

BMJ Open

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005777
Article Type:	Research
Date Submitted by the Author:	24-May-2014
Complete List of Authors:	Iwabuchi, Hiroshi; Kanagawa Dental University, Department of Oral and Maxillofacial Surgery Imai, Yutaka; Dokkyo Medical University School of Medicine, Department of Oral & Maxillofacial Surgery Asanami, Soichiro; Sanno Hospital, Department of Dentistry and Implant Center Shirakawa, Masayori; Nippon Dental University, Yamane, Gen-yuki; Tokyo Dental College, Ogiuchi, Hideki; Tokyo Women's Medical University, Kurashina, Kenji; Aizawa Hospital, Oral & Dental Center Miyata, Masaru; Ishikawa Prefectural Central Hospital, Department of Dentistry and Oral Surgery Nakao, Hiroyuki; National Institute of Public Health, Department of Epidemiology Imai, Hirohisa; National Institute of Public Health, Department of Epidemiology
Primary Subject Heading:	Dentistry and oral medicine
Secondary Subject Heading:	Dentistry and oral medicine
Keywords:	ORAL & MAXILLOFACIAL SURGERY, ORAL MEDICINE, Oral & maxillofacial surgery < SURGERY

SCHOLARONE™
Manuscripts

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Hiroshi Iwabuchi¹⁾, Yutaka Imai²⁾, Soichiro Asanami³⁾, Masayori Shirakawa⁴⁾, Gen-yuki Yamane⁵⁾, Hideki Ogiuchi⁶⁾, Kenji Kurashina⁷⁾, Masaru Miyata⁸⁾, Hiroyuki Nakao⁹⁾, Hirohisa Imai⁹⁾

Department of Oral and Maxillofacial Surgery, Kanagawa Dental University¹⁾, Department of Oral & Maxillofacial Surgery, Dokkyo Medical University School of Medicine²⁾, Department of Dentistry and Implant Center, Sanno Hospital³⁾, Nippon Dental University⁴⁾, Tokyo Dental College⁵⁾, Tokyo Women's Medical University⁶⁾, Aizawa Hospital, Oral & Dental Center⁷⁾, Department of Dentistry and Oral Surgery, Ishikawa Prefectural Central Hospital⁸⁾, Department of Epidemiology, National Institute of Public Health of Japan⁹⁾

Corresponding author: Hiroshi Iwabuchi
Department of Oral and Maxillofacial Surgery, Kanagawa Dental University
82 Inaokamachi, Yokosuka-shi, Kanagawa 238-8580, Japan
TEL: 81-46-822-8810, ext 2395
e-mail: Hiroshi Iwabuchi : iwabuchi@kdu.ac.jp

Word count: 2,777

Keywords: tooth extraction, post-extraction bleeding, warfarin, risk factors

ABSTRACT

Objectives: Difference in the incidence of post-extraction bleeding events in patients receiving and not-receiving warfarin therapy, along with associating risk factors were investigated.

Design: Crossectional multicenter observational study

Setting: 26 hospitals where oral surgeon is available.

Participants: Data on 2,817 teeth (496: receiving warfarin, 2,321: not receiving warfarin; mean age (SD): 62.16 (17.59)) extracted from November 1, 2008 to March 31, 2010, were collected. For warfarin-receiving patients to be eligible for the study, PT-INR within 7 days prior to the extraction should be less than 3.0

Interventions: Simple dental extraction was performed and incidence of post-extraction bleeding and comorbidities were recorded.

Primary and Secondary Outcome Measures: Post extraction bleeding not controlled by basic hemostasis procedure as clinically significant.

Results: Bleeding events were reported for 35 (7.1%) and 49 (2.1%) teeth, of which 18 (3.6%) and 9 (0.4%) teeth were considered as clinically significant, in warfarin and non-warfarin groups, respectively. The difference in post-extraction bleeding incidences between warfarin and non-warfarin groups was 3.24% (95% CI: 1.49% to 4.99%). Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), mandibular foramen conduction anesthesia (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) significantly correlate with the bleeding incidence. Multivariate analysis revealed that age (OR: 7.930, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding.

Conclusion: Our results demonstrated that patients receiving warfarin therapy had an approximately 10 times higher probability of post-extraction bleeding than those not on warfarin, though absolute incidence was low in both groups.

Strength and Limitation of this Study

- The present study examined difference of the incidences for post-extraction bleeding between the patients receiving and not-receiving warfarin, which few previous studies to date have been reported.
- The study included dental facilities where at least one or more certified oral surgeons are available in order to standardize skills of the operators and capability of the facilities for providing advanced care in the event of significant bleeding.
- We also analyzed the risk factors for post-extraction bleeding events in patients receiving warfarin.
- Due to the study design, we may have underestimated the incidence of post-extraction bleeding that may occur in community dental clinics.
- Although we tried to standardize the dental extraction procedure, there might have been inter-facility differences.

INTRODUCTION

Until recently, the common procedure for tooth extraction in patients continuously receiving warfarin or other antiplatelet therapy was to discontinue or reduce the dose to minimize the risks of odontorrhagia. However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1] This study raised wide concern about the adverse effects of warfarin discontinuation in dental surgery, and this issue was subsequently addressed by many randomized clinical trials,[2–4] cohort studies,[5–7] and meta-analyses.[8–10] Overall, these studies suggested that dental extraction could be performed safely in patients whose prothrombin time–international normalized ratio (PT-INR) was in the recommended therapeutic ranges, showing no significant differences in the incidence of post-extraction bleeding between the patients who continued warfarin and those whose warfarin was temporarily discontinued or reduced. Clinical guidelines published after these studies advised that patients whose PT-INR values were within the recommended therapeutic ranges should continue warfarin when undergoing dental extraction.[11–13] However, no studies to date have investigated the differences in post-extraction bleeding incidences between patients receiving and not receiving warfarin. In addition, few studies focused on the risk factors for post-extraction bleeding in warfarin-treated patients.

Given these circumstances, this study compared the incidence rates of post-extraction hemorrhage between patients whose PT-INR values were 3.0 or below and those who were not on anticoagulant therapy. The PT-INR of 3.0 was indicated as the maximum safety threshold for tooth extraction in the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction in Japanese.[14] We also investigated the risk factors for the

incidence of post-extraction bleeding in patients receiving warfarin therapy.

MATERIALS AND METHODS

This was a prospective multicenter observational study of post-extraction bleeding events in patients receiving and not receiving warfarin therapy.

Study Period and Eligibility Criteria

Twenty-six hospitals located across Japan participated. This study included patients who underwent simple tooth extraction from November 1, 2008 to March 31, 2010 at the department of oral surgery of these hospitals and who met the eligibility criteria listed below. Simple tooth extraction referred to a tooth removed without traumatizing the surrounding alveolar bone or elevating a mucoperiosteal flap.

Eligibility criteria included the following: 20 or more years of age at the time of tooth extraction; no contraindications for tooth extraction; surgery was performed by oral surgeon with a minimum of 3 years of experience in dental practice; the oral extraction procedure lasted for no longer than 15 minutes; and platelet count within 7 days prior to the procedure was greater than 10,000/mm³. In addition, in patients receiving warfarin therapy, PT-INR measured within 7 days prior to the procedure should be less than 3.0. Patients receiving anti-platelet medication were not excluded but recorded as such. According to “The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction”[14], we instructed the participating hospitals that dental extraction should be performed without discontinuing or reducing the dose of warfarin in patients whose PT-INR was not exceeding 3.0 when measured within 7 days prior to the procedure.

Study Variables

The variables analyzed in this study were: bleeding events, patient's age and sex, position of the removed tooth, instruments used for removal (forceps only, elevators only, forceps and elevators), reasons for extraction, use of antiplatelet drugs, PR-INR values measured within 7 days before exodontia (only for patients receiving chronic warfarin therapy), comorbidities possibly influencing hemostasis, use of vasoconstrictors, combined use of local anesthetics and vasoconstrictors, use of mandibular foramen conduction anesthesia, severity of gingivitis after extraction (none, mild, moderate, severe), formation of abnormal granulation tissue in the extraction socket (none, little, medium, much), history of acute inflammation at extraction site, and post-extraction infection.

Hemostasis

The hemostatic methods for patients not receiving warfarin were chosen at the discretion of the dentist or oral surgeon performing the procedure. In patients on warfarin therapy, either absorbable oxidized cellulose or gelatin sponge was implanted into the alveolar socket, and wound margins were sutured. In both groups of patients, topical hemostatic agents other than epinephrine, systemic hemostatic agents, and splints were prohibited until primary hemostasis was observed.. In patients who had multiple teeth extracted in one session, possible post-extraction bleeding was examined for each tooth. In a patient receiving warfarin, the post-extraction procedure defined above was performed each time after a tooth was removed.

Permitted Drugs

Use of local anesthetics containing vasoconstrictors (e.g., epinephrine and felypressin) was allowed at doses commonly practiced. In warfarin-treated patients, penicillins or cefems (e.g., cefcapene pivoxil and cefditoren pivoxil) was the primary choice of prophylactic

antibiotics for their minimal interaction with warfarin. , For those who were allergic to penicillins, clarithromycin was recommended. Use of analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors was allowed at ordinary doses.

Confirmation of Hemostasis

All patients were asked to bite down on a roll gauze for a maximum of 30 minutes for astriction of the wound. After release of the biting pressure, the wound was examined for hemostasis. Patients visited the hospital on the next day of surgery to check for possible bleeding, and were instructed to present at the hospital for treatment, if bleeding should occur later. The follow-up period was 7 days postoperatively.

Follow-up of Bleeding Events

If a patient had a bleeding event during the follow-up period, the severity of the hemorrhage and blood pressure were recorded. If the patient was on warfarin therapy, his or her PR-INR values were measured in addition.

Evaluation of Bleeding Events

In this study, bleeding events occurring in the follow-up period were classified into one of the following 5 grades: 0, no bleeding; 1, excessive blood clotting in the socket, no treatment required; 2-1, hemostasis achieved by compressing the wound longer than 30 minutes; 2-2, blood oozing from socket, ceased by wound compression only; 3, bleeding required treatments other than wound compression. Grade 2-2 and higher events were regarded as clinically significant, and were defined as post-extraction bleeds in this study.

Statistical Analysis

Data were collected by a tooth, but not by a patient.. This means that patients who had multiple teeth extraction were counted multiple times for the number of extracted teeth. Data were then sorted and analyzed by the anatomical positions. The difference in post-extraction bleeding incidence between patients receiving and not receiving warfarin therapy and its 95% confidence interval (CI) were calculated. In addition, a multivariate logistic regression analysis was conducted to identify risk factors for post-extraction bleeding in warfarin-treated patients. Adjusted odds ratios (ORs), their 95% CIs and *p*-values were calculated controlling for major confounders. Explanatory variables with a significance level of $P < 0.20$ on univariate analyses were included in the multivariate logistic regression model. Statistical analyses were performed using the SPSS software (version 15.0, SPSS Japan Inc., Tokyo, Japan).

Ethics

The objective of this study was explained in details to potential study participants so that they could make an informed decision. Patients' personal information was stored in a de-identified but linkable format during the 7-day follow-up period, and was rendered completely anonymous thereafter. This study was reviewed and approved by the ethics committee of the National Hospital Organization Tochigi Medical Center, Tochigi, Japan, prior to its conduct. The approved protocol and forms for informed consent were distributed to the participating hospitals to keep the uniformity of the study.

RESULTS

Totally, 3,515 case reports were submitted from the participating investigators. Of these, 698 cases were eliminated because of protocol deviations and/or insufficient data

documentation, leaving 2,817 for further analysis.

Post-extraction Bleeding Incidence

Bleeding events including minor hemorrhagic episodes were reported for 35 out of 496 teeth (7.1%) of the warfarin group and for 49 out of 2,321 teeth (2.1%) of the non-warfarin group, with a total of 84 teeth. Clinically significant post-extraction bleeds (i.e., grade 2-2 or higher) were reported for 27 teeth, including 18 (3.6%) and 9 (0.4%) from the warfarin and non-warfarin groups, respectively (Table 1). All bleeding episodes were controlled by local hemostatic interventions. No warfarin-treated patients showed a notable PT-INR change from baseline postoperatively, and none of the reported PT-INR values were above 3.0.

Breakdown of Removed Teeth by Sex and Study Group

The mean (SD) age of all study participants was 62.16 (17.59) years, and 1,446 and 1,371 teeth were removed from males (51.3%) and females (48.7%), respectively. The warfarin group had a mean (SD) age of 70.28 (10.92) years, and reported removal of 496 teeth, 320 from males (64.5%) and 176 from females (35.5%). Non-warfarin group had a mean (SD) age of 60.42 (18.25) years, and reported removal of 2321 teeth, 1126 from males (48.5%) and 1,195 from females (51.5%) (Table 1).

The difference in post-extraction bleeding incidence between the warfarin group and non-warfarin group was 3.24% and its 95% CI was 1.49% to 4.99% (Table 2).

Risk Factors for Post-extraction Bleeding in Warfarin-Treated Patients

Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), mandibular foramen conduction anesthesia (OR: 4.854, $P = 0.050$), and formation of

abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) were significantly correlated with post-extraction bleeding (Table 3). In addition to these variables, position of the removed tooth, reasons for extraction, antiplatelet drugs, comorbidities possibly influencing hemostasis, and history of acute inflammation at extraction site were found to have P values smaller than 0.2 by univariate analysis. Consequently, these parameters were included as explanatory variables in the multivariate regression analysis. The results showed that age (OR: 7.930, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding (Table 5).

DISCUSSION

We conducted a nation-wide, prospective multicenter observational study to compare post-extraction bleeding incidences between patients receiving and not receiving warfarin therapy. Both study groups reported low incidence rates of bleeding events. However, the warfarin group had higher incidence by 3.24% (95% CI: 1.49-4.99).

Clinically significant post-extraction hemorrhagic events occurred at an incidence of 0.4% in the group of patients not receiving warfarin in this study. Whereas in the warfarin receiving group, although none of the PT-INR values measured within 7 days before surgery were greater than 3.0, post-extraction bleeding incidence rate was 3.6%, which was approximately 10 times higher than that observed in patients not receiving chronic warfarin therapy. Our results indicate that, albeit that absolute incidence rate is low, patients receiving warfarin therapy had a definitely higher probability of post-extraction bleeding than those who were not on chronic warfarin therapy. These findings suggest that when performing exodontia in a patient receiving chronic warfarin therapy, particularly in a situation such as emergency operation at nights or weekends or in a institution where additional procedures

other than standard hemostatic methods could not be performed, clinical experience of the operator and the capability of the facility in performing advanced care should also be taken into consideration, instead of solely relying on the PT-INR values when planning the procedure.

Our study identified age (≥ 65 years), antiplatelet drugs, PT-INR, and history of acute inflammation at extraction site as significant risk factors for post-extraction hemorrhage in warfarin-treated patients. Instruments used for removal, reasons for extraction, and comorbidities possibly influencing hemostasis were not significantly contributed as risk factors.

Few studies reported to date examined the relationship between age and the incidence of post-extraction bleeding. Our finding indicated that extra caution should be taken when conducting exodontia in elderly patients receiving warfarin therapy, and the frequency of such situations would increase with aging population.

A study that investigated the impact of comorbid conditions on hemostasis suggested that patients with liver dysfunction are another group at high risk for post-extraction bleeding.[15] The present study did not identify liver dysfunction or other comorbid conditions that would affect hemostasis as a risk factor for increased incidence of post-extraction bleeding. The attribution of such condition may have been underestimated in the present study as only 4.2% of the study participants had some sort of liver dysfunction.

