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This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/145431 since

Published version:

DOI:10.1016/j.joms.2013.12.026

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11 November 2026

Bleeding Rate During Oral Surgery of Oral Anticoagulant Therapy Patients With Associated Systemic Pathologic Entities: A Prospective Study of More Than 500 Extractions

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Purpose: Oral anticoagulant therapy (OAT) patients have international normalized ratio (INR) safety windows for oral surgery, the lower limit of which is determined by the thromboembolic risk, with the upper limit typically 3.0. We sought to assess whether these limits will also be true with comorbidities that favor bleeding, such as diabetes, liver disease, and chronic renal failure.

Materials and Methods: The study was designed for 500 consecutive extractions. Patients with an INR greater than 3.0 were switched to heparin and used as controls. The primary outcome was the incidence of bleeding with the need for reoperation, in connection with 3 principal predictors: the INR, reasons for OAT, and comorbidity type. Continuous variables were analyzed using the Mann-Whitney *U* test and categorical variables using χ^2 or Fisher's exact test. Statistical significance was set at $P < .05$. The reliability of the INR as a bleeding predictor was assessed using receiver operating characteristic (ROC) curves.

Results: Extractions in patients receiving OAT without comorbidities had a success rate of 99.7% against severe bleeding. Despite equivalent INR values, patients with comorbidities had a significantly lower rate (81.3%, $P < .001$). For these patients, the ROC curve procedure indicated lower INR upper limits, 2.8 for mechanical heart prosthesis subjects and 2.3 for all others. Among the comorbidities, diabetes was associated with the greatest frequency of bleeding (31%) compared with liver disease (15%) and kidney failure (11%).

Conclusions: Patients with comorbidities should be advised to bring their INR within narrower safety windows (upper limit of 2.5 to 2.8 for mechanical prosthesis and 2.0 to 2.3 otherwise) or be switched to heparin. Alternatively, we propose applying to the socket, a platelet-rich growth factor preparation to foster hemostasis.

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J Oral Maxillofac Surg 72:858-867, 2014

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Received October 9 2013

Accepted December 17 2013

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0278-2391/14/00062-7$36.00/0

http://dx.doi.org/10.1016/j.joms.2013.12.026

The number of patients receiving oral anticoagulant therapy (OAT) and requiring dental surgery has been increasing simply owing to the increase in the elderly population, who will also be the most afflicted by various cardiovascular problems. Perioperative management in this population is both challenging and clinically important, because it involves 2 main concerns: the risk of thromboembolism, with anticoagulation interruption, versus the risk of procedural or postprocedural bleeding, with anticoagulation continuation.[1-3]

In the past, many oral surgical procedures were performed after the patient had interrupted OAT to be switched to heparin. Switching to low-molecular-weight heparin, however, does not allow tight control of the patient's coagulation state. In contrast, choosing "traditional" unfractionated heparin will increase the hospitalization stay, because the infusion must be managed in the hospital. Even then, it exposes a not-insignificant number of patients to the side effects of a continuous heparin infusion. Moreover, switching increases the hemorrhagic risk, particularly in the bridging phase, when both anticoagulants could be acting simultaneously.

The prothrombin time (PT) is the laboratory test of choice for monitoring the anticoagulation status of patients treated with oral anticoagulants. The standardization of PT with the international normalized ratio (INR) allows for uniform measurements and permitted the development of effective recommendations for the use of oral anticoagulants in various clinical settings.

Patients with mechanical valves and those who have experienced a thromboembolic event within 3 months before the discontinuation of anticoagulation have been considered to be at high risk of new or recurrent thromboembolism[4-6] and have been advised to keep the INR at 2.5 or greater. In contrast, patients receiving anticoagulation for indications such as atrial fibrillation will be at lower risk[7,8] and can have an INR of 2.0 or more. Factors that increase the risk level include age older than 75 years, hypertension, stroke, transient ischemic attack, and heart failure.[9-11] In most cases, an INR of at least 2.0 will be required for effective anticoagulation. As the INR increases, the blood will take longer to clot, and the patient will be at increased risk of bleeding. Thus, there is an upper limit for the allowable INR therapeutic levels in cases of surgery; for dental extractions, it has generally been set at an INR of 3.0 or less. However, this should be considered a general limit, applied independently of comorbidities. The present report presents the results of a prospective study of 500 dental extractions conducted in patients receiving OAT for prophylaxis against cardioembolism.

Our hypothesis was that the validity of this INR limit should not to be assumed correct in the case of patients affected by diabetes, liver disease, or kidney failure,[12-14] pathologic entities that have been demonstrated to hinder healing. We believed the issue needed to be tested in a clinical trial designed specifically to address the following questions:

1. Among all patients receiving OAT and undergoing dental extraction with an INR of 3.0 or less, what is the incidence of the most common postoperative complications: severe bleeding needing reoperation and hematoma?
2. Does the presence of comorbidities often associated with cardiovascular problems, such as diabetes, liver disease, and kidney failure, exacerbate bleeding?
3. If the answer to question 2 is yes, could the problem be avoided by lowering the INR upper limit? If so, what would be the advisable upper limit for the INR for this particular subclass of patients? Finally, could a new limit coexist with the lower limits set according to thromboembolic risk?

