periodontal disease	Simple	1	Generalized	Small ooze

Abbreviations: F, female; INR, international normalized ratio; M, male.

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bleeding rates between patients with an INR no higher than 2.2 and those not on anticoagulation was small, but a higher bleeding rate cannot be excluded.

Previously published data from the literature were used for the prior probability, which enabled the calculation of the credible interval of bleeding (Table 4).[13,14] The small number of patients with an INR of at least 3 limits precision. Increasing the credence given to the literature prior tightens up the credible intervals and has a major effect on decreasing the likely upper bound of bleeding events. To show this graphically, the effects of using cutoffs of 2.2 and 3 were used to reflect the treatment algorithm and the meta-analysis data on major bleeding risk. The posterior probability is shown in Figure 1 using the broad informative prior. For completeness from a frequentist perspective, there was a statistically significant difference between patients using an anticoagulant and those not using an

Table 4. INCIDENCE OF BLEEDING BY INR

INR	Bleeding Cases	95% Credible Interval	
		Broad Prior	Tight Prior
<2	0	0.1-1.9	0.5-2.6
2-3	4	0.8-4	1.2-4
>3	5	2.9-12.6	2.9-8.9

Abbreviation: INR, international normalized ratio.

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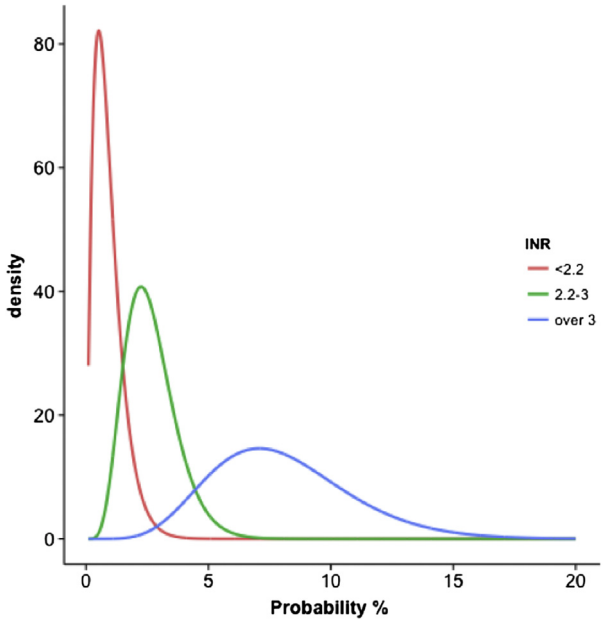

FIGURE 1. Posterior probability of bleeding varies with INR. INR, international normalized ratio.

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anticoagulant and between those who received therapeutic anticoagulation and those who did not (P = .012).

Discussion

The protocol followed in this study is in line with current international practices.[5,19,20] This is based on the rationale that patients taking warfarin with an INR higher than 4 have a markedly increased bleeding risk for no medical benefit. Most studies have been conducted in institutions with highly skilled practitioners. There is little research exploring postoperative bleeding after dental extractions by less skilled professionals. Overall, there was a low incidence of bleeding in patients taking an anticoagulant using this protocol. Relevant associations were found between the degree of anticoagulation and risk of bleeding and between the number of extractions and risk of bleeding, although numerically the former was more important. The credible intervals were very broad, reflecting the small numbers of events. No difference in the rate of bleeding was found between patients with an INR no higher than 2.2 and control patients not taking an anticoagulant, although the credible intervals do not exclude a higher rate of bleeding in the anticoagulated group.

In accordance with recent studies, this study suggests that halting warfarin is unnecessary and potentially dangerous for patients whose anticoagulant achieves the therapeutic range (2 to 3.5).[5,6,13] Zanon et al[21] and later Bacci et al[5] used a similar protocol as this study but differed by not including the use of tranexamic mouthwash in the immediate postoperative period. These studies found no difference in bleeding events between patients taking an anticoagulant treated under their protocol and controls. Although the present study shows a statistically relevant difference between groups, there is a similar incidence of postoperative bleeding in patients taking an anticoagulant (3.4%) as these 2 previous studies (2.1 and 1.6%, respectively).[5,21]

Nematullah et al[13] in their systematic review evaluating the effect of continuing or modifying the dose of warfarin before dental extractions suggested a 5.5% rate of clinically minor bleeding in patients taking an anticoagulant. The more recent multicenter prospective study with more than 450 patients by Bacci et al[5] suggested a rate of postoperative bleeding of 1.6% in patients taking an anticoagulant.

Various local hemostatic adjuncts are used in different centers, such as resorbable hemostatic agents, suturing, and tranexamic acid. Salam et al[22] in their case series used absorbable oxy-cellulose and suturing and determined a postoperative bleeding incidence of 7%. Carter et al[7,8] conducted a review and later a prospective randomized control trial that suggested a benefit in the use of tranexamic acid in patients taking an anticoagulant.

Morimoto et al[10] found no correlation between the INR and postoperative bleeding. In this study, all patients taking an anticoagulant had oxidized cellulose placed into the socket and sutured. Although a different protocol was used in the present study, with the additional use of tranexamic acid, all postoperative bleeding occurred in patients with an INR of at least 2.2, which was statistically different from controls or patients with an INR lower than 2.2.

Five of the 9 patients in this study had postoperative bleeding in the posterior maxilla and another 3 had generalized ooze with no specific localization documented. Svensson et al[6] and Rodríguez-Cabrera et al[14] noted a propensity for postoperative bleeding in the maxilla compared with the mandible. As in the study by Svensson et al, the present study showed an increased incidence of bleeding in patients receiving multiple rather than single extractions.[6]

Practicing general dentists can use this information in the following ways. They are likely to use the data from the broad prior because this represents uncertainty in translating specialist results to general practice. Hence, they can quote likely bleeding rates for patients treated with a nontherapeutic anticoagulant as being broadly similar to the general population. For those with an INR of 2 to 3, there is a 95% probability that the risk of bleeding is approximately 1 in 100 to 1 in 25. For those with an INR higher than 3, there is a 95% probability that the risk of bleeding is approximately 1 in 30 to 1 in 7. Because patients with INRs higher than 4 were excluded, no comment on their bleeding risk can be made. Undoubtedly, their risk of bleeding would be much greater with no medical preventative value. Therefore, it can be concluded that the protocol used in this study and substantiated through previous research is directly applicable and can be translated into general dental practice.

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