Our results also showed that the incidence of post-extraction bleeding events increased with higher PT-INR, even though the values did not exceed 3.0. This finding suggests that a special attention would be needed in patients whose PT-INR are close to 3.0 or higher to prevent post-extraction hemorrhagic event. Because warfarin sensitivity may vary among

individuals and different ethnic groups,, further studies will be needed to verify if the current findings are generalizable to other ethnic groups. To date, no randomized trial examining incidence of post-extraction bleeding, comparing patients receiving only warfarin therapy versus those who also take anti-platelet medications, has been reported. An observational study by Morimoto et al. reported no significant differences in the incidence rates between patients receiving warfarin therapy only and those receiving the combination of warfarin and antiplatelet medications.[6] In a cohort study that investigated the occurrences of general hemorrhagic events in Japanese patients receiving anticoagulants,[16] the incidence rates of hemorrhagic complications were higher in the group receiving the combination of warfarin and antiplatelet drugs than those receiving warfarin only. Morimoto et al. speculated in their report [6] that post-extraction bleeding is in general controllable with topical compression or other non-invasive means to achieve hemostasis even in patients receiving combination of warfarin and anti-platelet medications, whereas intracranial hemorrhages or other more serious hemorrhagic complications are not topically accessible, therefore leading to a higher bleeding incidence in the group of patients receiving anti-platelet drugs in addition to warfarin as found in a Cohort study.[20]

The study subjects in the latter study included population who requires anti-coagulation therapy in general, which would contain patients with severer co-morbidities that would contribute to higher incidence for hemorrhagic event. On the other hand, the studies by Morimoto et al. and ours focused on patients after tooth extraction, which could be managed by topical treatment. It is intriguing that the present study did not find use of anti-platelet medication as a risk factor for increasing incidence of post-extraction bleeding. The difference may be due to difference in study design or subjects included. Further study is necessary to determine if addition of anti-platelet medication increases a risk for post-extraction bleeding in patients receiving warfarin therapy. .

Several aspects of our study design that may have affected the outcome of the present study should be noted. First, we collected data of dental extraction cases performed only in institutions where care by one or more certified oral surgeons is available. This criterion was adopted to minimize the differences in skills of the operator. However, this criterion could have also resulted in lower-than-average post-extraction bleeding incidences for both warfarin and non-warfarin patients. There remains a reasonable possibility that the between-group differences would be higher if general dental clinics were included. Second, we included PT-INR values measured within 7 days prior to tooth extraction, considering the availability of measurement results. However, because warfarin can be affected by diet and other drugs, experts suggested to measure PT-INR within 24 [8,9,17,18] and 48 [19] hours before the procedure. The British Committee for Standards in Hematology recommended 72 hours before surgery [11]. In this study, no patients showed a significant PT-INR change between before and after tooth extraction, and no reported values exceeded 3.0. Third, bleeding events were reported on the basis of removed teeth and not of individuals. We chose this design based on the previous findings reporting no significant correlation between the numbers of dental extractions and post-extraction bleeding incidences.[2,4,5,7] The present study design is also superior as it takes the potential difference in risks of post-extraction bleeding by the position of the tooth and/or gingival condition into account. However, multiple counts from the same patient may have biased the results.

CONCLUSION

The difference in the post-extraction bleeding incidences between patients receiving warfarin or not was approximately 5%. Age, PT-INR, and history of acute inflammation at extraction site were risk factors for post-extraction bleeding in warfarin receiving patients.

Warfarin receiving patients had a considerable risk for post-extraction bleeding, even if their PT-INR values did not exceed 3.0. This study suggest that patients whose PT-INR values are close to 3.0 or who have other risk factors for uncontrollable bleeding should undergo dental extraction under the management of an oral surgeon specifying in invasive dental procedures or at a dental facility that has access to a hospital that could provide advanced medical care in the event of uncontrollable bleeding.

Competing interest: None disclosed.

Contributorship:

H. Iwabuchi designed the study protocol and wrote the manuscript. H. Imai analyzed the data and contributed to edition of the manuscript. H. Nakao also participated in data analyses. Y. Imai is the Principle Investigator of the present study. Rest of the authors participated in data collection.

Data sharing: There are no additional unpublished data.

REFERENCES

1 Wahl MJ. Dental surgery in anticoagulated patients. Arch Inter Med 1998;158:1610-16.

2 Evans IL, Sayers MS, Gibbons AJ, et al. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. Br J Oral Maxillofac Surg 2002;40:248-252.

3 Sacco R, Sacco M, Carpenedo M, et al. Oral surgery in patients on oral anticoagulant therapy: A randomized comparison of different intensity targets. Oral Surg Oral med Oral Pathol Oral RadiolEndod. 2007;104:e18-21.

4 Al-Mubarak S, Al-Ali N, Rass MA, et al. Evaluation of dental extractions, suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. Br Dent J.2007;203:1-5.

5 Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery: Should the Anticoagulation regiment be altered? J Oral Maxillofac Surg. 2000;58:131-5.

6 Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in patients on oral antithrombotic therapy. J Oral Maxillofac Surg.2008;66:51-7.

7 Barrero MV, Knezevic M, Martin MT, et al. Oral surgery in the patients undergoing oral anticoagulant therapy. Med oral.2002;7:63-70.

8 Aframian DJ, Lalla RV, Peterson DE. Management of dental patients taking common hemostasis –altering medications. Oral Surg Oral med Oral Pathol Oral RadiolEndod.2007;103(suppl 1):S45e1-11.

9 Goodchild JH, Donaldson M. An evidence-based dentistry challenge:Treating patients on warfarin(Coumadin). Dental aimplantol Update 2009;20:1-8.

10 Nematullah A, Alabousi A, Blanas N, et al. Dental surgery for patients on anticoagulant therapy with warfarin:asystematic review and meta-analysis. J can Dent Assoc. 2009;75:41-41i.

- 11 Perry DJ, Noakes TJC, Helliwell PS. Guidelines for the management of patients on oral anticoagulants requiring dental surgery. *Br Dent J.* 2007;203:389-393.
- 12 Sasanuki H, et al: Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease. *Circ J.* 2004;68 suppl IV:1153-1219.
- 13 Jcs Joint Working Group: Guidelines for pharmacotherapy of atrial fibrillation –Digest Version-. *Circ J.* 2010;74:2479-2500.
- 14 Japanese Society of Dentistry for Medically Compromised Patient ,Japanese Society of Oral and Maxillofacial Surgeons, Japanese Society of Gerodontology:The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction.2010 version Gakujutsusha Corporation Tokyo 2010.
- 15 Devani P, Lavery KM, Howell CJT. Dental extractions in patients on warfarin –Is alternation of anticoagulant regime necessary? *Br J Oral Maxillofac Surg.* 1998;36:107-111.
- 16 Toyoda K, Yasaka M, Iwade K, et al.Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease –A prospective, multicenter, observational study. *Stroke.*2008;39:1740-45.
- 17 Chugani V. Management of dental patients on warfarin therapy in a primary care setting. *Dental Update.* 2004;31:379-384.
- 18 Pototski M, Amenabar JM: Dental management of patients receiving anticoagulation or antiplatelet treatment. *J Oral Sci.*2007;49:253-8.
- 19 Brennan MT, Hong C, Furney SL, et al. Utility of an international normalized ratio testing device in a hospital-based dental practice. *J Am Dent Assoc.*2008;139:697-703.

Table 1. Breakdown of extracted teeth by important classification variables

No. of teeth by:		Warfarin	No Warfarin	Total	P value
		n=496	n=2321	N = 2817	
Age (years)					
	< 65	124 (25.0)	1131 (48.7)	1255 (44.6)	< 0.0001
	≥ 65	372 (75.0)	1190 (51.3)	1562 (55.4)	
Sex					
	Male	320 (64.5)	1126 (48.5)	1446 (51.3)	< 0.0001
	Female	176 (35.5)	1195 (51.5)	1371 (48.7)	
Type					
	Foretooth	132 (26.6)	663 (28.6)	795 (28.2)	0.550
	Premolar	127 (25.6)	552 (23.8)	679 (24.1)	
	Molar	237 (47.8)	1106 (47.7)	1343 (47.7)	
Instrument					
	Forceps only	171 (34.5)	604 (26.0)	775 (27.5)	0.000
	Elavators only	226 (45.6)	919 (39.6)	1145 (40.6)	
	Forceps and elevators	99 (20.0)	798 (34.4)	897 (31.8)	
Cause for extraction					
	Periodontitis	160 (32.3)	533 (23.0)	693 (24.6)	< 0.0001
	Caries	87 (17.5)	477 (20.6)	564 (20.0)	
	Apical periodontitis	219 (44.2)	1002 (43.2)	1221 (46.6)	
	Wisdom tooth pericoronitis	23 (4.6)	192 (8.3)	215 (7.6)	
	Other	7 (1.4)	117 (5.0)	124 (4.4)	
Status of antiplatelet therapy					
	Yes	122 (24.6)	433 (18.7)	555 (19.7)	0.003
Use of local anesthetics containing vasoconstrictors					
	Yes	491 (99.0)	2265 (97.6)	2756 (97.8)	0.105
Use of mandibular foramen conduction anesthesia					
	Yes	14 (2.8)	82 (3.5)	96 (3.4)	0.429
Comorbidity possibly influencing hemostatis					
	Hypertension	267 (53.8)	715 (30.8)	982 (34.9)	< 0.0001
	Diabetes mellitus	89 (17.9)	267 (11.5)	356 (12.6)	
	Chronic hepatitis	21 (4.2)	110 (4.7)	131 (4.7)	
	Other	68 (13.7)	212 (9.1)	280 (9.9)	
	Multiple disorders	341 (68.8)	1039 (44.8)	1380 (49.0)	
History of acute inflammation at extraction site					
	Yes	216 (43.5)	829 (35.7)	1045 (37.1)	0.001
Gingival inflammation at extraction site					
	None	298 (60.1)	1266 (54.5)	1564 (55.5)	0.000
	Mild	95 (19.2)	264 (11.4)	359 (12.7)	
	Moderate	13 (2.6)	38 (1.6)	51 (1.8)	
	Severe	90 (18.1)	753 (32.4)	843 (29.9)	
Abnormal granulation tissue in extraction socket					

None	87 (17.5)	818 (35.2)	905 (32.1)	
Little	230 (46.4)	917 (39.5)	1147 (40.7)	0.003
Medium	134 (27.0)	441 (19.0)	575 (20.4)	
Much	45 (9.1)	145 (6.2)	190 (6.7)	
Severity of post-extraction bleeding				
G1	9 (1.8)	29 (1.2)	38 (1.3)	
G2-1	8 (1.6)	11 (0.5)	19 (0.7)	
G2-2	1 (0.2)	8 (0.3)	9 (0.3)	
G3	17 (3.4)	1 (0.04)	18 (0.6)	
total	35 (7.1)	49 (2.1)	84 (3.0)	< 0.0001
G2-2+G3	18 (3.6)	9 (0.4)	27 (1.0)	< 0.0001
PT-INR				
(mean ± SD)	1.90±0.49			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 2. Difference in post-extraction bleeding incidences between patients receiving and not receiving warfarin (%)

		95% CL	
	Post-extraction bleeding incidences	Lower	Upper
Warfarin	3.63		
No Warfarin	0.39	0.0150	0.0499

For peer review only

Table 3. Univariate analysis of post-extraction bleeding events by potential risk factors

		Incidence of post-extraction bleeding (%)	OR	95%CL		P-value
				Lower	Upper	
Age (years)						
	< 65	8.9	1 (Ref)			
	≥ 65	1.9	0.197	0.075	0.520	0.001*
Sex						
	Male	3.4	1 (Ref)			
	Female	4.0	1.164	0.443	3.057	0.759
Type						
	Foretooth or premolar	2.3	1 (Ref)			
	Molar	5.1	2.2249	0.830	6.091	0.111
Instrument						
	Forceps only	2.9	1 (Ref)			
	Elevators alone or with forceps	4	1.383	0.485	3.947	0.544
Cause for extraction						
	Caries, apical periodontitis, or other	2.6	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	5.5	2.204	0.854	5.688	0.102
Status of antiplatelet therapy						
	No	4.5	1 (Ref)			
	Yes	0.8	0.174	0.023	1.318	0.090
PT-INR			3.635	1.5640	8.448	0.003*
Use of vasoconstrictors						
	No	4.1	1 (Ref)			
	Yes	0				
Use of local anesthetics containing vasoconstrictors						
	No	0	1 (Ref)			
	Yes	3.7				
Use of mandibular foramen conduction anesthesia						
	No	3.3	1 (Ref)			
	Yes	14.3	4.854	1.002	23.513	0.050*
Comorbidity possibly influencing hemostatis						
	No	5.8	1 (Ref)			
	Yes	2.6	0.440	0.171	1.131	0.088
History of acute inflammation at extraction site						
	No	2.5	1 (Ref)			
	Yes	5.1	2.093	0.7970	5.492	0.134
Gingival inflammation at extraction site						
	None to mild	3.3	1 (Ref)			
	Moderate to severe	4.9	1.491	0.519	4.283	0.458

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abnormal granulation tissue in extraction socket					
None to little	2.2	1 (Ref)			
Medium to much	6.1	2.900	1.1040	7.619	0.031*

For peer review only

Table 4. Multivariate analysis of post-extraction bleeding events by potential risk factors

		OR	95%CL		P-Value
			Lower	Upper	
Age (years)					
	< 65	1 (Ref)			
	≥ 65	7.930	2.230	28.200	0.001*
Type					
	Foretooth or premolar	1 (Ref)			
	Molar	0.953	0.288	3.151	0.937
Cause for extraction					
	Caries, apical periodontitis, or other	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	2.301	0.742	7.142	0.149
Status of antiplatelet therapy					
	No	1 (Ref)			
	Yes	0.100	0.010	0.986	0.049*
PT-INR					
		7.797	2.2930	26.510	0.001*
Use of mandibular foramen conduction anesthesia					
	No	1 (Ref)			
	Yes	2.437	0.336	17.659	0.378
Comorbidity possibly influencing hemostatis					
	No	1 (Ref)			
	Yes	0.503	0.157	1.612	0.247
History of acute inflammation at extraction site					
	No	1 (Ref)			
	Yes	3.722	1.0850	12.773	0.037*
Abnormal granulation tissue in extraction socket					
	None to little	1 (Ref)			
	Medium to much	2.895	0.8940	9.369	0.076

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

		Item No	Recommendation
Title and Abstract	✓	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
	✓		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	✓	2	Explain the scientific background and rationale for the investigation being reported
Objectives	✓	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	✓	4	Present key elements of study design early in the paper
Setting	✓	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	✓	6	(a) Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants
	N/A		(b) Cohort study
Variables	✓	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effects modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	✓	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	✓	9	Describe any efforts to address potential sources of bias
Study size	✓	10	Explain how the study size was arrived at
	✓	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	✓	12	(a) Describe all statistical methods, including those used to control for confounding
	✓		(b) Describe any methods used to examine subgroups and interactions
	✓		(c) Explain how missing data were addressed
	✓		(d) Cross-sectional study – If applicable, describe analytical methods taking accounting of sampling strategy
	✓		(e) Describe any sensitivity analyses
Results			
	✓	13	(a) Report numbers of individuals at each stage of study – e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed
	N/A		(b) Give reasons for non-participation at each stage
	N/A		(c) Consider use of a flow diagram
Descriptive data	✓	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
	✓		(b) Indicate numbers of participants with missing data for each variable of interest
	N/A		(c) Cohort study
Outcome data	✓	15	Cross-sectional study – Report numbers of outcomes events or summary measures
Main results	✓	16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (e.g. 95 confidence interval). Make clear which confounders were adjusted for and why they were included
	✓		(b) Report category boundaries when continuous variable were categorized
	✓		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	✓	17	Report other analyses done – e.g. analyses of subgroups, and sensitivity analyses

Discussion		
✓	18	Summarize key results with reference to study objectives
✓	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
✓	20	Give a cautious overall interpretations of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
✓	21	Discuss the generalizability (external validity) or the study results
Other information		
Funding	✓ 22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

BMJ Open

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005777.R1
Article Type:	Research
Date Submitted by the Author:	15-Aug-2014
Complete List of Authors:	Iwabuchi, Hiroshi; Kanagawa Dental University, Department of Oral and Maxillofacial Surgery Imai, Yutaka; Dokkyo Medical University School of Medicine, Department of Oral & Maxillofacial Surgery Asanami, Soichiro; Sanno Hospital, Department of Dentistry and Implant Center Shirakawa, Masayori; Nippon Dental University, Yamane, Gen-yuki; Tokyo Dental College, Ogiuchi, Hideki; Tokyo Women's Medical University, Kurashina, Kenji; Aizawa Hospital, Oral & Dental Center Miyata, Masaru; Ishikawa Prefectural Central Hospital, Department of Dentistry and Oral Surgery Nakao, Hiroyuki; National Institute of Public Health, Department of Epidemiology Imai, Hirohisa; National Institute of Public Health, Department of Epidemiology
Primary Subject Heading:	Dentistry and oral medicine
Secondary Subject Heading:	Dentistry and oral medicine
Keywords:	ORAL & MAXILLOFACIAL SURGERY, ORAL MEDICINE, Oral & maxillofacial surgery < SURGERY

SCHOLARONE™
Manuscripts

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Hiroshi Iwabuchi¹⁾, Yutaka Imai²⁾, Soichiro Asanami³⁾, Masayori Shirakawa⁴⁾, Gen-yuki Yamane⁵⁾, Hideki Ogiuchi⁶⁾, Kenji Kurashina⁷⁾, Masaru Miyata⁸⁾, Hiroyuki Nakao⁹⁾, Hirohisa Imai⁹⁾

Department of Oral and Maxillofacial Surgery, Kanagawa Dental University¹⁾, Department of Oral & Maxillofacial Surgery, Dokkyo Medical University School of Medicine²⁾, Department of Dentistry and Implant Center, Sanno Hospital³⁾, Nippon Dental University⁴⁾, Tokyo Dental College⁵⁾, Tokyo Women's Medical University⁶⁾, Aizawa Hospital, Oral & Dental Center⁷⁾, Department of Dentistry and Oral Surgery, Ishikawa Prefectural Central Hospital⁸⁾, Department of Epidemiology, National Institute of Public Health of Japan⁹⁾

Corresponding author: Hiroshi Iwabuchi
Department of Oral and Maxillofacial Surgery, Kanagawa Dental University
82 Inaokamachi, Yokosuka-shi, Kanagawa 238-8580, Japan
TEL: 81-46-822-8810, ext 2395
e-mail: iwabuchi@kdu.ac.jp

Word count: 3502

Keywords: tooth extraction, post-extraction bleeding, warfarin, risk factors

ABSTRACT

Objectives: The 95% confidence interval for the difference of post-extraction bleeding incidences in patients receiving or not-receiving warfarin was assessed along with associating risk factors were investigated.