The final goal was to determine the best scenario capable of reconciling as much as possible the most effective surgical conditions—minimum bleeding and hematoma—with the most appropriate coverage against thromboembolic risk in the various categories of OAT patients.

Materials and Methods

STUDY DESIGN AND SAMPLE

Our study was designed to include 500 consecutive extractions in patients receiving OAT. The large number was chosen to allow division into the groups and subgroups of interest without the loss of statistical power.

The study sample was derived from the population of patients who were referred to the oral surgery section of our institution (Dental School, University of Torino, Azienda Ospedaliera Città della Salute e della Scienza of Torino; 1 of the largest hospitals in northern Italy) by in-hospital departments, general practitioners, or cardiologists. Because of the high turnover at the hospital, the target of 500 extractions was reached within slightly less than 1 year.

To be included, the patients had to be receiving OAT, need a dental extraction because of root or crown fractures, nonrestorable caries, residual roots, or periodontal and endodontic abnormalities, and be willing to cooperate with the study protocol and follow-up program. No exclusion criteria were applied regarding age, gender, or associated comorbidity; however, the patients were required, according to the present protocol at our hospital, to have an INR value of 3 or less. Patients with an INR greater than 3.0 were switched to heparin and were used as controls for the OAT patients.

All patients provided written informed consent before enrolling. The study was conducted in accordance with the Declaration of Helsinki, as updated, and was approved by the local ethics committee.

SURGICAL PROTOCOL

The same surgeon, with extensive clinical experience, performed all extractions. After the induction of local anesthesia (mepivacaine 3% without adrenaline), the teeth were extracted in a nontraumatic manner, with rotation and traction movement using dental forceps and elevators. The alveolar sockets were first treated with a fibrin sponge (Spongostan, Ethicon, Cincinnati, OH) and then sutured with 3-0 silk thread; the sutures were removed after 7 days. Analgesic therapy (paracetamol 1,000, 1 tablet twice daily for 2 days) was provided. Antibiotic prophylaxis was given when necessary. The same postoperative instructions were given to all the patients. The surgeon who performed the extractions checked each patient at 1, 3, and 7 days after the extraction to assess the healing process and the possible presence of severe bleeding and/or hematoma. Additional follow-up sessions were added as needed.

STUDY VARIABLES

At baseline, the patients were characterized according to the following variables: age, gender, tooth to be extracted (molar, premolar, canine, or incisor and relative arcade), number of extractions, number of sessions, reasons for OAT, drug used for OAT, INR value, and the presence of diabetes, liver disease, and chronic renal failure. The principal predictor variables were the INR, reason for OAT, and type of comorbidity. The adverse events rate was evaluated as a function of each baseline variable, with particular emphasis on the 3 principal predictors.

The primary outcome variable of interest was the incidence of severe bleeding at the 3 follow-up sessions; the secondary variable was the incidence of hematoma. Severe bleeding was defined as bleeding not manageable by the patient, extending into the days after the extraction and requiring reintervention by a surgeon to remove the build-up of the necrotic clot. This will create damage, although minimal, and discomfort for the patient, because of the necessity to intervene in a wound still in the process of healing, with possibly edematous tissues. Such hematomas do not represent a danger to the patient, only a temporary esthetic deficit, typically of short duration. However, these will nevertheless often be considered disturbing by many patients.

STATISTICAL ANALYSIS

The statistical analysis involved continuous, binary, and categorical variables. The former, reported as the mean ± standard deviation, were compared using analysis of variance and the nonparametric Mann-Whitney U test. Binary and categorical variables are reported as counts and percentages, with 95% confidence intervals (CIs), arranged in 2×2 or $r \times c$ contingency tables and examined using the χ^2 test (with Yates' correction for 2×2) or, where appropriate, Fisher's exact test. The risk ratio (RR) was computed with its 95% CI. Statistical significance was set at $P < .05$.

The discriminatory ability of the INR as an indicator of possible bleeding problems was assessed using a receiving operating characteristic (ROC) curve, commonly used in medical studies to determine the cutoff values for clinical tests. The ROC curve is a graph of the true-positive rate (ie, sensitivity) versus the false-positive rate (ie, 1 − specificity). The area under the resulting curve (AUC) measures the accuracy of discrimination, ranging from 0.5 (no discrimination) to 1 (perfect). The cutoff value will be chosen to minimize the number of false-positive and false-negative results (ie, maximize the sensitivity and specificity; because they have opposite behaviors, their simultaneous maximization is performed by maximizing their harmonic mean). To increase the reliability of the determination, we also used the simultaneous maximization of Cohen's coefficient, κ, associated with the ROC curve.

Results

The 500 extractions were performed in 166 patients with an average age of 72.1 ± 10.4 years (range 23 to 89); 42.7% were women. Each patient underwent 1.5 ± 0.9 surgery sessions (range 1 to 6) and 2.5 ± 2.3 extractions (range 1 to 13).