Design: Crossectional multicenter observational study

Setting: 26 hospitals where oral surgeon is available.

Participants: Data on 2,817 teeth (496: receiving warfarin, 2,321: not receiving warfarin; mean age (SD): 62.2 (17.6)) extracted from November 1, 2008 to March 31, 2010, were collected. For warfarin-receiving patients to be eligible for the study, PT-INR within 7days prior to the extraction should be less than 3.0.

Interventions: Simple dental extraction was performed and incidence of post-extraction bleeding and comorbidities were recorded.

Primary and Secondary Outcome Measures: Post extraction bleeding not controlled by basic hemostatis procedure as clinically significant.

Results: Bleeding events were reported for 35 (7.1%) and 49 (2.1%) teeth, of which 18 (3.6%) and 9 (0.4%) teeth were considered as clinically significant, in warfarin and non-warfarin groups, respectively. The 95% confidence interval for the difference of incidences in non-warfarin and warfarin groups was 1.58 – 4.90%. Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), mandibular foramen conduction anesthesia (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) significantly correlate with the bleeding incidence. Multivariate analysis revealed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding.

Conclusion: Our results suggest that there is significant increase, demonstrated as 95% confidence interval for the difference, in incidences for the post extraction bleeding in patients receiving warfarin. Although absolute incidence was low in both groups, the bleeding risk is not negligible.

Strength and Limitation of this Study

- The present study examined difference of the incidences for post-extraction bleeding between the patients receiving and not-receiving warfarin, which few previous studies to date have been reported.
- The study included dental facilities where at least one or more certified oral surgeons are available in order to standardize skills of the operators and capability of the facilities for providing advanced care in the event of significant bleeding.
- We also analyzed the risk factors for post-extraction bleeding events in patients receiving warfarin.
- Due to the study design, we may have underestimated the incidence of post-extraction bleeding that may occur in community dental clinics.
- Although we tried to standardize the dental extraction procedure, there might have been inter-facility differences.

INTRODUCTION

Until recently, the common procedure for tooth extraction in patients continuously receiving warfarin or other antiplatelet therapy was to discontinue or reduce the dose to minimize the risks of odontorrhagia. However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1] This study raised wide concern about the adverse effects of warfarin discontinuation in dental surgery, and this issue was subsequently addressed by many randomized clinical trials,[2–4] cohort studies,[5–7] and meta-analyses.[8–10] Overall, these studies suggested that dental extraction could be performed safely in patients whose prothrombin time–international normalized ratio (PT-INR) was in the recommended therapeutic ranges, showing no significant differences in the incidence of post-extraction bleeding between the patients who continued warfarin and those whose warfarin was temporarily discontinued or reduced. Clinical guidelines published after these studies advised that patients whose PT-INR values were within the recommended therapeutic ranges should continue warfarin when undergoing dental extraction.[11–13] However, there have been little studies that specifically addressed difference in the bleeding incidences and its 95% confidence interval comparing tooth extraction cases in patients receiving and not receiving warfarin.

Given these circumstances, we evaluated the difference in the post-extraction bleeding incidences in otherwise healthy control without warfarin administration (non-WF group) and in patients under reasonable coagulation control with warfarin (WF group). We selected the subjects for the latter group whose PT-INR was 3.0 or lower at the time of the procedure, as the PT-INR of 3.0 was indicated as the maximum safety threshold for tooth extraction in the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction in Japanese.[14] We also investigated the risk factors for the incidence of post-extraction

bleeding in patients receiving warfarin therapy.

MATERIALS AND METHODS

This was a prospective multicenter observational study of post-extraction bleeding events in patients receiving and not receiving warfarin therapy.

Study Period and Eligibility Criteria

Twenty-six hospitals located across Japan participated. This study included patients who underwent simple tooth extraction from November 1, 2008 to March 31, 2010 at the department of oral surgery of these hospitals and who met the eligibility criteria listed below. Simple tooth extraction referred to a tooth removed without traumatizing the surrounding alveolar bone or elevating a mucoperiosteal flap.

Eligibility criteria included the following: 20 or more years of age at the time of tooth extraction; no contraindications for tooth extraction; surgery was performed by oral surgeon with a minimum of 3 years of experience in dental practice; the oral extraction procedure lasted for no longer than 15 minutes; and platelet count within 7 days prior to the procedure was normal. In addition, in patients receiving warfarin therapy, PT-INR measured within 7 days prior to the procedure should be less than 3.0. Patients receiving anti-platelet medication were not excluded but recorded as such. According to “The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction”[14], we instructed the participating hospitals that dental extraction should be performed without discontinuing or reducing the dose of warfarin in patients whose PT-INR was not exceeding 3.0 when measured within 7 days prior to the procedure.

Study Variables

The variables analyzed in this study were: bleeding events, patient's age and sex, position of the removed tooth, instruments used for removal (forceps only, elevators only, forceps and elevators), reasons for extraction, use of antiplatelet drugs, PT-INR values measured within 7 days before exodontia (only for patients receiving chronic warfarin therapy), comorbidities possibly influencing hemostasis, use of vasoconstrictors, combined use of local anesthetics and vasoconstrictors, use of inferior alveolar nerve block, severity of gingivitis after extraction (none, mild, moderate, severe), formation of abnormal granulation tissue in the extraction socket (none, little, medium, much), history of acute inflammation at extraction site, and post-extraction infection.

Hemostasis

The hemostatic methods for patients not receiving warfarin were chosen at the discretion of the dentist or oral surgeon performing the procedure. In patients on warfarin therapy, either absorbable oxidized cellulose or gelatin sponge was implanted into the alveolar socket, and wound margins were sutured. In both groups of patients, topical hemostatic agents other than epinephrine, systemic hemostatic agents, and splints were prohibited until primary hemostasis was observed. In patients who had multiple teeth extracted in one session, possible post-extraction bleeding was examined for each tooth. In a patient receiving warfarin, the post-extraction procedure defined above was performed each time after a tooth was removed.

Permitted Drugs

Use of local anesthetics containing vasoconstrictors (e.g., epinephrine and felypressin) was allowed at doses commonly practiced. In warfarin-treated patients, penicillins or cefems (e.g., cefcapene pivoxil and cefditoren pivoxil) was the primary choice of prophylactic

antibiotics for their minimal interaction with warfarin. For those who were allergic to penicillins, clarithromycin was recommended. Use of analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors was allowed at ordinary doses.

Confirmation of Hemostasis

All patients were asked to bite down on a roll gauze for a maximum of 30 minutes for astriction of the wound. After release of the biting pressure, the wound was examined for hemostasis. Patients visited the hospital on the next day of surgery to check for possible bleeding, and were instructed to present at the hospital for treatment, if bleeding should occur later. The follow-up period was 7 days postoperatively.

Follow-up of Bleeding Events

If a patient had a bleeding event during the follow-up period, the severity of the hemorrhage and blood pressure were recorded. If the patient was on warfarin therapy, his or her PR-INR values were measured in addition.

Evaluation of Bleeding Events

In this study, bleeding events occurring in the follow-up period were classified into one of the following 5 grades: 0, no bleeding; 1, excessive blood clotting in the socket, no treatment required; 2-1, hemostasis achieved by compressing the wound longer than 30 minutes; 2-2, oozing hemorrhage observed on or after the next day of the procedure, which hemostasis was achieved by simple compression; 3, bleeding required treatments other than wound compression, such as application of compression brace and/or coagulation by electrotome was needed. Grade 2-2 and higher events were regarded as clinically significant,

and were defined as post-extraction bleeds in this study.

Statistical Analysis

Data were collected by a tooth, but not by a patient. This means that patients who had multiple teeth extraction were counted multiple times for the number of extracted teeth. Data were then sorted and analyzed by the anatomical positions. The difference in post-extraction bleeding incidence between patients receiving and not receiving warfarin therapy and its 95% confidence interval (CI) were calculated. In addition, a multivariate logistic regression analysis was conducted to identify risk factors for post-extraction bleeding in warfarin-treated patients. Adjusted odds ratios (ORs), their 95% CIs and *p*-values were calculated controlling for major confounders. Explanatory variables with a significance level of $P < 0.20$ on univariate analyses were included in the multivariate logistic regression model. Statistical analyses were performed using the SPSS software (version 15.0, SPSS Japan Inc., Tokyo, Japan).

Ethics

The objective of this study was explained in details to potential study participants so that they could make an informed decision. Informed consent was obtained orally or by a written document, according to the recommendation to the ethics committee of each participating facilities. Patients' personal information was stored in a de-identified but linkable format during the 7-day follow-up period, and was rendered completely anonymous thereafter. This study was reviewed and approved by the ethics committee of the National Hospital Organization Tochigi Medical Center, Tochigi, Japan, prior to its conduct. The approved protocol was distributed to the participating hospitals to keep the uniformity of the study.

RESULTS

Totally, 3,515 case reports were submitted from the participating investigators. Of these, 698 cases were eliminated because of protocol deviations and/or insufficient data documentation, leaving 2,817 for further analysis.

Post-extraction Bleeding Incidence

Bleeding events including minor hemorrhagic episodes were reported for 35 out of 496 teeth (7.1%) of the warfarin group and for 49 out of 2,321 teeth (2.1%) of the non-warfarin group, with a total of 84 teeth. Clinically significant post-extraction bleeds (i.e., grade 2-2 or higher) were reported for 27 teeth, including 18 (3.6%) and 9 (0.4%) from the warfarin and non-warfarin groups, respectively (Table 1).

Breakdown of Removed Teeth by Sex and Study Group

The mean (SD) age of all study participants was 62.2 (17.6) years, and 1,446 and 1,371 teeth were removed from males (51.3%) and females (48.7%), respectively. The warfarin group had a mean (SD) age of 70.3 (10.9) years, and reported removal of 496 teeth, 320 from males (64.5%) and 176 from females (35.5%). Non-warfarin group had a mean (SD) age of 60.4 (18.3) years, and reported removal of 2321 teeth, 1126 from males (48.5%) and 1,195 from females (51.5%) (Table 1).

The difference in post-extraction bleeding incidence between the warfarin group and non-warfarin group was 3.24% and its 95% CI was 1.58% to 4.90% (Table 2).

Risk Factors for Post-extraction Bleeding in Warfarin-Treated Patients

Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P =$

0.003), inferior alveolar nerve block (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) were significantly correlated with post-extraction bleeding (Table 3). In addition to these variables, position of the removed tooth, reasons for extraction, antiplatelet drugs, comorbidities possibly influencing hemostasis, and history of acute inflammation at extraction site were found to have P values smaller than 0.2 by univariate analysis. Consequently, these parameters were included as explanatory variables in the multivariate regression analysis. The results showed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding (Table 4).

DISCUSSION

There have been many studies evaluating safety and associated complications when performing tooth extraction in patients receiving warfarin.[1-20] Wahl et al evaluated 496 patients/524 tooth extractions where warfarin was temporarily discontinued prior to the procedure, and observed thromboembolism in 5 cases (0.95%), 4 out of which died.[1] In a cohort study, incidences of serious bleeding complications and thromboembolic events were compared between the patients whose maintenance warfarin intake was discontinued in preparation of minor outpatient surgeries including dental surgery and the patients in which heparin bridging was utilized without warfarin cessation.[15] During the 1 month observation period after warfarin was discontinued, thromboembolic complication occurred in approximately 0.7% of the patients who discontinued warfarin, whereas serious bleeding complication was observed in 4 cases with heparin bridging and in 2 cases without heparin bridging.[15] A study conducted in Japan also found that in 1 out of 128 cases in which dental extraction was performed with discontinuation or reduction of the dose of warfarin, cerebral

infarction occurred and the patient was deceased.[16] Those findings led to discussion on whether or not warfarin should be continued, or discontinued or reduced, with an emphasis on prevention of thromboembolic complications. In addition, multiple studies reported that dental extraction is safely performed and post-extraction bleeding can be sufficiently controlled by topical hemostasis only in patients receiving warfarin without discontinuing the mediation.[2-10] Based on these findings, the current guidelines recommend that dental extraction be performed with continuing maintenance dosage of warfarin.[11-13] However, Balevi et al recently reevaluated the data reported by Wahl et al with a distinct analytical approach and found that incidence of cardiovascular accident after 3 days of warfarin cessation was 0.059%, which was significantly lower than that was originally reported.[17, 18] Taken together, the literature indicate that thromboembolic complication does occur, though absolute numbers are small and suggest that decision whether or not to continue maintenance dose of warfarin when performing dental extraction in patients receiving warfarin should be made carefully taking risks and benefits that warfarin could cause into account. The present study was conducted to further identify risks and associating factors for post-extraction bleeding in patients receiving warfarin.

The present study is a nation-wide, multi-institutional prospective study and evaluated frequency of clinically significant post-extraction bleeding and its difference between the non-warfarin and warfarin groups. Clinically significant post-extraction bleeding occurred in low rate in both study groups. Nonetheless, the difference between the two groups was 3.24% with its 95% confidence interval between 1.58 – 4.90%, suggesting that the difference can be as big as approximately 5%. In all cases of post-extraction bleeding, sufficient hemostasis was achieved only with topical measures, but about 10% of those patients required hemostasis after office hours at night. In the present study, all the extraction was performed by oral surgeon at a facility where emergency care is available 24 hrs a day, where sufficient

hemostasis can be performed even after hours, but if clinically significant bleeding happened in a community dental clinic at night or in holidays, successful hemostasis in some of such bleeding could have been difficult. The present study revealed factors associated with increased incidence of post-extraction bleeding in patients receiving warfarin. Therefore, when performing dental extraction in high-risk patients such as those taking warfarin, capability of the facility for means of hemostasis other than simple topical hemostasis and availability of personnel at afterhours should carefully be considered.

Among the patients receiving warfarin, older patients showed lower risks for post-extraction bleeding in the present study. Few studies have addressed influence of patients' age on incidence of post-extraction bleeding. Mean PT-INR in the patients who experienced clinically significant post-extraction bleeding was 2.57 ± 0.62 in patients 65 years old or older, which was significantly higher compared to that in patients younger than 65 years old ($2.10 \pm 0.39, P = 0.048$). These results suggest that younger patients tend to experience clinically significant post-extraction bleeding at lower PT-INR, which might have contributed to the lower bleeding risks in the elderly patients in the present study.

Few studies reported to date examined the relationship between age and the incidence of post-extraction bleeding. Our finding indicated that extra caution should be taken when conducting exodontia in elderly patients receiving warfarin therapy, and the frequency of such situations would increase with aging population.

A study that investigated the impact of comorbid conditions on hemostasis suggested that patients with liver dysfunction are another group at high risk for post-extraction bleeding.[19] The present study did not identify liver dysfunction or other comorbid conditions that would affect hemostasis as a risk factor for increased incidence of post-extraction bleeding. The attribution of such condition may have been underestimated in the present study as only 4.2% of the study participants had chronic hepatitis.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Our results also showed that the incidence of post-extraction bleeding events increased with higher PT-INR, even though the values did not exceed 3.0. This finding suggests that a special attention would be needed in patients whose PT-INR are close to 3.0 or higher to prevent post-extraction hemorrhagic event. Because warfarin sensitivity may vary among individuals and different ethnic groups, further studies will be needed to verify if the current findings are generalizable to other ethnic groups.