The outcome of each extraction was characterized by the binary conditions of bleeding (yes vs no) and hematoma (yes vs no). Figure 1 illustrates the sequence of stages in the extraction of 4 teeth with no postoperative complications in a patient with a mechanical heart valve. Figure 2 shows 2 typical cases of adverse events: severe bleeding with the need for reintervention and a long-lasting hematoma. No complication was observed after the day 7 follow-up examination.

The patients were subdivided into 4 groups according to their reason for requiring OAT. Their principal characteristics are listed in Table 1.

Group A (patients who had been switched to heparin) included 24% with an artificial cardiac valve. In this group, 25 had a comorbidity: 44% had diabetes, 28% had liver disease, and 28% had kidney failure. Their INR ranged from 0.92 to 1.5 (average 1.18 ± 0.19). As expected, no severe bleeding was observed in this group, neither in the subgroup with comorbidities nor in those without, and only 1 hematoma was observed in the second subgroup. Group A was used

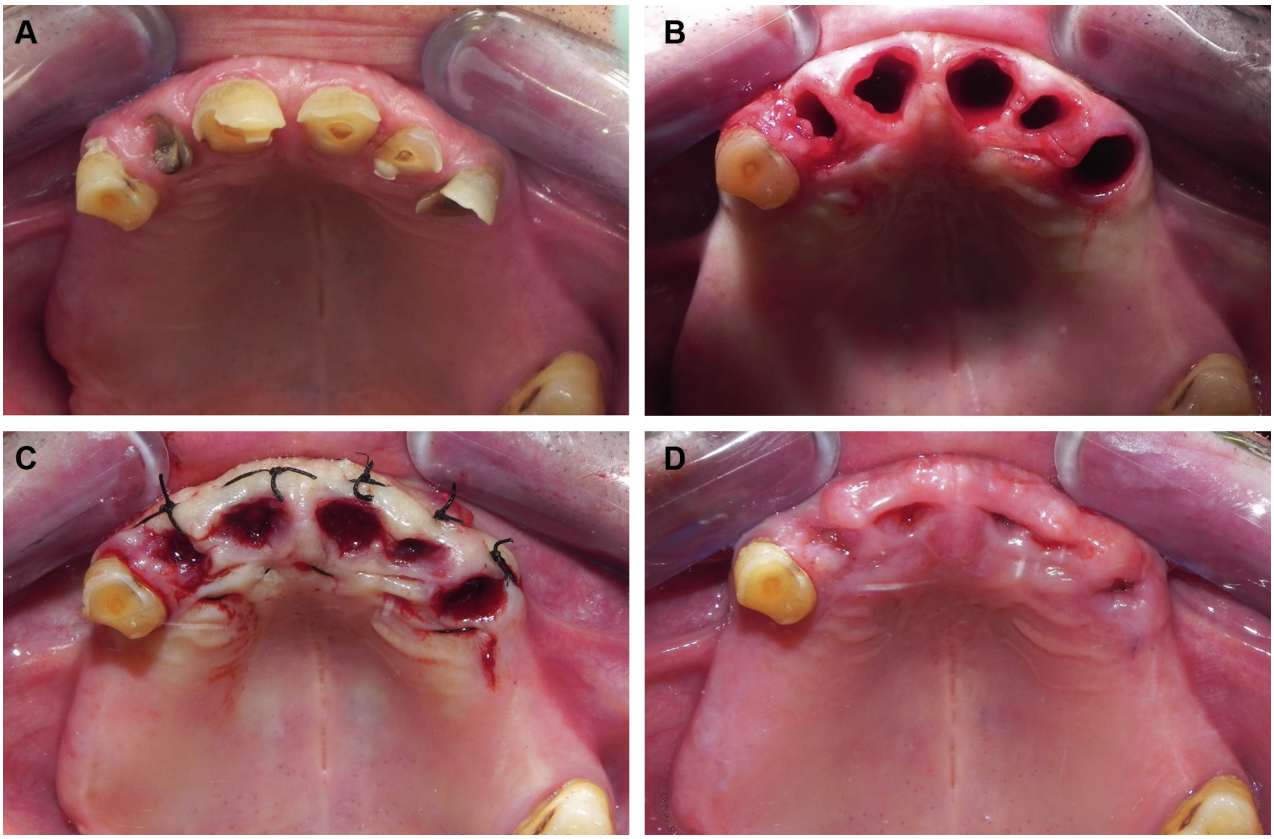

FIGURE 1. Typical evolution of a case with no adverse events. Extraction of 4 teeth was performed simultaneously in a patient with a mechanical heart valve.

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as the control group for the 3 groups of patients receiving OAT.

Groups B, C, and D included 435 extractions performed on patients receiving standard OAT (91.6% receiving warfarin and 8.4% acenocoumarin). Of these patients, 107 (24.6%) had comorbidities. The results of our trial showed very good outcomes for the 328 dental extractions performed in patients without

FIGURE 2. Two typical cases with adverse events. One patient experienced severe bleeding with the need for reintervention and another developed a long-lasting hematoma.

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Table 1. PATIENT CHARACTERISTICS

Group	Extractions (n)	INR Safety Window	Comorbidity Present (%)
A (switched to heparin)	65	NA	35
B (biologic cardiac valves)	38	2.0-3.0	18
C (mechanical cardiac valves)	133	2.5-3.0	18
D (all other cardiovascular diseases)	264	2.0-3.0	29

Abbreviations: INR, international normalized ratio; NA, not applicable.

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comorbidities, with a success rate of 99.7% (95% CI 98.5% to 100%) against bleeding and 98.8% (95% CI 97.1% to 99.6%) against hematoma formation.

The outcomes for the 107 extractions performed in those with comorbidities was less satisfactory. The success rate was 81.3% (95% CI 73.1% to 87.9%) against bleeding and 90.7% (95% CI 84.0% to 95.2%) against hematoma formation. The differences between the adverse event rates in the comorbidity and no-comorbidity samples were statistically significant ($P < 10^{-7}$), with a RR of 61 (95% CI 8 to 451) for bleeding and RR of 8 (95% CI 3 to 24) for hematoma formation ($P = .0001$). Thus, patients with comorbidities had a markedly greater chance of experiencing these adverse events.

The incidence of severe bleeding and hematoma were not influenced by gender ($P = .85$) or by the type of drug used for OAT ($P = .45$). An apparent difference was seen with age, with younger people seemingly the most affected ($P = .0003$), but this was likely because the comorbidities increased the rate of adverse events significantly, and the patients with comorbidities were significantly younger than the patients without (68.5 ± 11.8 vs 73.9 ± 9.5 years; $P = 2 \times 10^{-5}$).

Severe bleeding with regard to tooth type was, as expected, greater for molars (17.2%) than for premolars (1.4%) and incisors and canines (1.0%; $P = 2 \times 10^{-6}$, RR 15, 95% CI 4 to 64), regardless of the arcade ($P = .78$). The prevalence of molar cases was similar between those with and without comorbidities.

In the following subsections, we present the results of the 3 groups (B, C, and D) separately and their comparison with the control (group A).

GROUP B: BIOLOGIC CARDIAC VALVES

In group B, the extractions were in patients receiving OAT because of recently implanted biological cardiac valves (7 with comorbidities). The INR in the presence and absence of comorbidities was essentially identical: 2.29 ± 0.30 (range 1.90 to 2.98) and 2.17 ± 0.26 (range 1.80 to 2.40; $P = .29$). Group B was free from adverse events, with no severe bleeding and no hematoma, consistent with the results of the control group (group A).

GROUP C: MECHANICAL CARDIAC VALVES

In group C, the extractions were performed in patients receiving OAT because they had mechanical cardiac valves. These patients, considered at high risk of new or recurrent thromboembolism, had an INR of 2.5 or more but not greater than 3.0. This value had been met by those with comorbidities; however, 13% of those without comorbidities had an INR of 1.81 or more but less than 2.5.

The presence of comorbidities had a considerable negative effect (Table 2). Despite a statistically significantly younger age and similar INR, the bleeding and hematoma rates were significantly greater for those with comorbidities than for those without. The differences were striking: for the bleeding rate, $P = 10^{-5}$, with a very high RR of 12 (95% CI 4 to 42) and for the hematoma rate, $P = 5 \times 10^{-4}$ and RR of 9 (95% CI 2 to 34) for comorbidities.

The outcomes in the no-comorbidity subgroup in group C was essentially similar to its counterpart in the control group ($P = .69$ for bleeding and $P = .63$ for hematoma). The situation was markedly different when comparing the comorbidity subgroups within the 2 groups ($P = .006$ for bleeding and $P = .03$ for hematoma, against group C).

Table 2. RESULTS FOR GROUP C (MECHANICAL CARDIAC VALVES)

Variable	No Comorbidity	Comorbidity	*P* Value
Patients (n)	109	24	
Age (yr)	69.0 ± 11.7	58.7 ± 10.1	.0001*
INR	2.77 ± 0.28	2.84 ± 0.12	.23
Severe bleeding	3/109 (2.8)	8/24 (33.3)	10^{-5}*
Hematoma	3/109 (2.8)	6/24 (25.0)	5×10^{-4}*

Data presented as mean ± standard deviation or n (%).
Abbreviation: INR, international normalized ratio.
* Statistically significant.

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GROUP D: OTHER CARDIOVASCULAR DISEASES

Group D included extractions in patients receiving OAT because of cardiovascular problems other than those related to heart valves, mainly atrial fibrillation and venous thromboembolism. Their thromboembolic risks are lower than those associated with mechanical prostheses; thus, their INR lower limit has been placed by cardiologists at 2.0. This limit, however, was not observed in 36% of our patients in the no-comorbidity subgroup and 14% in the comorbidity subgroup.

The outcomes for group D are listed in Table 3. The pattern that emerged was similar to that seen for Group C. Despite a younger age and equivalent INR, the comorbidity subgroup had bleeding and hematoma rates both significantly greater than those for the no-comorbidity subgroup ($P = 10^{-6}$ and $P = .03$, respectively). Also, the no-comorbidity subgroup of group D had results very similar to those of the control group (group A). In contrast, the comparison between the comorbidity subgroups of the 2 groups yielded $P = .0008$ for the bleeding rate and $P = .31$ for the hematoma rate against group D (for hematomas, the test power was very low, $\Pi = 20\%$, corresponding to a β error of 0.80; to reach the conventionally accepted value of $\Pi = 80\%$, the sample sizes would have needed to be at least 4 times larger).