No randomized comparative trials that addressed incidences of post-extraction bleeding in patients receiving warfarin with or without anti-platelet medicine has so far been reported. An observational study by Morimoto et al found no significant difference in incidences of post-extraction bleeding between the patients receiving warfarin alone and those in combination with an anti-platelet medicine.[6] In contrast, Scully et al reported that, in patients with oral surgeries, post-operative bleeding incidence was higher in patients under the combination therapy of warfarin and an anti-platelet medicine.[20] Besides reports regarding the bleeding events associated with oral surgeries, increased incidence of hemorrhagic complications in patients receiving anti-platelet medicine in addition to warfarin compared to those receiving warfarin only was observed in a cohort study in Japanese patients under anti-coagulation therapies.[21]. The results from the present study suggested that incidence for post-extraction bleeding is lower in patients receiving both warfarin and an anti-platelet medicine. Although findings vary in those studies, anti-platelet medicine alone is in general considered to minimally affect incidences of post-operative bleeding in the cases of dental extraction[8] or of surgeries [22], and may as well in patients under the control of warfarin.

Suturing of wound and filling of the socket with oxidized cellulose or gel foam have been widely recognized as efficient means of hemostasis after dental extraction.[23-25] However, some guidelines do not necessarily recommend suture of the wound, while supporting the use

of oxidized cellulose, gelfoam or fibrin glue.[8] Several reports also found that suturing would could rather damage the tissue at the socket.[26,27] In the present study, incidences of post-extraction bleeding in patients not receiving warfarin were not significantly different between the patients whose wound was sutured and those without suture (0.6 and 0.2%, respectively). However, we were unable to tell whether suturing increased the incidence of post-extraction bleeding in the patients receiving warfarin as wounds were sutured in all the patients receiving warfarin in the present study. Evaluation of the outcome of suturing in patients receiving warfarin would be worthy of future study. Heparin bridging is another effective means to prevent thromboembolism and to reduce risk for post-operative bleeding [28,29], application of which is primarily limited to a major surgery that topical hemostasis is not applicable. Efficacy of heparin bridging was evaluated by a randomized comparative study,[30] which found no significant differences in incidences of post-extraction bleeding or thromboembolic complications with and without addition of heparin bridging with continuing warfarin therapy, concluding that heparin bridging is not required when dental extraction is performed as long as topical hemostasis is applicable. On the other hand, comparative studies examined cases of minor surgeries performed with cessation of warfarin with or without additional heparin bridging reported severe hemorrhagic event in cases receiving heparin bridging, though no thromboembolic complication had occurred.[31,32] Furthermore, heparin needs to be continuously administered intravenously when performing heparin bridging, necessitating hospital admission with resulting higher cost and demands for medical personnel. The results from the present study further supported the notion that topical hemostasis provides sufficient hemostasis in cases of simple tooth extraction without discontinuing warfarin, and therefore heparin bridging is not necessary.

Several aspects of our study design that may have affected the outcome of the present study should be noted. First, we included PT-INR values measured within 7 days prior to tooth

extraction, considering the availability of measurement results. However, because effects of warfarin can be affected by diet and other drugs, experts suggested to measure PT-INR within 24 [8,9,33,34] and 48 [35] hours before the procedure. The British Committee for Standards in Hematology recommended 72 hours before surgery [11]. Therefore, pre-extraction PT-INR values we utilized may not have accurately reflected the coagulation status immediately prior to the extraction, skewing the results of our analyses. To minimize the bias, we conducted another PT-INR measurement in patients receiving warfarin who experienced clinically significant bleeding events soon after the event observation. In such patients, PT-INR values before and after the tooth extraction were 2.27 and 2.26, respectively, and not significantly changed. These data suggest that the possible bias derived from PT-INR values measured within 7 days in advance were minimal. Second, we performed all the analyses by tooth, not by patients. We hypothesized, based on previous studies that found no significant correlation between the numbers of tooth extracted and incidence of post extraction bleeding,[2,4,5,7] that risks for post-extraction bleeding may vary depending the position and/or conditions of the tooth extracted even in the same individual. In order for detecting possible influence of local factors, such as position of tooth extracted (foretooth vs. molar tooth) and gum conditions (presence of inflammation and/or inappropriate granulation) on risks for post-extraction bleeding, we chose to present our data by tooth, despite a possible bias of including some of the patient data multiple times when multiple teeth was extracted from a single patient. When the same dataset was analyzed by patient, incidence rate of clinically significant post-extraction bleeding was 2.77% in 361 patients receiving warfarin, while the incident rate among 1,785 patients in non-warfarin group was 0.39%, with the 95% confidential interval for the difference of incidence between the two groups was between 0.65 and 4.10%, which was very similar to the findings from the analyses performed by tooth. These data suggest that the bias that might arise from the analyses by tooth was minimal.

Third, evaluation of the post-extraction bleeding events was not blinded and choice of secondary hemostasis means were left at the discretion by the operator in charge, which might have affected the outcome of our analyses. However, the definition of the clinically significant bleeding events was made clear, minimizing the influence by the person who evaluated the individual event.

CONCLUSION

The 95% confidence interval for the difference of post-extraction bleeding incidences between the patients receiving or not receiving warfarin was 1.58 – 4.90% (risk ratio 9.31). Age, PT-INR, and history of acute inflammation at extraction site were risk factors for post-extraction bleeding in warfarin receiving patients.

Contributorship statement

H. Iwabuchi designed the study protocol and wrote the manuscript. H. Imai analyzed the data and contributed to edition of the manuscript. H. Nakao also participated in data analyses. Y. Imai is the Principle Investigator of the present study. Rest of the authors participated in data collection.

Competing interests

I/We have read and understood BMJ policy on declaration of interests and declare the following interests.

Copyright and license for the publication:

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity,

in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.”

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding

There is no involvement of funding sources in this research.

Data sharing statement

Data sharing: patient level data [and/or] full dataset [and/or] technical appendix [and/or] statistical code [and/or] are available from the corresponding author upon request. Consent for additional data sharing was not obtained but the presented data are anonymised and risk of identification is low.

REFERENCES

- 1 Wahl MJ. Dental surgery in anticoagulated patients. *Arch Inter Med*1998;158:1610-16.
- 2 Evans IL, Sayers MS, Gibbons AJ, et al. Can warfarin be continued during dental extraction?Results of a randomized controlled trial. *Br J Oral Maxillofac Surg*2002;40:248-252.
- 3 Sacco R, Sacco M, CarpenedoM,et al.Oral surgery in patients on oral anticoagulant therapy: A randomized comparison of different intensity targets. *Oral Surg Oral med Oral Pathol Oral RadiolEndod.*2007;104:e18-21.
- 4 Al-Mubarak S, Al-Ali N, Rass MA, et al.Evaluation of dental extractions,suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. *Br Dent J.*2007;203:1-5.
- 5 Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery:Should the Anticoagulation regiment be altered? *J Oral Maxillofac Surg.*2000;58:131-5.
- 6 Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in patients on oral antithrombotic therapy. *J Oral Maxillofac Surg.*2008;66:51-7.
- 7 Barrero MV, Knezevic M, Martin MT, et al. Oral surgery in the patients undergoing oral anticoagulant therapy. *Med oral.*2002;7:63-70.
- 8 Aframian DJ, Lalla RV, Peterson DE. Management of dental patients taking common hemostasis –altering medications. *Oral Surg Oral med Oral Pathol Oral RadiolEndod.*2007;103(suppl 1):S45e1-11.
- 9 Goodchild JH, Donaldson M. An evidence-based dentistry challenge:Treating patients on warfarin(Coumadin). *Dental aimplantol Update*2009;20:1-8.
- 10 Nematullah A, Alabousi A, Blanas N, et al. Dental surgery for patients on anticoagulant therapy with warfarin:asystematic review and meta-analysis. *J can Dent Assoc.*2009;75:41-41i.

11 Perry DJ, Noakes TJC, Helliwell PS. Guidelines for the management of patients on oral anticoagulants requiring dental surgery. *Br Dent J.*2007;203:389-393.

12 Sasanuki H, et al: Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease. *Circ J.*2004;68suppl IV:1153-1219.

13 Jcs Joint Warking Group: Guidelines for pharmacotherapy of atrial fibrillation –Digest Version-. *Circ J.*2010;74:2479-2500.

14 Japanese Society of Dentistry for Medically Compromised Patient,Japanese Society of Oral and Maxillofacial Surgeons, Japanese Society ofGerodontology:The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction.2010 versionGakujutsusha CorporationTokyo 2010.

15 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Inter Med.* 2008;168:63-69.

16 Ogiuchi H, Ando T, Tanaka M, et al. Clinical reports on dental extraction from patients undergoing oral anticoagulant therapy. *Bull Tokyo Dent Coll.* 1985;26:205-212.

17 Balevi B. Should warfarin be discontinued before a dental extracion? A decision-tree analysis. *Oral Surg Oral Med Oral Pathol Oral RadiolEndod* 2010;110:691–697.

18 Balevi B.Should warfarin be discontinued before a dental extraction? *Oral Surg Oral Med Oral Pathol Oral RadiolEndod* 2012;113:150-152.

19 Devani P, Lavery KM, Howell CJT. Dental extractions in patients on warfarin –Is alternation of anticoagulant regime necessary? *Br J Oral Maxillofac Surg.*1998;36:107-111.

20 Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy.*Oral Surg Oral Med Oral Pathol* 2002;94:57-64.

21 Toyoda K, Yasaka M, Iwade K, etal.Dualantithrombotie therapy increases severe bleeding events in patients with stroke and cardiovascular disease –A

- prospective,multicenter,observational study. *Stroke*.2008;39:1740-45.
- 22 Maulaz AB, BezerraDC, Michel P, et al. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. *Arch Neurol*.2005;62:1217-1220.
- 23 Halfpenny W, Fraser JS,Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. *Oral Surg Oral Med Oral Phthol Oral Radiol Endnd*.2001;92:257-259.
- 24 Carter G, Goss A, Lloyd J,et al. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. *J Oral Maxillofac Surg*.2003;61:1432-1435.
- 25 Blinder D, Manor Y, Martinowitz U, et al. Dental extraction in patients maintained on continued oral anticoagulant. Comparison of local hemostatic modalities.*Oral Surg Oral Med Oral Phthol Oral Radiol Endnd*.1999;88:137-140.
- 26 Salam S, Yusuf H, Milosevic A. Bleeding after dental extractions in patients taking warfarin. *Br J Oral Maxillofac Surg*. 2007;45:463-466.
- 27 Al-Belasy FA, Amer MZ. Hemostatic effect of n-butyl-2-cyano- acrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. *J Oral Maxillofac Surg*. 2003; 61: 1405-1409.
- 28 Dunn AS,Alexander G,G Turpie. Perioperative management of patients receiving oral b Anticoagulants A systemic review. *Arch Intern Med*. 2003;163:901-908.
- 29 Kovacs MJ, Kearon C, Rodger M, et al; Single-arm study of bridging therapy eith low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. *Circulation*. 2004;110:1658-1663.
- 30 Bajkin BV, Popovic SL, Selakovic SDJ. Randomized prospective trial comparing bridging therapy using low-molecular-weight heparin with maintenance of oral anticoagulation during extraction of teeth. *J Oral Maxillofac Surg*. 2009; 67: 990-995.

31 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med.* 2008;168:63-69.

32 Bloomer CR. Excessive hemorrhage after dental extractions using low-molecular-weight heparin (Lovenox) anticoagulation therapy. *J Oral Maxillofac Surg.* 2004;62:101-103.

33 Chugani V. Management of dental patients on warfarin therapy in a primary care setting. *Dental Update.* 2004;31:379-384.

34 Pototski M, Amenabar JM: Dental management of patients receiving anticoagulation or antiplatelet treatment. *J Oral Sci.* 2007;49:253-8.

35 Brennan MT, Hong C, Furney SL, et al. Utility of an international normalized ratio testing device in a hospital-based dental practice. *J Am Dent Assoc.* 2008;139:697-703.

Table 1. Breakdown of extracted teeth by important classification variables

No. of teeth by:		Warfarin n=496	No Warfarin n=2321	Total N = 2817	P value
Age (years)					
	< 65	124 (25.0)	1131 (48.7)	1255 (44.6)	< 0.0001
	≥ 65	372 (75.0)	1190 (51.3)	1562 (55.4)	
Sex					
	Male	320 (64.5)	1126 (48.5)	1446 (51.3)	< 0.0001
	Female	176 (35.5)	1195 (51.5)	1371 (48.7)	
Type					
	Foretooth	132 (26.6)	663 (28.6)	795 (28.2)	0.550
	Premolar	127 (25.6)	552 (23.8)	679 (24.1)	
	Molar	237 (47.8)	1106 (47.7)	1343 (47.7)	
Instrument					
	Forceps only	171 (34.5)	604 (26.0)	775 (27.5)	0.000
	Elevators only	226 (45.6)	919 (39.6)	1145 (40.6)	
	Forceps and elevators	99 (20.0)	798 (34.4)	897 (31.8)	
Cause for extraction					
	Periodontitis	160 (32.3)	533 (23.0)	693 (24.6)	< 0.0001
	Caries	87 (17.5)	477 (20.6)	564 (20.0)	
	Apical periodontitis	219 (44.2)	1002 (43.2)	1221 (46.6)	
	Wisdom tooth pericoronitis	23 (4.6)	192 (8.3)	215 (7.6)	
	Other	7 (1.4)	117 (5.0)	124 (4.4)	
Status of antiplatelet therapy					
	Yes	122 (24.6)	433 (18.7)	555 (19.7)	0.003
Use of local anesthetics containing vasoconstrictors					
	Yes	491 (99.0)	2265 (97.6)	2756 (97.8)	0.105
Use of inferior alveolar nerve block					
	Yes	14 (2.8)	82 (3.5)	96 (3.4)	0.429
Comorbidity possibly influencing hemostasis					
	Hypertension	267 (53.8)	715 (30.8)	982 (34.9)	< 0.0001
	Diabetes mellitus	89 (17.9)	267 (11.5)	356 (12.6)	
	Chronic hepatitis	21 (4.2)	110 (4.7)	131 (4.7)	
	Other	68 (13.7)	212 (9.1)	280 (9.9)	
	Multiple disorders	341 (68.8)	1039 (44.8)	1380 (49.0)	
History of acute inflammation at extraction site					
	Yes	216 (43.5)	829 (35.7)	1045 (37.1)	0.001
Gingival inflammation at extraction site					
	None	298 (60.1)	1266 (54.5)	1564 (55.5)	0.000
	Mild	95 (19.2)	264 (11.4)	359 (12.7)	
	Moderate	13 (2.6)	38 (1.6)	51 (1.8)	
	Severe	90 (18.1)	753 (32.4)	843 (29.9)	
Abnormal granulation tissue in extraction socket					

None	87 (17.5)	818 (35.2)	905 (32.1)	0.003
Little	230 (46.4)	917 (39.5)	1147 (40.7)	
Medium	134 (27.0)	441 (19.0)	575 (20.4)	
Much	45 (9.1)	145 (6.2)	190 (6.7)	
Severity of post-extraction bleeding				
G1	9 (1.8)	29 (1.2)	38 (1.3)	< 0.0001
G2-1	8 (1.6)	11 (0.5)	19 (0.7)	
G2-2	1 (0.2)	8 (0.3)	9 (0.3)	
G3	17 (3.4)	1 (0.04)	18 (0.6)	
total	35 (7.1)	49 (2.1)	84 (3.0)	
G2-2+G3	18 (3.6)	9 (0.4)	27 (1.0)	< 0.0001
PT-INR				
(mean ± SD)	1.90±0.49			

Table 2. Incidences of clinically significant post-extraction bleeding and their difference in patients receiving and not receiving warfarin

	Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence(%)	95%CL (%)	
			LOWER	UPPER
Warfarin	3.63	3.24	0.0158	0.0490
No Warfarin	0.39			

Table 3. Univariate analysis of post-extraction bleeding events by potential risk factors