DETERMINATION OF INR UPPER SAFETY LIMITS FOR OAT PATIENTS WITH COMORBIDITIES

The present results have shown that patients in groups C and D with no associated comorbidities presented with the same low bleeding and hematoma rates as patients in the control group (group A). In contrast, patients with associated comorbidities had markedly greater numbers of adverse events.

The INR values for the comorbidity subgroups of groups C and D, subdivided into bleeding and nonbleeding extractions, are listed in Table 4. For both groups, the INR relative to extractions followed by bleeding was significantly greater than those whose extractions were not followed by bleeding, confirming our hypothesis that the INR limit of 3 or less, prescribed in standard surgical protocols as a safeguard against bleeding, might actually be inappropriate in the presence of comorbidities.

Table 3. RESULTS OF 133 EXTRACTIONS IN GROUP D (OTHER CARDIOVASCULAR DISEASES)

Variable	No Comorbidity	Comorbidities	*P* Value
Patients (n)	188	76	
Age (yr)	76.1 ± 7.5	70.2 ± 11.2	.00005*
INR	2.34 ± 0.35	2.30 ± 0.26	.37
Severe bleeding	0/188 (0.0)	12/76 (15.8)	10^{-6}*
Hematoma	1/188 (0.5)	4/76 (5.3)	.03*

Data presented as mean ± standard deviation or n (%).
Abbreviation: INR, international normalized ratio.
* Statistically significant.

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To determine the safe upper limits for the INR, we followed standard ROC curve procedures. Figure 3 shows that the 2 INR distributions relative to bleeding and nonbleeding in groups C and D tended to occupy distinct regions of the INR axis, with the bleeding component shifted toward greater values and a limited region of overlap. These distributions were used as the inputs for the 2 ROC curves plotted in Figure 4A.

For group C (mechanical valves), the AUC of the ROC curve was 0.86 (95% CI 0.71 to 1.00), a value generally considered "very good." Maximization of the harmonic mean of the specificity and sensitivity and of Cohen's index, κ, put the threshold between not bleeding and bleeding at an INR of 2.8 (Fig 4B). The total number of extractions under this limit was 9, with zero bleeding (0%). In contrast, for an INR of greater than 2.8 but 3 or less, bleeding occurred in 8 of 15 patients (53.3%), with a statistically significant difference ($P = .02$), confirming the discriminant ability of the derived cutoff.

For group D (other cardiovascular disease), the AUC was 0.73 (95% CI 0.60 to 0.86), a value generally considered "good," with a threshold set at an INR of 2.30 (Fig 4C). At less than this limit, bleeding occurred in 1 of 31 (3.2%). In contrast, for an INR of less than 2.3 but 3 or less, it increased to 11 of 46 (23.9%). Comparison of the former and latter yielded $P = .03$ and RR of 7 (95% CI 1 to 54).

The results of the ROC curve procedure indicated that, in the presence of comorbidities, the INR upper limit should be lowered from the general value of 3.0 to the 2 more specific limits of 2.8 for group C and 2.3 for group D. The improvement in bleeding rates thus obtained (0% vs 33% for group C and 3% vs 16% for group D) is clearly visible in Figure 5.

How setting these new upper limits affected only the comorbidity subgroups is presented in Table 5. At less than these new thresholds, the presence or absence of comorbidities will be irrelevant, with low bleeding rates regardless. In contrast, at greater than these thresholds, the presence of comorbidities was the factor that increased the bleeding rate significantly.

BLEEDING RATE ACCORDING TO COMORBIDITY

The comorbidities considered were diabetes, liver disease, and kidney failure. Figure 6 shows their association with bleeding: diabetes led with 12 bleeding cases in 39 patients (30.8%), a rate twice as great as

Table 4. PARAMETERS OF TWO COMORBIDITY SAMPLES IN GROUP C (MECHANICAL VALVES) AND GROUP D (OTHER CARDIOVASCULAR DISEASES)

	Group C (No Comorbidities, n = 24)			Group D (No Comorbidities, n = 76)		
Variable	Bleeding	No Bleeding	*P* Value	Bleeding	Non-Bleeding	*P* Value
Extractions	8 (33.3)	16 (66.7)	NA	12 (15.8)	64 (84.2)	NA
INR	2.93 ± 0.04	2.79 ± 0.11	.002	2.44 ± 0.17	2.27 ± 0.26	.036

Data presented as mean ± standard deviation or n (%).
Abbreviations: INR, international normalized ratio; NA, not applicable.

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that for those with liver disease (5 of 33; 15.6%) or kidney failure (3 of 28; 10.7%). The difference was, however, of only borderline statistical significance (P = .09), possibly because of the small numbers involved. A more powerful comparison could be performed by considering the bleeding rate for those with diabetes versus the bleeding rate for the other 2 comorbidities combined (ie, 8 of 61; 13.3%). The χ^2 test, applied to the resulting 2 × 2 table yielded P = .058; however, the RR was 2.4 (95% CI 1.1 to 5.2) pointing to diabetes as the most important among the 3 associated pathologic entities.

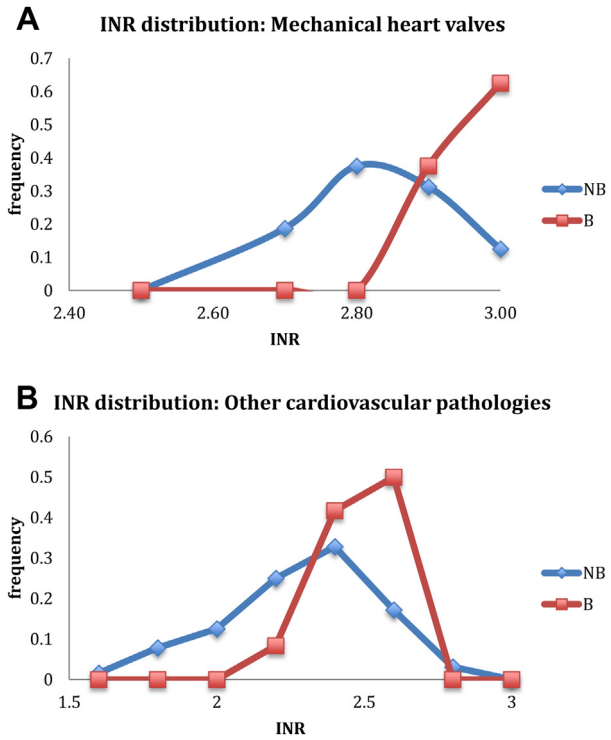

FIGURE 3. *A*, International normalized ratio (INR) distributions for mechanical valve patients (group C). *B*, INR distributions for patients with other cardiovascular diseases (group D). B, bleeding; NB, no bleeding.

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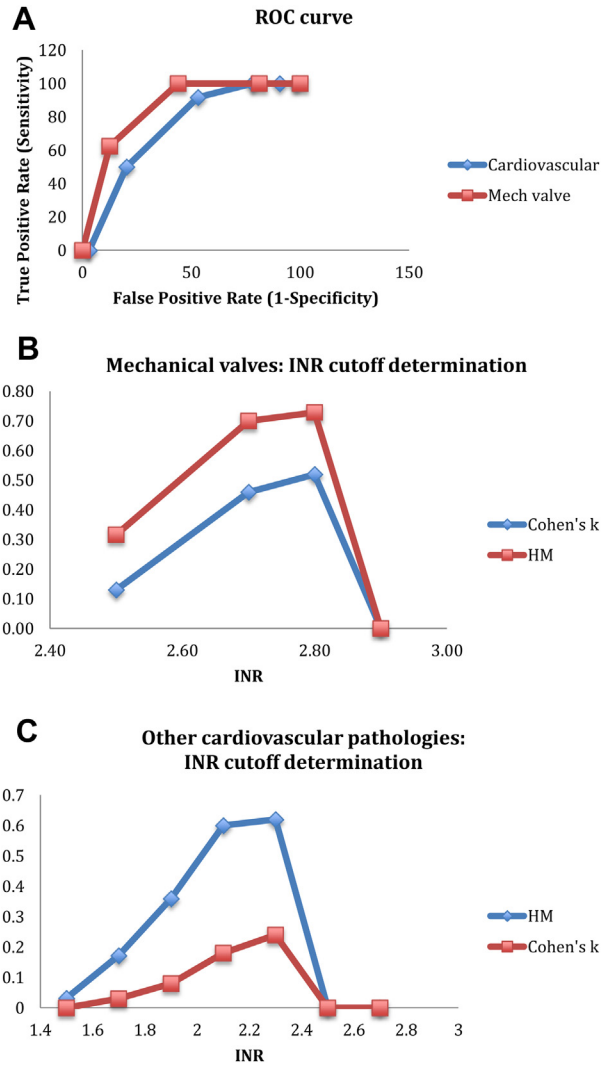

FIGURE 4. *A*, Receiver operating characteristic (ROC) curves, with area under the curve of 0.86 for mechanical valves and 0.73 for other cardiovascular disease. *B*, Harmonic mean (HM) of sensitivity and specificity and Cohen's index, κ, plotted as a function of the INR. The value at which they reach their maximum identifies the best cutoff (INR 2.8 for mechanical valves and 2.3 for other cardiovascular diseases).

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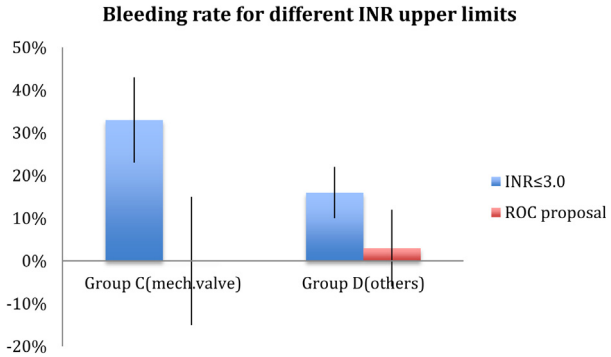

FIGURE 5. Bleeding rates using the surgical upper limit of the international normalized ratio (INR) of 3.0 compared with those obtained using the lower values indicated by the receiver operating characteristic (ROC) curves (INR 2.8 for group C [mechanical valves] and 2.3 for group D [others]).