		Incidence of post-extraction bleeding (%)	OR	95%CL		P-value
				Lower	Upper	
Age (years)						
	< 65	8.9	1 (Ref)			
	≥ 65	1.9	0.197	0.075	0.520	0.001*
Sex						
	Male	3.4	1 (Ref)			
	Female	4.0	1.164	0.443	3.057	0.759
Type						
	Foretooth or premolar	2.3	1 (Ref)			
	Molar	5.1	2.2249	0.830	6.091	0.111
Instrument						
	Forceps only	2.9	1 (Ref)			
	Elevators alone or with forceps	4	1.383	0.485	3.947	0.544
Cause for extraction						
	Caries, apical periodontitis, or other	2.6	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	5.5	2.204	0.854	5.688	0.102
Status of antiplatelet therapy						
	No	4.5	1 (Ref)			
	Yes	0.8	0.174	0.023	1.318	0.090
PT-INR						
			3.635	1.5640	8.448	0.003*
Use of vasoconstrictors						
	No	4.1	1 (Ref)			
	Yes	0				
Use of local anesthetics containing vasoconstrictors						
	No	0	1 (Ref)			
	Yes	3.7				
Use of inferior alveolar nerve block						
	No	3.3	1 (Ref)			
	Yes	14.3	4.854	1.002	23.513	0.050*
Comorbidity possibly influencing hemostatis						
	No	5.8	1 (Ref)			
	Yes	2.6	0.440	0.171	1.131	0.088
History of acute inflammation at extraction site						
	No	2.5	1 (Ref)			
	Yes	5.1	2.093	0.7970	5.492	0.134
Gingival inflammation at extraction site						
	None to mild	3.3	1 (Ref)			
	Moderate to severe	4.9	1.491	0.519	4.283	0.458

**Abnormal granulation tissue in
extraction socket**

None to little	2.2	1 (Ref)			
Medium to much	6.1	2.900	1.1040	7.619	0.031*

For peer review only

Table 4. Multivariate analysis of post-extraction bleeding events by potential risk factors

		OR	95%CL		P-Value
			Lower	Upper	
Age (years)					
	< 65	1 (Ref)			
	≥ 65	0.126	0.035	0.448	0.001*
Type					
	Foretooth or premolar	1 (Ref)			
	Molar	0.953	0.288	3.151	0.937
Cause for extraction					
	Caries, apical periodontitis, or other	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	2.301	0.742	7.142	0.149
Status of antiplatelet therapy					
	No	1 (Ref)			
	Yes	0.100	0.010	0.986	0.049*
PT-INR					
		7.797	2.2930	26.510	0.001*
Use of inferior alveolar nerve block					
	No	1 (Ref)			
	Yes	2.437	0.336	17.659	0.378
Comorbidity possibly influencing hemostatis					
	No	1 (Ref)			
	Yes	0.503	0.157	1.612	0.247
History of acute inflammation at extraction site					
	No	1 (Ref)			
	Yes	3.722	1.0850	12.773	0.037*
Abnormal granulation tissue in extraction socket					
	None to little	1 (Ref)			
	Medium to much	2.895	0.8940	9.369	0.076

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Hiroshi Iwabuchi¹⁾, Yutaka Imai²⁾, Soichiro Asanami³⁾, Masayori Shirakawa⁴⁾, Gen-yuki Yamane⁵⁾, Hideki Ogiuchi⁶⁾, Kenji Kurashina⁷⁾, Masaru Miyata⁸⁾, Hiroyuki Nakao⁹⁾, Hirohisa Imai⁹⁾

Department of Oral and Maxillofacial Surgery, Kanagawa Dental University¹⁾, Department of Oral & Maxillofacial Surgery, Dokkyo Medical University School of Medicine²⁾, Department of Dentistry and Implant Center, Sanno Hospital³⁾, Nippon ~~Dental~~ ~~University~~⁴⁾ ~~DentalUniversity~~⁴⁾, Tokyo Dental College⁵⁾, Tokyo Women's Medical University⁶⁾, Aizawa Hospital, Oral & Dental Center⁷⁾, Department of Dentistry and Oral Surgery, Ishikawa Prefectural Central ~~Hospital~~⁸⁾ ~~Hospital~~⁸⁾, Department of Epidemiology, National Institute of Public Health of ~~Japan~~⁹⁾ ~~Japan~~⁹⁾

Corresponding author: Hiroshi Iwabuchi

Department of Oral and Maxillofacial Surgery, Kanagawa Dental University

82 Inaokamachi, Yokosuka-shi, Kanagawa 238-8580, Japan

TEL: 81-46-822-8810, ext 2395

e-mail: ~~Hiroshi Iwabuchi~~ ~~:-~~ iwabuchi@kdu.ac.jp

Word count: ~~2,777~~ 3502

Keywords: tooth extraction, post-extraction bleeding, warfarin, risk factors

ABSTRACT

Objectives: ~~Difference in~~The 95% confidence interval for the ~~incidence~~difference of post-extraction bleeding ~~events~~incidences in patients receiving ~~and/or~~ not-receiving warfarin ~~therapy, was assessed~~ along with associating risk factors were investigated.

Design: Crossectional multicenter observational study

Setting: 26 ~~hospitals where oral surgeon~~hospitals where oral surgeon is available.

Participants: Data on 2,817 teeth (496: receiving warfarin, 2,321: not receiving warfarin; mean age (SD): 62.462 (17.596)) extracted from November 1, 2008 to March 31, 2010, were collected. For warfarin-receiving patients to be eligible for the study, PT-INR within 7 days prior to the extraction should be less than 3.0

Interventions: Simple dental extraction was performed and incidence of post-extraction bleeding and comorbidities were recorded.

Primary and Secondary Outcome Measures: Post extraction bleeding not controlled by basic hemostatis procedure as clinically significant.

Results: Bleeding events were reported for 35 (7.1%) and 49 (2.1%) teeth, of which 18 (3.6%) and 9 (0.4%) teeth were considered as clinically significant, in warfarin and non-warfarin groups, respectively. ~~The 95% confidence interval for the difference in post-extraction bleeding of~~ incidences ~~between warfarin and in~~ non-warfarin ~~and warfarin~~ groups was ~~3.24% (95% CI: 1.49% to 58 – 4.99%) 90%.~~ Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), mandibular foramen conduction anesthesia (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) significantly correlate with the bleeding incidence. Multivariate analysis revealed that age (OR: ~~7.93~~0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding.

Conclusion: Our results ~~suggest that there is significant increase,~~ demonstrated ~~that as 95% confidence interval for the difference, in incidences for the post extraction bleeding in~~ patients receiving warfarin ~~therapy had an approximately 10 times higher probability of post-extraction bleeding than those not on warfarin, though~~Although absolute incidence was low in both groups, ~~the bleeding risk is not negligible.~~

Strength and Limitation of this Study

- The present study examined difference of the incidences for post-extraction bleeding between the patients receiving and not-receiving warfarin, which few previous studies to date have been reported.
- The study included dental facilities where at least one or more certified oral surgeons are available in order to standardize skills of the operators and capability of the facilities for providing advanced care in the event of significant bleeding.
- We also analyzed the risk factors for post-extraction bleeding events in patients receiving warfarin.
- Due to the study design, we may have underestimated the incidence of post-extraction bleeding that may occur in community dental clinics.
- Although we tried to standardize the dental extraction procedure, there might have been inter-facility differences.

INTRODUCTION

Until recently, the common procedure for tooth extraction in patients continuously receiving warfarin or other antiplatelet therapy was to discontinue or reduce the ~~dose to~~doseto minimize the risks of odontorrhagia. However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1] This study raised wide concern about the adverse effects of warfarin discontinuation in dental surgery, and this issue was subsequently addressed by many randomized clinical trials,[2–4] cohort studies,[5–7] and meta-analyses.[8–10] Overall, these studies suggested that dental extraction could be performed safely in patients whose prothrombin time–international normalized ratio (PT-INR) was in the recommended therapeutic ranges, showing no significant differences in the incidence of post-extraction bleeding between the patients who continued warfarin and those whose warfarin was temporarily discontinued or reduced. Clinical guidelines published after these studies advised that patients whose PT-INR values were within the recommended therapeutic ranges should continue warfarin when undergoing dental extraction.[11–13]

However, ~~nothere have been little~~ studies ~~to date have investigated that specifically addressed difference in the differences in post-extraction~~ bleeding incidences ~~betweenand its 95% confidence interval comparing tooth extraction cases in~~ patients receiving and not receiving warfarin. ~~In addition, few studies focused on the risk factors for post-extraction bleeding in warfarin treated patients.~~

Given these circumstances, ~~this study comparedwe evaluated~~ the ~~incidence rates of difference in the~~ post-extraction ~~hemorrhage betweenbleeding incidences in otherwise healthy control without warfarin administration (non-WF group) and in patients under reasonable coagulation control with warfarin (WF group).~~ We selected the subjects for the latter group whose PT-INR ~~values werewas~~ 3.0 or ~~below and those who were not on anticoagulant~~

~~therapy lower at the time of the procedure, as~~ the PT-INR of 3.0 was indicated as the maximum safety threshold for tooth extraction in the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction in Japanese.[14] We also investigated the risk factors for the incidence of post-extraction bleeding in patients receiving warfarin therapy.

MATERIALS AND METHODS

This was a prospective multicenter observational study of post-extraction bleeding events in patients receiving and not receiving warfarin therapy.

Study Period and Eligibility Criteria

Twenty-six hospitals located across Japan participated. This study included patients who underwent simple tooth extraction from November 1, 2008 to March 31, 2010 at the department of oral surgery of these hospitals and who met the eligibility criteria listed below. Simple tooth extraction referred to a tooth removed without traumatizing the surrounding alveolar bone or elevating a mucoperiosteal flap.

Eligibility criteria included the following: 20 or more years of age at the time of tooth extraction; no contraindications for tooth extraction; surgery was performed by oral surgeon with a minimum of 3 years of experience in dental practice; the oral extraction procedure lasted for no longer than 15 minutes; and platelet count within 7 days prior to the procedure was ~~greater than 10,000/mm³ -normal~~. In addition, in patients receiving warfarin therapy, PT-INR measured within 7 days prior to the procedure should be less than 3.0. Patients receiving anti-platelet medication were not excluded but recorded as such. According to “The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction”[14], we

instructed the participating hospitals that dental extraction should be performed without discontinuing or reducing the dose of warfarin in patients whose PT-INR was not exceeding 3.0 when measured within 7 days prior to the procedure.

Study Variables

The variables analyzed in this study were: bleeding events, patient’s age and sex, position of the removed tooth, instruments used for removal (forceps only, elevators only, forceps and elevators), reasons for extraction, use of antiplatelet drugs, PRPT-INR values measured within 7 days before exodontia (only for patients receiving chronic warfarin therapy), comorbidities possibly influencing hemostasis, use of vasoconstrictors, combined use of local anesthetics and vasoconstrictors, use of mandibular foramen conduction anesthesia inferior alveolar nerve block, severity of gingivitis after extraction (none, mild, moderate, severe), formation of abnormal granulation tissue in the extraction socket (none, little, medium, much), history of acute inflammation at extraction site, and post-extraction infection.

Hemostasis

The hemostatic methods for patients not receiving warfarin were chosen at the discretion of the dentist or oral surgeon performing the procedure. In patients on warfarin therapy, either absorbable oxidized cellulose or gelatin sponge was implanted into the alveolar socket, and wound margins were sutured. In both groups of patients, topical hemostatic agents other than epinephrine, systemic hemostatic agents, and splints were prohibited until primary hemostasis was observed. In patients who had multiple teeth extracted in one session, possible post-extraction bleeding was examined for each tooth. In a patient receiving warfarin, the post-extraction procedure defined above was performed each time after a tooth was removed.

Permitted Drugs

Use of local anesthetics containing vasoconstrictors (e.g., epinephrine and felypressin) was allowed at doses commonly practiced. In warfarin-treated patients, penicillins or cefems (e.g., cefcapene pivoxil and cefditoren pivoxil) was the primary choice of prophylactic antibiotics for their minimal interaction with warfarin. For those who were allergic to penicillins, clarithromycin was recommended. Use of analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors was allowed at ordinary doses.

Confirmation of Hemostasis

All patients were asked to bite down on a roll gauze for a maximum of 30 minutes for astriction of the wound. After release of the biting pressure, the wound was examined for hemostasis. Patients visited the hospital on the next day of surgery to check for possible bleeding, and were instructed to present at the hospital for treatment, if bleeding should occur later. The follow-up period was 7 days postoperatively.

Follow-up of Bleeding Events

If a patient had a bleeding event during the follow-up period, the severity of the hemorrhage and blood pressure were recorded. If the patient was on warfarin therapy, his or her PR-INR values were measured in addition.

Evaluation of Bleeding Events

In this study, bleeding events occurring in the follow-up period were classified into one of the following 5 grades: 0, no bleeding; 1, excessive blood clotting in the socket, no treatment required; 2-1, hemostasis achieved by compressing the wound longer than 30

minutes; 2-2, ~~blood oozing from socket, ceased~~ hemorrhage observed on or after the next day
of the procedure, which hemostasis was achieved by ~~wound~~ simple compression ~~only~~; 3,
bleeding required treatments other than wound compression, such as application of
compression brace and/or coagulation by electrotome was needed. Grade 2-2 and higher
events were regarded as clinically significant, and were defined as post-extraction bleeds in
this study.

Statistical Analysis

Data were collected by a tooth, but not by a patient. This means that patients who had
multiple teeth extraction were counted multiple times for the number of extracted teeth. Data
were then sorted and analyzed by the anatomical positions. The difference in post-extraction
bleeding incidence between patients receiving and not receiving warfarin therapy and its 95%
confidence interval (CI) were calculated. In addition, a multivariate logistic regression
analysis was conducted to identify risk factors for post-extraction bleeding in warfarin-treated
patients. Adjusted odds ratios (ORs), their 95% CIs and *p*-values were calculated controlling
for major confounders. Explanatory variables with a significance level of $P < 0.20$ on
univariate analyses were included in the multivariate logistic regression model. Statistical
analyses were performed using the SPSS software (version 15.0, SPSS Japan Inc., Tokyo,
Japan).

Ethics

The objective of this study was explained in details to potential study participants so that
they could make an informed decision. Informed consent was obtained orally or by a written
document, according to the recommendation to the ethics committee of each participating
facilities. Patients' personal information was stored in a de-identified but linkable format

during the 7-day follow-up period, and was rendered completely anonymous thereafter. This study was reviewed and approved by the ethics committee of the National Hospital Organization Tochigi Medical Center, Tochigi, Japan, prior to its conduct. The approved protocol ~~and forms for informed consent were~~was distributed to the participating hospitals to keep the uniformity of the study.

RESULTS

Totally, 3,515 case reports were submitted from the participating investigators. Of these, 698 cases were eliminated because of protocol deviations and/or insufficient data documentation, leaving 2,817 for further analysis.

Post-extraction Bleeding Incidence

Bleeding events including minor hemorrhagic episodes were reported for 35 out of 496 teeth (7.1%) of the warfarin group and for 49 out of 2,321 teeth (2.1%) of the non-warfarin group, with a total of 84 teeth. Clinically significant post-extraction bleeds (i.e., grade 2-2 or higher) were reported for 27 teeth, including 18 (3.6%) and 9 (0.4%) from the warfarin and non-warfarin groups, respectively (Table 1). ~~All bleeding episodes were controlled by local hemostatic interventions. No warfarin-treated patients showed a notable PT-INR change from baseline postoperatively, and none of the reported PT-INR values were above 3.0.~~

Breakdown of Removed Teeth by Sex and Study Group

The mean (SD) age of all study participants was 62.~~462~~17.596 years, and 1,446 and 1,371 teeth were removed from males (51.3%) and females (48.7%), respectively. The warfarin group had a mean (SD) age of 70.~~283~~10.929 years, and reported removal of 496 teeth, 320 from males (64.5%) and 176 from females (35.5%). Non-warfarin group had a

mean (SD) age of 60.424 (18.253) years, and reported removal of 2321 teeth, 1126 from males (48.5%) and 1,195 from females (51.5%) (Table 1).

The difference in post-extraction bleeding incidence between the warfarin group and non-warfarin group was 3.24% and its 95% CI was 1.49% to 4.99% (Table 2).

Risk Factors for Post-extraction Bleeding in Warfarin-Treated Patients

Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), ~~mandibular foramen conduction anesthesia~~ inferior alveolar nerve block (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) were significantly correlated with post-extraction bleeding (Table 3). In addition to these variables, position of the removed tooth, reasons for extraction, antiplatelet drugs, comorbidities possibly influencing hemostasis, and history of acute inflammation at extraction site were found to have P values smaller than 0.2 by univariate analysis. Consequently, these parameters were included as explanatory variables in the multivariate regression analysis. The results showed that age (OR: ~~7.93~~ 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding (Table 54).

DISCUSSION

~~We conducted a nation-wide, prospective multicenter observational study to compare post-extraction bleeding incidences between patients receiving and not receiving warfarin therapy. Both study groups reported low incidence rates of bleeding events. However, the warfarin group had higher incidence by 3.24% (95% CI: 1.49-4.99).~~

Clinically significant post-extraction hemorrhagic events occurred at an incidence of 0.4% in the group of patients not receiving warfarin in this study. Whereas in the warfarin-receiving group, although none of the PT-INR values measured within 7 days before surgery were greater than 3.0, post-extraction bleeding incidence rate was 3.6%, which was approximately 10 times higher than that observed in patients not receiving chronic warfarin therapy. Our results indicate that, albeit that absolute incidence rate is low, patients receiving warfarin therapy had a definitely higher probability of post-extraction bleeding than those who were not on chronic warfarin therapy. These findings suggest that when performing exodontia in a patient receiving chronic warfarin therapy, particularly in a situation such as emergency operation at nights or weekends or in a institution where additional procedures other than standard hemostatic methods could not be performed, clinical experience of the operator and the capability of the facility in performing advanced care should also be taken into consideration, instead of solely relying on the PT-INR values when planning the procedure.

Our study identified age (≥ 65 years), antiplatelet drugs, PT-INR, and history of acute inflammation at extraction site as significant risk factors for post-extraction hemorrhage in warfarin-treated patients. Instruments used for removal, reasons for extraction, and comorbidities possibly influencing hemostasis were not significantly contributed as risk factors.

There have been many studies evaluating safety and associated complications when performing tooth extraction in patients receiving warfarin.[1-20] Wahl et al evaluated 496 patients/524 tooth extractions where warfarin was temporarily discontinued prior to the procedure, and observed thromboembolism in 5 cases (0.95%), 4 out of which died.[1] In a cohort study, incidences of serious bleeding complications and thromboembolic events were

compared between the patients whose maintenance warfarin intake was discontinued in preparation of minor outpatient surgeries including dental surgery and the patients in which heparin bridging was utilized without warfarin cessation.[15] During the 1 month observation period after warfarin was discontinued, thromboembolic complication occurred in approximately 0.7% of the patients who discontinued warfarin, whereas serious bleeding complication was observed in 4 cases with heparin bridging and in 2 cases without heparin bridging.[15] A study conducted in Japan also found that in 1 out of 128 cases in which dental extraction was performed with discontinuation or reduction of the dose of warfarin, cerebral infarction occurred and the patient was deceased.[16] Those findings led to discussion on whether or not warfarin should be continued, or discontinued or reduced, with an emphasis on prevention of thromboembolic complications. In addition, multiple studies reported that dental extraction is safely performed and post-extraction bleeding can be sufficiently controlled by topical hemostasis only in patients receiving warfarin without discontinuing the mediation.[2-10] Based on these findings, the current guidelines recommend that dental extraction be performed with continuing maintenance dosage of warfarin.[11-13] However, Balevi et al recently reevaluated the data reported by Wahl et al with a distinct analytical approach and found that incidence of cardiovascular accident after 3 days of warfarin cessation was 0.059%, which was significantly lower than that was originally reported.[17, 18] Taken together, the literature indicate that thromboembolic complication does occur, though absolute numbers are small and suggest that decision whether or not to continue maintenance dose of warfarin when performing dental extraction in patients receiving warfarin should be made carefully taking risks and benefits that warfarin could cause into account. The present study was conducted to further identify risks and associating factors for post-extraction bleeding in patients receiving warfarin.

The present study is a nation-wide, multi-institutional prospective study and evaluated

frequency of clinically significant post-extraction bleeding and its difference between the non-warfarin and warfarin groups. Clinically significant post-extraction bleeding occurred in low rate in both study groups. Nonetheless, the difference between the two groups was 3.24% with its 95% confidence interval between 1.58 – 4.90%, suggesting that the difference can be as big as approximately 5%. In all cases of post-extraction bleeding, sufficient hemostasis was achieved only with topical measures, but about 10% of those patients required hemostasis after office hours at night. In the present study, all the extraction was performed by oral surgeon at a facility where emergency care is available 24 hrs a day, where sufficient hemostasis can be performed even after hours, but if clinically significant bleeding happened in a community dental clinic at night or in holidays, successful hemostasis in some of such bleeding could have been difficult. The present study revealed factors associated with increased incidence of post-extraction bleeding in patients receiving warfarin. Therefore, when performing dental extraction in high-risk patients such as those taking warfarin, capability of the facility for means of hemostasis other than simple topical hemostasis and availability of personnel at afterhours should carefully be considered.

Among the patients receiving warfarin, older patients showed lower risks for post-extraction bleeding in the present study. Few studies have addressed influence of patients' age on incidence of post-extraction bleeding. Mean PT-INR in the patients who experienced clinically significant post-extraction bleeding was 2.57 ± 0.62 in patients 65 years old or older, which was significantly higher compared to that in patients younger than 65 years old ($2.10 \pm 0.39, P = 0.048$). These results suggest that younger patients tend to experience clinically significant post-extraction bleeding at lower PT-INR, which might have contributed to the lower bleeding risks in the elderly patients in the present study.

Few studies reported to date examined the relationship between age and the incidence of post-extraction bleeding. Our finding indicated that extra caution should be taken when

conducting exodontia in elderly patients receiving warfarin therapy, and the frequency of such situations would increase with aging population.

A study that investigated the impact of comorbid conditions on hemostasis suggested that patients with liver dysfunction are another group at high risk for post-extraction bleeding.^[15,19] The present study did not identify liver dysfunction or other comorbid conditions that would affect hemostasis as a risk factor for increased incidence of post-extraction bleeding. The attribution of such condition may have been underestimated in the present study as only 4.2% of the study participants had ~~some sort of liver dysfunction~~chronic hepatitis.

Our results also showed that the incidence of post-extraction bleeding events increased with higher PT-INR, even though the values did not exceed 3.0. This finding suggests that a special attention would be needed in patients whose PT-INR are close to 3.0 or higher to prevent post-extraction hemorrhagic event. Because warfarin sensitivity may vary among individuals and different ethnic groups,^{7,22} further studies will be needed to verify if the current findings are generalizable to other ethnic groups. ~~To date, no randomized trial examining incidence of post extraction bleeding, comparing patients receiving only warfarin therapy versus those who also take anti platelet medications, has been reported. An observational study by Morimoto et al. reported no significant differences in the incidence rates between patients receiving warfarin therapy only and those receiving the combination of warfarin and antiplatelet medications.[6] In a cohort study that investigated the occurrences of general hemorrhagic events in Japanese patients receiving anticoagulants,[16] the incidence rates of hemorrhagic complications were higher in the group receiving the combination of warfarin and antiplatelet drugs than those receiving warfarin only. Morimoto et al. speculated in their report [6] that post extraction bleeding is in general controllable with topical compression or~~

other non-invasive means to achieve hemostasis even in patients receiving combination of warfarin and anti-platelet medications, whereas intracranial hemorrhages or other more serious hemorrhagic complications are not topically accessible, therefore leading to a higher bleeding incidence in the group of patients receiving anti-platelet drugs in addition to warfarin as found in a Cohort study.[20]

The study subjects in the latter study included population who requires anti-coagulation therapy in general, which would contain patients with severer co-morbidities that would contribute to higher incidence for hemorrhagic event. On the other hand, the studies by Morimoto et al. and ours focused on patients after tooth extraction, which could be managed by topical treatment. It is intriguing that the present study did not find use of anti-platelet medication as a risk factor for increasing incidence of post-extraction bleeding. The difference may be due to difference in study design or subjects included. Further study is necessary to determine if addition of anti-platelet medication increases a risk for post-extraction bleeding in patients receiving warfarin therapy.

No randomized comparative trials that addressed incidences of post-extraction bleeding in patients receiving warfarin with or without anti-platelet medicine has so far been reported. An observational study by Morimoto et al found no significant difference in incidences of post-extraction bleeding between the patients receiving warfarin alone and those in combination with an anti-platelet medicine.[6] In contrast, Scully et al reported that, in patients with oral surgeries, post-operative bleeding incidence was higher in patients under the combination therapy of warfarin and an anti-platelet medicine.[20] Besides reports regarding the bleeding events associated with oral surgeries, increased incidence of hemorrhagic complications in patients receiving anti-platelet medicine in addition to warfarin compared to those receiving warfarin only was observed in a cohort study in Japanese patients under

1
2
3 anti-coagulation therapies.[21]. The results from the present study suggested that incidence
4 for post-extraction bleeding is lower in patients receiving both warfarin and an anti-platelet
5 medicine. Although findings vary in those studies, anti-platelet medicine alone is in general
6 considered to minimally affect incidences of post-operative bleeding in the cases of dental
7 extraction[8] or of surgeries [22], and may as well in patients under the control of warfarin.

14 Suturing of wound and filling of the socket with oxidized cellulose or gel foam have been
15 widely recognized as efficient means of hemostasis after dental extraction.[23-25] However,
16 some guidelines do not necessarily recommend suture of the wound, while supporting the use
17 of oxidized cellulose, gelfoam or fibin glue.[8] Several reports also found that suturing would
18 could rather damage the tissue at the socket.[26,27] In the present study, incidences of
19 post-extraction bleeding in patients not receiving warfarin were not significantly different
20 between the patients whose wound was sutured and those without suture (0.6 and 0.2%,
21 respectively). However, we were unable to tell whether suturing increased the incidence of
22 post-extraction bleeding in the patients receiving warfarin as wounds were sutured in all the
23 patients receiving warfarin in the present study. Evaluation of the outcome of suturing in
24 patients receiving warfarin would be worthy of future study. Heparin bridging is another
25 effective means to prevent thromboembolism and to reduce risk for post-operative bleeding
26 [28,29], application of which is primarily limited to a major surgery that topical hemostasis is
27 not applicable. Efficacy of heparin bridging was evaluated by a randomized comparative
28 study,[30] which found no significant differences in incidences of post-extraction bleeding or
29 thromboembolic complications with and without addition of heparin bridging with continuing
30 warfarin therapy, concluding that heparin bridging is not required when dental extraction is
31 performed as long as topical hemostasis is applicable. On the other hand, comparative studies
32 examined cases of minor surgeries performed with cessation of warfarin with or without
33 additional heparin bridging reported severe hemorrhagic event in cases receiving heparin

bridging, though no thromboembolic complication had occurred.[31,32] Furthermore, heparin needs to be continuously administered intravenously when performing heparin bridging, necessitating hospital admission with resulting higher cost and demands for medical personnel. The results from the present study further supported the notion that topical hemostasis provides sufficient hemostasis in cases of simple tooth extraction without discontinuing warfarin, and therefore heparin bridging is not necessary.

Several aspects of our study design that may have affected the outcome of the present study should be noted. ~~First, we collected data of dental extraction cases performed only in institutions where care by one or more certified oral surgeons is available. This criterion was adopted to minimize the differences in skills of the operator. However, this criterion could have also resulted in lower than average post-extraction bleeding incidences for both warfarin and non-warfarin patients. There remains a reasonable possibility that the between-group differences would be higher if general dental clinics were included.~~ ~~Second~~First, we included PT-INR values measured within 7 days prior to tooth extraction, considering the availability of measurement results. However, because effects of warfarin can be affected by diet and other drugs, experts suggested to measure PT-INR within 24 [8,9,17,18,33,34] and 48 [19,35] hours before the procedure. The British Committee for Standards in Hematology recommended 72 hours before surgery [11]. ~~In this study, no patients showed a significant PT-INR change between before and after tooth extraction, and no reported values exceeded 3.0. Third, bleeding events were reported on the basis of removed teeth and not of individuals. We chose this design based on the previous findings reporting no significant correlation between the numbers of dental extractions and post-extraction bleeding incidences.[2,4,5,7]. The present study design is also superior as it takes the potential difference in risks of post-extraction bleeding by the position of the tooth and/or gingival condition into account. However, multiple counts from the same patient may have biased the results. Therefore,~~

pre-extraction PT-INR values we utilized may not have accurately reflected the coagulation status immediately prior to the extraction, skewing the results of our analyses. To minimize the bias, we conducted another PT-INR measurement in patients receiving warfarin who experienced clinically significant bleeding events soon after the event observation. In such patients, PT-INR values before and after the tooth extraction were 2.27 and 2.26, respectively, and not significantly changed. These data suggest that the possible bias derived from PT-INR values measured within 7 days in advance were minimal. Second, we performed all the analyses by tooth, not by patients. We hypothesized, based on previous studies that found no significant correlation between the numbers of tooth extracted and incidence of post extraction bleeding,[2,4,5,7] that risks for post-extraction bleeding may vary depending the position and/or conditions of the tooth extracted even in the same individual. In order for detecting possible influence of local factors, such as position of tooth extracted (foretooth vs. molar tooth) and gum conditions (presence of inflammation and/or inappropriate granulation) on risks for post-extraction bleeding, we chose to present our data by tooth, despite a possible bias of including some of the patient data multiple times when multiple teeth was extracted from a single patient. When the same dataset was analyzed by patient, incidence rate of clinically significant post-extraction bleeding was 2.77% in 361 patients receiving warfarin, while the incident rate among 1,785 patients in non-warfarin group was 0.39%, with the 95% confidential interval for the difference of incidence between the two groups was between 0.65 and 4.10%, which was very similar to the findings from the analyses performed by tooth. These data suggest that the bias that might arise from the analyses by tooth was minimal. Third, evaluation of the post-extraction bleeding events was not blinded and choice of secondary hemostasis means were left at the discretion by the operator in charge, which might have affected the outcome of our analyses. However, the definition of the clinically significant bleeding events was made clear, minimizing the influence by the person who

evaluated the individual event.

CONCLUSION

The 95% confidence interval for the difference in the of post-extraction bleeding incidences between the patients receiving or not receiving warfarin ~~or not~~ was approximately 5%:1.58 – 4.90% (risk ratio 9.31). Age, PT-INR, and history of acute inflammation at extraction site were risk factors for post-extraction bleeding in warfarin receiving patients. ~~Warfarin receiving patients had a considerable risk for post-extraction bleeding, even if their PT-INR values did not exceed 3.0. This study suggest that patients whose PT-INR values are close to 3.0 or who have other risk factors for uncontrollable bleeding should undergo dental extraction under the management of an oral surgeon specifying in invasive dental procedures or at a dental facility that has access to a hospital that could provide advanced medical care in the event of uncontrollable bleeding.~~

Competing interest; None disclosed.

Contributorship statement

H. Iwabuchi designed the study protocol and wrote the manuscript. H. Imai analyzed the data and contributed to edition of the manuscript. H. Nakao also participated in data analyses. Y. Imai is the Principle Investigator of the present study. Rest of the authors participated in data collection.

Competing interests

I/We have read and understood BMJ policy on declaration of interests and declare the following interests.

Copyright and license for the publication:

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.”

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding

There is no involvement of funding sources in this research.

Data sharing statement

Data sharing: patient level data [and/or] full dataset [and/or] technical appendix [and/or] statistical code [and/or] are available from the corresponding author upon request. Consent for additional data sharing was not obtained but the presented data are anonymised and risk of identification is low.

For peer review only

REFERENCES

1 Wahl MJ. Dental surgery in anticoagulated patients. Arch Inter ~~Med~~
~~1998~~Med1998;158:1610-16.

2 Evans IL, Sayers MS, Gibbons AJ, et al. Can warfarin be continued during dental
extraction?Results of a randomized controlled trial. Br J Oral ~~Maxillofac Surg~~
~~2002~~MaxillofacSurg2002;40:248-252.

3 Sacco R, Sacco M, ~~Carpeneo M~~CarpeneoM,et al.Oral surgery in patients on oral
anticoagulant therapy: A randomized comparison of different intensity targets. Oral Surg
Oral med Oral Pathol Oral RadiolEndod.2007;104:e18-21.

4 Al-Mubarak S, Al-Ali N, Rass MA, et al.Evaluation of dental extractions,suturing and
INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. Br
Dent J.2007;203:1-5.

5 Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery:Should
the Anticoagulation regiment be altered? J Oral Maxillofac Surg.2000;58:131-5.

6 Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in
patients on oral antithrombotic therapy. J Oral Maxillofac Surg.2008;66:51-7.

7 Barrero MV, Knezevic M, Martin MT, et al. Oral surgery in the patients undergoing oral
anticoagulant therapy. Med oral.2002;7:63-70.