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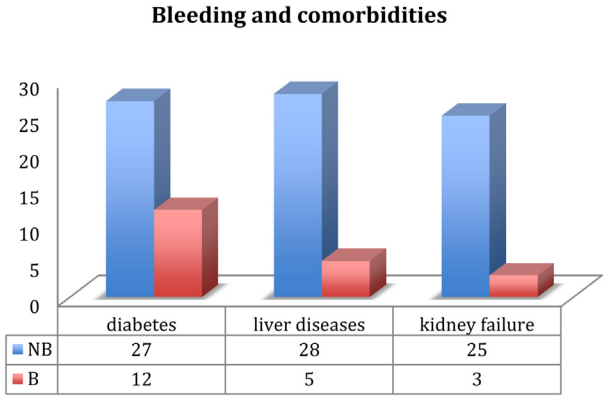

FIGURE 6. Number of bleeding (B) and no-bleeding (NB) extractions in patients with comorbidities (groups C and D).

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The type of comorbidity had no effect on the INR value. In group C, the INR was 2.85 ± 0.09 for those diabetes versus 2.83 ± 0.14 (P = .44) for those with liver or kidney disease. For Group D, the INR was 2.27 ± 0.26 for those with diabetes versus 2.32 ± 0.26 for those with liver or kidney disease (P = .41).

Discussion

The present analysis of 500 dental extractions in patients receiving OAT showed that their outcomes, in terms of bleeding and hematoma, were the result of the cumulative and intertwined effects of the INR, the reasons underlying the OAT, and the presence and types of comorbidities. The most used INR upper limit for surgical procedures (INR ≤ 3.0) did not consider the issue of comorbidities associated with cardiovascular problems. We investigated whether the INR limit of 3.0 or less would be valid in patients with comorbidities, such as diabetes, liver disease, and kidney failure. We hypothesized that because these pathologic entities are known to hinder healing, patients with any of them might be exposed to a non-negligible number of adverse events and should thus be safeguarded differently from patients without such comorbidities. The outcomes of 65 extractions in patients who had been switched to heparin (group A) were used as controls for the results of the dental extractions in patients receiving OAT.

Table 5. BLEEDING RATES IN GROUPS C AND D AT GREATER THAN AND LESS THAN THE ROC CUTOFF

Group	No Comorbidity	Comorbidities	P Value
C (mechanical valves)			
INR > 2.8	2/50 (4)	8/15 (53)	9×10^{-5}
INR ≤ 2.8	1/59 (2)	0/9 (0)	≥.99
P value	.88	.02	—
Group D (others)			
INR > 2.8	0/95 (0)	11/46 (24)	4×10^{-6}
INR ≤ 2.8	0/93 (0)	1/30 (3)	.49
P value	>.99	.03	

Data presented as n (%).

Abbreviations: INR, international normalized ratio; ROC, receiver operating characteristic.

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Overall, the results confirmed our hypothesis. The success rate against bleeding was 99.7% for the 328 dental extractions performed in patients receiving OAT who did not have comorbidities. However, it was only 81.3% for the 107 extractions performed in patients with comorbidities.

The 435 extractions were subdivided into 3 groups for a more detailed analysis according to the reason for OAT: group B, biological cardiac valves; group C, mechanical cardiac valves; and group D, all other cardiovascular diseases. Our results showed that patients receiving OAT after the insertion of biologic cardiac valves (group B) can be considered at low risk, not only of thromboembolism, but also of severe bleeding. For these patients, the previous upper limit of an INR of 3.0 worked well.

The issue of comorbidities was crucial in groups C and D, increasing the rate of adverse events markedly, especially severe bleeding with the need for reoperation. In group C, those with comorbidities experienced a 33% bleeding rate, significantly greater than the 2.8% rate in the no-comorbidity subgroup (P < .001). Similarly, in group D, the comorbidity subgroup had a much greater bleeding rate than did the no-comorbidity subgroup (15.8% vs 0%; $P = 10^{-6}$).

Continuing from the hypothesis that the INR limit of 3 or less for most oral surgery protocols might actually need to be lowered for patients in groups C and D with comorbidities, we used the standard ROC curve procedure to determine more appropriate cutoff values. For group C, the ROC curve analysis indicated the upper limit of the safety window should be set at an INR of 2.8 instead of at 3.0. In our sample, this would have reduced the bleeding rate from 33% to 0%. For group D, the new limit was an INR of 2.3, leading to a reduction in the bleeding rate from 16% to 3%. For patients without comorbidities, we found no need to reduce the standard upper INR limit.