8 Aframian DJ, Lalla RV, Peterson DE. Management of dental patients taking common
hemostasis –altering medications. Oral Surg Oral med Oral Pathol Oral
RadiolEndod.2007;103(suppl 1):S45e1-11.

9 Goodchild JH, Donaldson M. An evidence-based dentistry challenge:Treating patients on
warfarin(Coumadin). Dental aimplantol ~~Update 2009~~Update2009;20:1-8.

10 Nematullah A, Alabousi A, Blanas N, et al. Dental surgery for patients on anticoagulant
therapy with warfarin:asystematic review and meta-analysis. J can Dent

- Assoc.2009;75:41-41i.
- 11 Perry DJ, Noakes TJC, Helliwell PS. Guidelines for the management of patients on oral anticoagulants requiring dental surgery. Br Dent J.2007;203:389-393.
 - 12 Sasanuki H, et al: Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease. Circ J.2004;~~68-suppl~~68suppl IV:1153-1219.
 - 13 Jcs Joint Working Group: Guidelines for pharmacotherapy of atrial fibrillation –Digest Version-. Circ J.2010;74:2479-2500.
 - 14 Japanese Society of Dentistry for Medically Compromised Patient,Japanese Society of Oral and Maxillofacial Surgeons, Japanese Society of ~~Gerodontology~~Gerodontology:The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction.2010 ~~version—Gakujutsusha—Corporation Tokyo~~versionGakujutsusha CorporationTokyo 2010.
 - 15 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Inter Med. 2008;168:63-69.
 - 16 Ogiuchi H, Ando T, Tanaka M, et al. Clinical reports on dental extraction from patients undergoing oral anticoagulant therapy. Bull Tokyo Dent Coll. 1985;26:205-212.
 - 17 Balevi B. Should warfarin be discontinued before a dental extraction? A decision-tree analysis. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2010;110:691–697.
 - 18 Balevi B.Should warfarin be discontinued before a dental extraction? Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2012;113:150-152.
 - 1519 Devani P, Lavery KM, Howell CJT. Dental extractions in patients on warfarin –Is alternation of anticoagulant regime necessary? Br J Oral Maxillofac Surg.1998;36:107-111.
 - 20 Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy.Oral Surg Oral Med Oral Pathol 2002;94:57-64.

1621 Toyoda K, Yasaka M, Iwade K, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease –A prospective, multicenter, observational study. Stroke.2008;39:1740-45.

22 Maulaz AB, Bezerra DC, Michel P, et al. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol.2005;62:1217-1220.

23 Halfpenny W, Fraser JS, Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. Oral Surg Oral Med Oral Phthol Oral Radiol Endnd.2001;92:257-259.

24 Carter G, Goss A, Lloyd J, et al. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. J Oral Maxillofac Surg.2003;61:1432-1435.

25 Blinder D, Manor Y, Martinowitz U, et al. Dental extraction in patients maintained on continued oral anticoagulant. Comparison of local hemostatic modalities. Oral Surg Oral Med Oral Phthol Oral Radiol Endnd.1999;88:137-140.

26 Salam S, Yusuf H, Milosevic A. Bleeding after dental extractions in patients taking warfarin. Br J Oral Maxillofac Surg. 2007;45:463-466.

27 Al-Belasy FA, Amer MZ. Hemostatic effect of n-butyl-2-cyano- acrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. J Oral Maxillofac Surg. 2003; 61: 1405-1409.

28 Dunn AS, Alexander G, G Turpie. Perioperative management of patients receiving oral b Anticoagulants A systemic review. Arch Intern Med. 2003;163:901-908.

29 Kovacs MJ, Kearon C, Rodger M, et al; Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. Circulation. 2004;110:1658-1663.

30 Bajkin BV, Popovic SL, Selakovic SDJ. Randomized prospective trial comparing

- bridging therapy using low-molecular-weight heparin with maintenance of oral anticoagulation during extraction of teeth. J Oral Maxillofac Surg. 2009; 67: 990-995.
- 31 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Intern Med. 2008;168:63-69.
- 32 Bloomer CR. Excessive hemorrhage after dental extractions using low-molecular-weight heparin(Lovenox) anticoagulation therapy. J Oral Maxillofac Surg. 2004;62:101-103.
- 1733 Chugani V. Management of dental patients on warfarin therapy in a primary care setting. Dental Update.2004;31:379-384.
- 1834 Pototski M, Amenabar JM: Dental management of patients receiving anticoagulation or antiplatelet treatment. J Oral Sci.2007;49:253-8.
- 1935 Brennan MT, Hong C, Furney SL, et al. Utility of an international normalized ratio testing device in a hospital-based dental practice. J Am Dent Assoc.2008;139:697-703.

Table 1. Breakdown of extracted teeth by important classification variables

No. of teeth by:		Warfarin n=496	No Warfarin n=2321	Total N = 2817	P value
Age (years)					
	< 65	124 (25.0)	1131 (48.7)	1255 (44.6)	< 0.0001
	≥ 65	372 (75.0)	1190 (51.3)	1562 (55.4)	
Sex					
	Male	320 (64.5)	1126 (48.5)	1446 (51.3)	< 0.0001
	Female	176 (35.5)	1195 (51.5)	1371 (48.7)	
Type					
	Foretooth	132 (26.6)	663 (28.6)	795 (28.2)	0.550
	Premolar	127 (25.6)	552 (23.8)	679 (24.1)	
	Molar	237 (47.8)	1106 (47.7)	1343 (47.7)	
Instrument					
	Forceps only	171 (34.5)	604 (26.0)	775 (27.5)	0.000
	Elavators only	226 (45.6)	919 (39.6)	1145 (40.6)	
	Forceps and elevators	99 (20.0)	798 (34.4)	897 (31.8)	
Cause for extraction					
	Periodontitis	160 (32.3)	533 (23.0)	693 (24.6)	< 0.0001
	Caries	87 (17.5)	477 (20.6)	564 (20.0)	
	Apical periodontitis	219 (44.2)	1002 (43.2)	1221 (46.6)	
	Wisdom tooth pericoronitis	23 (4.6)	192 (8.3)	215 (7.6)	
	Other	7 (1.4)	117 (5.0)	124 (4.4)	
Status of antiplatelet therapy					
	Yes	122 (24.6)	433 (18.7)	555 (19.7)	0.003
Use of local anesthetics containing vasoconstrictors					
	Yes	491 (99.0)	2265 (97.6)	2756 (97.8)	0.105
Use of inferior alveolar nerve block					
	Yes	14 (2.8)	82 (3.5)	96 (3.4)	0.429
Comorbidity possibly influencing hemostatis					
	Hypertension	267 (53.8)	715 (30.8)	982 (34.9)	< 0.0001
	Diabetes mellitus	89 (17.9)	267 (11.5)	356 (12.6)	
	Chronic hepatitis	21 (4.2)	110 (4.7)	131 (4.7)	
	Other	68 (13.7)	212 (9.1)	280 (9.9)	
	Multiple disorders	341 (68.8)	1039 (44.8)	1380 (49.0)	
History of acute inflammation at extraction site					
	Yes	216 (43.5)	829 (35.7)	1045 (37.1)	0.001
Gingival inflammation at extraction site					
	None	298 (60.1)	1266 (54.5)	1564 (55.5)	0.000
	Mild	95 (19.2)	264 (11.4)	359 (12.7)	
	Moderate	13 (2.6)	38 (1.6)	51 (1.8)	
	Severe	90 (18.1)	753 (32.4)	843 (29.9)	
Abnormal granulation tissue in extraction socket					

None	87 (17.5)	818 (35.2)	905 (32.1)	
Little	230 (46.4)	917 (39.5)	1147 (40.7)	
Medium	134 (27.0)	441 (19.0)	575 (20.4)	0.003
Much	45 (9.1)	145 (6.2)	190 (6.7)	
Severity of post-extraction bleeding				
G1	9 (1.8)	29 (1.2)	38 (1.3)	
G2-1	8 (1.6)	11 (0.5)	19 (0.7)	
G2-2	1 (0.2)	8 (0.3)	9 (0.3)	
G3	17 (3.4)	1 (0.04)	18 (0.6)	
total	35 (7.1)	49 (2.1)	84 (3.0)	< 0.0001
G2-2+G3	18 (3.6)	9 (0.4)	27 (1.0)	< 0.0001
PT-INR				
(mean ± SD)	1.90±0.49			

Table 2. ~~Difference in Incidences of clinically significant~~ post-extraction bleeding ~~incidences between and~~
~~their difference in~~ patients receiving and not receiving warfarin

			95%CL (%)	
	Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence(%)	LOWER	UPPER
Warfarin	3.63			
No		3.24	0.0158	0.0490
Warfarin	0.39			
				(%)

(%)

Table 3. Univariate analysis of post-extraction bleeding events by potential risk factors

		Incidence of post-extraction bleeding (%)	OR	95%CL		P-value
				Lower	Upper	
Age (years)						
	< 65	8.9	1 (Ref)			
	≥ 65	1.9	0.197	0.075	0.520	0.001*
Sex						
	Male	3.4	1 (Ref)			
	Female	4.0	1.164	0.443	3.057	0.759
Type						
	Foretooth or premolar	2.3	1 (Ref)			
	Molar	5.1	2.2249	0.830	6.091	0.111
Instrument						
	Forceps only	2.9	1 (Ref)			
	Elevators alone or with forceps	4	1.383	0.485	3.947	0.544
Cause for extraction						
	Caries, apical periodontitis, or other	2.6	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	5.5	2.204	0.854	5.688	0.102
Status of antiplatelet therapy						
	No	4.5	1 (Ref)			
	Yes	0.8	0.174	0.023	1.318	0.090
PT-INR						
			3.635	1.5640	8.448	0.003*
Use of vasoconstrictors						
	No	4.1	1 (Ref)			
	Yes	0				
Use of local anesthetics containing vasoconstrictors						
	No	0	1 (Ref)			
	Yes	3.7				
Use of inferior alveolar nerve block						
	No	3.3	1 (Ref)			
	Yes	14.3	4.854	1.002	23.513	0.050*
Comorbidity possibly influencing hemostatis						
	No	5.8	1 (Ref)			
	Yes	2.6	0.440	0.171	1.131	0.088
History of acute inflammation at extraction site						
	No	2.5	1 (Ref)			
	Yes	5.1	2.093	0.7970	5.492	0.134
Gingival inflammation at extraction site						
	None to mild	3.3	1 (Ref)			
	Moderate to severe	4.9	1.491	0.519	4.283	0.458
		29				

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abnormal granulation tissue in extraction socket					
None to little	2.2	1 (Ref)			
Medium to much	6.1	2.900	1.1040	7.619	0.031*

For peer review only

Table 4. Multivariate analysis of post-extraction bleeding events by potential risk factors

		OR	95%CL		P-Value
			Lower	Upper	
Age (years)					
	< 65	1 (Ref)			
	≥ 65	0.126	0.035	0.448	0.001*
Type					
	Foretooth or premolar	1 (Ref)			
	Molar	0.953	0.288	3.151	0.937
Cause for extraction					
	Caries, apical periodontitis, or other	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	2.301	0.742	7.142	0.149
Status of antiplatelet therapy					
	No	1 (Ref)			
	Yes	0.100	0.010	0.986	0.049*
PT-INR					
		7.797	2.2930	26.510	0.001*
Use of inferior alveolar nerve block					
	No	1 (Ref)			
	Yes	2.437	0.336	17.659	0.378
Comorbidity possibly influencing hemostatis					
	No	1 (Ref)			
	Yes	0.503	0.157	1.612	0.247
History of acute inflammation at extraction site					
	No	1 (Ref)			
	Yes	3.722	1.0850	12.773	0.037*
Abnormal granulation tissue in extraction socket					
	None to little	1 (Ref)			
	Medium to much	2.895	0.8940	9.369	0.076

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

		Item No	Recommendation
Title and Abstract	✓	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
	✓		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	✓	2	Explain the scientific background and rationale for the investigation being reported
Objectives	✓	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	✓	4	Present key elements of study design early in the paper
Setting	✓	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	✓	6	(a) Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants
	N/A		(b) Cohort study
Variables	✓	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effects modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	✓	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	✓	9	Describe any efforts to address potential sources of bias
Study size	✓	10	Explain how the study size was arrived at
	✓	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	✓	12	(a) Describe all statistical methods, including those used to control for confounding
	✓		(b) Describe any methods used to examine subgroups and interactions
	✓		(c) Explain how missing data were addressed
	✓		(d) Cross-sectional study – If applicable, describe analytical methods taking accounting of sampling strategy
	✓		(e) Describe any sensitivity analyses
Results			
	✓	13	(a) Report numbers of individuals at each stage of study – e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed
	N/A		(b) Give reasons for non-participation at each stage
	N/A		(c) Consider use of a flow diagram
Descriptive data	✓	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
	✓		(b) Indicate numbers of participants with missing data for each variable of interest
	N/A		(c) Cohort study
Outcome data	✓	15	Cross-sectional study – Report numbers of outcomes events or summary measures
Main results	✓	16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (e.g. 95 confidence interval). Make clear which confounders were adjusted for and why they were included
	✓		(b) Report category boundaries when continuous variable were categorized
	✓		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	✓	17	Report other analyses done – e.g. analyses of subgroups, and sensitivity analyses

Discussion		
✓	18	Summarize key results with reference to study objectives
		Discuss limitations of the study, taking into account sources of potential bias or imprecision.
✓	19	Discuss both direction and magnitude of any potential bias
		Give a cautious overall interpretations of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
✓	20	
✓	21	Discuss the generalizability (external validity) or the study results
Other information		
Funding		
✓	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

BMJ Open

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005777.R2
Article Type:	Research
Date Submitted by the Author:	10-Sep-2014
Complete List of Authors:	Iwabuchi, Hiroshi; Kanagawa Dental University, Department of Oral and Maxillofacial Surgery Imai, Yutaka; Dokkyo Medical University School of Medicine, Department of Oral & Maxillofacial Surgery Asanami, Soichiro; Sanno Hospital, Department of Dentistry and Implant Center Shirakawa, Masayori; Nippon Dental University, Yamane, Gen-yuki; Tokyo Dental College, Ogiuchi, Hideki; Tokyo Women's Medical University, Kurashina, Kenji; Aizawa Hospital, Oral & Dental Center Miyata, Masaru; Ishikawa Prefectural Central Hospital, Department of Dentistry and Oral Surgery Nakao, Hiroyuki; National Institute of Public Health, Department of Epidemiology Imai, Hirohisa; National Institute of Public Health, Department of Epidemiology
Primary Subject Heading:	Dentistry and oral medicine
Secondary Subject Heading:	Dentistry and oral medicine
Keywords:	ORAL & MAXILLOFACIAL SURGERY, ORAL MEDICINE, Oral & maxillofacial surgery < SURGERY

SCHOLARONE™
Manuscripts

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Hiroshi Iwabuchi¹⁾, Yutaka Imai²⁾, Soichiro Asanami³⁾, Masayori Shirakawa⁴⁾, Gen-yuki Yamane⁵⁾, Hideki Ogiuchi⁶⁾, Kenji Kurashina⁷⁾, Masaru Miyata⁸⁾, Hiroyuki Nakao⁹⁾, Hirohisa Imai⁹⁾

Department of Oral and Maxillofacial Surgery, Kanagawa Dental University¹⁾, Department of Oral & Maxillofacial Surgery, Dokkyo Medical University School of Medicine²⁾, Department of Dentistry and Implant Center, Sanno Hospital³⁾, Nippon Dental University⁴⁾, Tokyo Dental College⁵⁾, Tokyo Women's Medical University⁶⁾, Aizawa Hospital, Oral & Dental Center⁷⁾, Department of Dentistry and Oral Surgery, Ishikawa Prefectural Central Hospital⁸⁾, Department of Epidemiology, National Institute of Public Health of Japan⁹⁾

Corresponding author: Hiroshi Iwabuchi
Department of Oral and Maxillofacial Surgery, Kanagawa Dental University
82 Inaokamachi, Yokosuka-shi, Kanagawa 238-8580, Japan
TEL: 81-46-822-8810, ext 2395
e-mail: iwabuchi@kdu.ac.jp

Word count:

Keywords: tooth extraction, post-extraction bleeding, warfarin, risk factors

ABSTRACT

Objectives: We investigated incidence and risk factors for post-extraction bleeding in patients receiving warfarin and those not under anti-coagulation therapy.

Design: Crossectional multicenter observational study

Setting: 26 hospitals where oral surgeon is available.