Among the comorbidities, diabetes was the most important, with the greatest degree of an association with bleeding (31%) compared with liver disease (15%) and kidney failure (11%). This propensity of diabetes to induce bleeding might have resulted from the alteration in glucose metabolism, which can cause dysfunction in polymorphonuclear leukocytes and fibroblasts, increasing the susceptibility to infection and impaired healing. This has been seen after dental extractions, with a slowing of the formation and replacement of the blood clot, inducing recurrent bleeding in the days after the extraction, and increasing the risk of bacterial infection. In patients with chronic liver disease, local infections and impaired wound healing have been favored by the conditions of immunosuppression and the reduced capacity for protein synthesis by hepatocytes. Hemostasis problems can be induced, not only by the reduced production of vitamin K-dependent factors, but also by hyperfibrinolysis and thrombocytopenia, owing to secondary hypersplenism caused by portal hypertension. Finally, kidney failure can cause impaired healing because of uremic conditions, which inhibit the proliferation of fibroblasts and endothelial cells within the granulation tissue. Toxin build-up in the blood can also cause hemostatic disorders owing to platelet dysfunction.

The results of our study can be interpreted as follows. The physiologic process of normal hemostasis, epithelialization, and maturation of the wound left after dental extraction occurs by the interaction among many biologic systems, involving blood vessels, platelets, and coagulation factors. OAT upsets the equilibrium of this system through drug-induced inhibition of the coagulation cascade, with the intention of reducing the thromboembolic risk. In patients without comorbidities, coagulation will generally be sufficient to prevent serious hemorrhage as long as the INR remains less than 3.0. The presence of comorbidities, such as diabetes, liver disease, and kidney failure, however, tilts the balance toward bleeding by acting at different levels of the chain of processes that control coagulation, shifting the maximum allowable INR lower. The contest between coagulation and bleeding-inducing factors is reflected in the INR distribution shown in Figure 3. For a low INR, for which coagulation prevails, nonbleeding extractions were dominant. In contrast, for a high INR, for which coagulation succumbs, bleeding extractions were dominant. In the intermediate region, at which the coagulation and bleeding factors were even, bleeding and nonbleeding extractions shared the territory. The cutoff limits derived for the comorbidity subgroups in groups C and D reflect the borderline across which coagulation is replaced by bleeding. Thus, for group C, for which coagulation will be a highly active (and, from a cardiovascular viewpoint, very risky) process, the INR limit was higher (INR = 2.8) than for group D (INR = 2.3).

In conclusion, the results of our trial showed very good outcomes (success rate close to 100%) for dental extractions performed using the standard surgical limit of an INR of 3 or less for patients without comorbidities. For patients with comorbidities, the ROC curve procedure suggested lowering the maximum allowable INR, from 3.0 to 2.80 for those with mechanical valves (minimum value 2.5) and 2.30 for other cardiovascular patients (minimum value 2.0) to reduce the risk of bleeding. This suggestion, even if sound statistically, is, however, not without drawbacks from a clinical viewpoint. It is not easy to simply alter doses to bring the patient's original INR within these narrow safety windows, which was seen for several patients who arrived with an INR lower than that prescribed in an attempt to reduce the bleeding risk, but leaving them exposed to a greater risk of thromboembolic complications. Furthermore, the process of reducing the INR requires several days, necessarily delaying the dental extraction. However, the patients often require an urgent intervention because of extreme pain or proximity to a major surgery.

To satisfy the need to balance the thromboembolic and bleeding risks, 1 solution could be to switch all patients with comorbidities, in particular those with diabetes, to heparin. However, this also is no panacea. Low-molecular-weight heparin does not allow the necessary control of patients' coagulation state, and "traditional" unfractionated heparin increases the duration of hospitalization. Furthermore, the very process of switching can also increase the hemorrhagic risk in the intermediate phase when the anticoagulant action of OAT has not yet completely declined and heparin has started to work.

On the basis of previous experience with several pathologic entities in our oral surgery unit, we have seen a totally different approach as an intriguing alternative, in which the oral surgeon addresses the bleeding issue "on-site" and in real time during the extraction using a platelet-rich growth factor (PRGF) preparation on the wound resulting from the dental

extraction. These platelet gels are concentrated preparations of autogenous platelets, which play a role in hemostasis, preventing bleeding at sites of vascular injury. They do so by forming a procoagulant surface, with thrombin generation and fibrin formation. Platelets also release substances favoring tissue repair and influencing the reactivity of vascular and other blood cells in angiogenesis and inflammation.[15] The use of blood-derived products to seal wounds and stimulate healing was originally proposed by Kingsley.[16] The first application of autologous fibrin glue in oral surgery was reported in 1994 by Tayapongsak et al,[17] who used autologous fibrin adhesive as a medium for compacting grafts, and its use has increased ever since.

Our center has used PRGF in patients with systemic pathologic entities. Positive results, in terms of enhancement of hemostatic action and epithelial closure, have been obtained with thrombocytopenic patients,[18] patients receiving bisphosphonate therapy,[19,20] patients with insulin-dependent diabetes mellitus,[21] and patients who had undergone radiotherapy for head and neck cancer.[22] Other studies have been conducted of hemophiliac patients and liver transplant candidates. We are thus confident in suggesting that a similar procedure could also be successful in patients receiving OAT, who could thus keep the standard upper limit at an INR of 3 without an increased bleeding risk. Also, in patients without comorbidities, the use of PRGF might allow increasing the INR upper limit to values greater than 3.0, without affecting OAT. A study is being initiated to assess this.

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