Participants: Data on 2,817 teeth (496: receiving warfarin, 2,321: not receiving warfarin; mean age (SD): 62.2 (17.6)) extracted from November 1, 2008 to March 31, 2010, were collected. Warfarin-receiving patients were eligible when PT-INR measured within 7days prior to the extraction was less than 3.0.

Interventions: Simple dental extraction was performed and incidence of post-extraction bleeding and comorbidities were recorded.

Primary and Secondary Outcome Measures: Post extraction bleeding not controlled by basic hemostatis procedure as clinically significant.

Results: Bleeding events were reported for 35 (7.1%) and 49 (2.1%) teeth, of which 18 (3.6%) and 9 (0.4%) teeth were considered as clinically significant, in warfarin and non-warfarin groups, respectively, the difference between which was 3.24% (confidence intervals 1.58 – 4.90%). The incidence rates by patients were 2.77 and 0.39%, in warfarinize- and non-warfarin group, respectively (incidence difference 2.38%, confidence intervals 0.65 – 4/10%). Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), mandibular foramen conduction anesthesia (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) significantly correlate with the bleeding incidence. Multivariate analysis revealed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding.

Conclusion: Our results suggest that there is slight but significant increase in incidences for the post-extraction bleeding in patients receiving warfarin. Although absolute incidence was low in both groups, the bleeding risk is not negligible.

Strength and Limitation of this Study

- The present study examined difference of the incidences for post-extraction bleeding between the patients receiving and not-receiving warfarin, which few previous studies to date have been reported.
- The study included dental facilities where at least one or more certified oral surgeons are available in order to standardize skills of the operators and capability of the facilities for providing advanced care in the event of significant bleeding.
- We also analyzed the risk factors for post-extraction bleeding events in patients receiving warfarin.
- Due to the study design, we may have underestimated the incidence of post-extraction bleeding that may occur in community dental clinics.
- Although we tried to standardize the dental extraction procedure, there might have been inter-facility differences.

INTRODUCTION

Until recently, the common procedure for tooth extraction in patients continuously receiving warfarin or other antiplatelet therapy was to discontinue or reduce the dose to minimize the risks of odontorrhagia. However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1] Thereafter, many studies including randomized trials [2-4], Cohort studies [5-7] and meta-analyses [8-10] have been conducted, all of which reported no significant differences in incidences of post-extraction bleeding and/or other hemorrhagic complications, concluding that, in patients whose prothrombin time- international normalized ratio (PT-INR) is within desirable therapeutic range, dental extraction can be performed safely without cessation of warfarin. Clinical guidelines published after these studies advised that patients whose PT-INR values were within the recommended therapeutic ranges should continue warfarin when undergoing dental extraction.[11–13] However, there have been little studies that specifically addressed difference in the bleeding incidences and its 95% confidence interval comparing tooth extraction cases in patients receiving and not receiving warfarin.

Given these circumstances, we evaluated the difference in the post-extraction bleeding incidences in otherwise healthy control without warfarin administration (non-WF group) and in patients under reasonable coagulation control with warfarin (WF group). We selected the subjects for the latter group whose PT-INR was 3.0 or lower at the time of the procedure, as the PT-INR of 3.0 was indicated as the maximum safety threshold for tooth extraction in the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction in Japanese.[14] We also investigated the risk factors for the incidence of post-extraction bleeding in patients receiving warfarin therapy.

MATERIALS AND METHODS

This was a prospective multicenter observational study of post-extraction bleeding events in patients receiving and not receiving warfarin therapy.

Study Period and Eligibility Criteria

Twenty-six hospitals located across Japan participated. This study included patients who underwent simple tooth extraction from November 1, 2008 to March 31, 2010 at the department of oral surgery of these hospitals and who met the eligibility criteria listed below. Simple tooth extraction referred to a tooth removed without traumatizing the surrounding alveolar bone or elevating a mucoperiosteal flap.

Eligibility criteria included the following: 20 or more years of age at the time of tooth extraction; no contraindications for tooth extraction; surgery was performed by oral surgeon with a minimum of 3 years of experience in dental practice; the oral extraction procedure lasted for no longer than 15 minutes; and platelet count within 7 days prior to the procedure was normal. In addition, in patients receiving warfarin therapy, PT-INR measured within 7 days prior to the procedure should be less than 3.0. Patients receiving anti-platelet medication were not excluded but recorded as such. According to “The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction” [14], we instructed the participating hospitals that dental extraction should be performed without discontinuing or reducing the dose of warfarin in patients whose PT-INR was not exceeding 3.0 when measured within 7 days prior to the procedure.

Study Variables

The variables analyzed in this study were: bleeding events, patient’s age and sex, position of the removed tooth, instruments used for removal (forceps only, elevators only, forceps and elevators), reasons for extraction, use of antiplatelet drugs, PT-INR values measured within 7 days before exodontia (only for patients receiving chronic warfarin therapy), comorbidities possibly influencing hemostasis, use of vasoconstrictors, combined use of local anesthetics

and vasoconstrictors, use of inferior alveolar nerve block, severity of gingivitis after extraction (none, mild, moderate, severe), formation of abnormal granulation tissue in the extraction socket (none, little, medium, much), history of acute inflammation at extraction site, and post-extraction infection.

Hemostasis

The hemostatic methods for patients not receiving warfarin were chosen at the discretion of the dentist or oral surgeon performing the procedure. In patients on warfarin therapy, either absorbable oxidized cellulose or gelatin sponge was implanted into the alveolar socket, and wound margins were sutured. In both groups of patients, topical hemostatic agents other than epinephrine, systemic hemostatic agents, and splints were prohibited until primary hemostasis was observed. In patients who had multiple teeth extracted in one session, possible post-extraction bleeding was examined for each tooth. In a patient receiving warfarin, the post-extraction procedure defined above was performed each time after a tooth was removed.

Permitted Drugs

Use of local anesthetics containing vasoconstrictors (e.g., epinephrine and felypressin) was allowed at doses commonly practiced. In warfarin-treated patients, penicillins or cefems (e.g., cefcapenepivoxil and cefditoren pivoxil) was the primary choice of prophylactic antibiotics for their minimal interaction with warfarin. For those who were allergic to penicillins, clarithromycin was recommended. Use of analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors was allowed at ordinary doses.

Confirmation of Hemostasis

All patients were asked to bite down on a roll gauze for a maximum of 30 minutes for astriction of the wound. After release of the biting pressure, the wound was examined for hemostasis. Patients visited the hospital on the next day of surgery to check for possible bleeding, and were instructed to present at the hospital for treatment, if bleeding should occur later. The follow-up period was 7 days postoperatively.

Follow-up of Bleeding Events

If a patient had a bleeding event during the follow-up period, the severity of the hemorrhage and blood pressure were recorded. If the patient was on warfarin therapy, his or her PR-INR values were measured in addition.

Evaluation of Bleeding Events

In this study, bleeding events occurring in the follow-up period were classified into one of the following 5 grades: 0, no bleeding; 1, excessive blood clotting in the socket, no treatment required; 2-1, hemostasis achieved by compressing the wound longer than 30 minutes; 2-2, oozing hemorrhage observed on or after the next day of the procedure, which hemostasis was achieved by simple compression; 3, bleeding required treatments other than wound compression, such as application of compression brace and/or coagulation by electrotome was needed. Grade 2-2 and higher events were regarded as clinically significant, and were defined as post-extraction bleeds in this study.

Statistical Analysis

Data were collected by a tooth, but not by a patient. This means that patients who had multiple teeth extraction were counted multiple times for the number of extracted teeth. Data were then sorted and analyzed by the anatomical positions. The difference in post-extraction

bleeding incidence between patients receiving and not receiving warfarin therapy and its 95% confidence interval (CI) were calculated. In addition, a multivariate logistic regression analysis was conducted to identify risk factors for post-extraction bleeding in warfarin-treated patients. Adjusted odds ratios (ORs), their 95% CIs and *p*-values were calculated controlling for major confounders. Explanatory variables with a significance level of $P < 0.20$ on univariate analyses were included in the multivariate logistic regression model. Statistical analyses were performed using the SPSS software (version 15.0, SPSS Japan Inc., Tokyo, Japan).

Ethics

The objective of this study was explained in details to potential study participants so that they could make an informed decision. Informed consent was obtained orally or by a written document, according to the recommendation to the ethics committee of each participating facilities. Patients' personal information was stored in a de-identified but linkable format during the 7-day follow-up period, and was rendered completely anonymous thereafter. This study was reviewed and approved by the ethics committee of the National Hospital Organization Tochigi Medical Center, Tochigi, Japan, prior to its conduct. The approved protocol was distributed to the participating hospitals to keep the uniformity of the study.

RESULTS

Totally, 3,515 case reports were submitted from the participating investigators. Of these, 698 cases were eliminated because of protocol deviations and/or insufficient data documentation, leaving 2,817 for further analysis.

Post-extraction Bleeding Incidence

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Bleeding events including minor hemorrhagic episodes were reported for 35 out of 496 teeth (7.1%) of the warfarin group and for 49 out of 2,321teeth (2.1%) of the non-warfarin group, with a total of 84 teeth. Clinically significant post-extraction bleeds (i.e., grade 2-2 or higher) were reported for 27 teeth, including 18 (3.6%) and 9 (0.4%) from the warfarin and non-warfarin groups, respectively (Table 1).

Breakdown of Removed Teeth by Sex and Study Group

The mean (SD) age of all study participants was 62.2 (17.6) years, and 1,446 and 1,371 teeth were removed from males (51.3%) and females (48.7%), respectively. The warfarin group had a mean (SD) age of 70.3 (10.9) years, and reported removal of 496 teeth, 320 from males (64.5%) and 176 from females (35.5%). Non-warfarin group had a mean (SD) age of 60.4 (18.3) years, and reported removal of 2321 teeth, 1126 from males (48.5%) and 1,195 from females (51.5%) (Table 1).

The difference in post-extraction bleeding incidence between the warfarin group and non-warfarin group was 3.24% and its 95% CI was1.58% to 4.90%. When analyze by patient, clinically significant bleeding occurred in total of 361 out of 2,146 patients (2.77 and 0.39%, in warfarin- and non-warfarin group, respectively, incidence difference between which was 2.38% (95% CI, 0.65 – 4.10%; Table 2).

Risk Factors for Post-extraction Bleeding in Warfarin-Treated Patients

Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), inferior alveolar nerve block (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) were significantly correlated with post-extraction bleeding (Table 3). In addition to these variables, position of the removed tooth, reasons for extraction, antiplatelet drugs, comorbidities possibly influencing hemostasis,

and history of acute inflammation at extraction site were found to have P values smaller than 0.2 by univariate analysis. Consequently, these parameters were included as explanatory variables in the multivariate regression analysis. The results showed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding (Table 4).

DISCUSSION

Recent report brought attention to cases of potentially-lethal thromboembolic complication associated with dental extraction in patients under anti-coagulation therapy with warfarin when warfarin was temporarily discontinued in preparation for dental extraction.[1,15,16] On the other hand, multiple studies reported that dental extraction is safely performed and post-extraction bleeding can be sufficiently controlled by topical hemostasis only in patients receiving warfarin without discontinuing the medication.[2-10] Based on these findings, the current guidelines recommend that dental extraction be performed with continuing maintenance dosage of warfarin.[11-13] In warfarinized patients, thromboembolic events were reported in varying frequency in literature ranging as low as 0.059% [17, 18] to as high as 1% [1] when warfarin was discontinued prior to dental extraction, while few life-threatening bleeding complication have been reported. These findings have strongly suggested that warfarin should not be discontinued when performing dental extraction in warfarinized patients. [6,19-21].

The present study is a nation-wide, multi-institutional prospective study and evaluated frequency of clinically significant post-extraction bleeding and its difference between the non-warfarin and warfarin groups. Clinically significant post-extraction bleeding occurred in low rate in both study groups. Nonetheless, the difference between the two groups was 3.24%

with its 95% confidence interval between 1.58 – 4.90%.

Among the patients receiving warfarin, older patients showed lower risks for post-extraction bleeding in the present study. Few studies have addressed influence of patients' age on incidence of post-extraction bleeding. Mean PT-INR in the patients who experienced clinically significant post-extraction bleeding was 2.57 ± 0.62 in patients 65 years old or older, which was significantly higher compared to that in patients younger than 65 years old ($2.10 \pm 0.39, P = 0.048$). These results suggest that younger patients tend to experience clinically significant post-extraction bleeding at lower PT-INR, which might have contributed to the lower bleeding risks in the elderly patients in the present study.

Few studies reported to date examined the relationship between age and the incidence of post-extraction bleeding. Our finding indicated that extra caution should be taken when conducting exodontia in elderly patients receiving warfarin therapy, and the frequency of such situations would increase with aging population.

A study that investigated the impact of comorbid conditions on hemostasis suggested that patients with liver dysfunction are another group at high risk for post-extraction bleeding.[22] The present study did not identify liver dysfunction or other comorbid conditions that would affect hemostasis as a risk factor for increased incidence of post-extraction bleeding. The attribution of such condition may have been underestimated in the present study as only 4.2% of the study participants had chronic hepatitis.

Our results also showed that the incidence of post-extraction bleeding events increased with higher PT-INR, even though the values did not exceed 3.0. This finding suggests that a special attention would be needed in patients whose PT-INR are close to 3.0 or higher to prevent post-extraction hemorrhagic event. Because warfarin sensitivity may vary among individuals and different ethnic groups, further studies will be needed to verify if the current

findings are generalizable to other ethnic groups.

No randomized comparative trials that addressed incidences of post-extraction bleeding in patients receiving warfarin with or without anti-platelet medicine has so far been reported. An observational study by Morimoto et al found no significant difference in incidences of post-extraction bleeding between the patients receiving warfarin alone and those in combination with an anti-platelet medicine.[6] In contrast, Scully et al reported that, in patients with oral surgeries, post-operative bleeding incidence was higher in patients under the combination therapy of warfarin and an anti-platelet medicine.[23] Besides reports regarding the bleeding events associated with oral surgeries, increased incidence of hemorrhagic complications in patients receiving anti-platelet medicine in addition to warfarin compared to those receiving warfarin only was observed in a cohort study in Japanese patients under anti-coagulation therapies.[24]. The results from the present study suggested that incidence for post-extraction bleeding is lower in patients receiving both warfarin and an anti-platelet medicine. Although findings vary in those studies, anti-platelet medicine alone is in general considered to minimally affect incidences of post-operative bleeding in the cases of dental extraction[8] or of surgeries [25], and may as well in patients under the control of warfarin.

Suturing of wound and filling of the socket with oxidized cellulose or gelfoam have been widely recognized as efficient means of hemostasis after dental extraction.[26-28] However, some guidelines do not necessarily recommend suture of the wound, while supporting the use of oxidized cellulose, gelfoam or fibrin glue.[8] Several reports also found that suturing would could rather damage the tissue at the socket.[29,30]In the present study, incidences of post-extraction bleeding in patients not receiving warfarin were not significantly different between the patients whose wound was sutured and those without suture (0.6 and 0.2%, respectively). However, we were unable to tell whether suturing increased the incidence of post-extraction bleeding in the patients receiving warfarin as wounds were sutured in all the

patients receiving warfarin in the present study. Evaluation of the outcome of suturing in patients receiving warfarin would be worthy of future study. Heparin bridging is another effective means to prevent thromboembolism and to reduce risk for post-operative bleeding.[31,32], application of which is primarily limited to a major surgery that topical hemostasis is not applicable. Efficacy of heparin bridging was evaluated by a randomized comparative study,[33] which found no significant differences in incidences of post-extraction bleeding or thromboembolic complications with and without addition of heparin bridging with continuing warfarin therapy, concluding that heparin bridging is not required when dental extraction is performed as long as topical hemostasis is applicable. On the other hand, comparative studies examined cases of minor surgeries performed with cessation of warfarin with or without additional heparin bridging reported severe hemorrhagic event in cases receiving heparin bridging, though no thromboembolic complication had occurred.[34,35] Furthermore, heparin needs to be continuously administered intravenously when performing heparin bridging, necessitating hospital admission with resulting higher cost and demands for medical personnel. The results from the present study further supported the notion that topical hemostasis provides sufficient hemostasis in cases of simple tooth extraction without discontinuing warfarin, and therefore heparin bridging is not necessary. Several aspects of our study design that may have affected the outcome of the present study should be noted. First,, we included PT-INR values measured within 7 days prior to tooth extraction, considering the availability of measurement results. However, because effects of warfarin can be affected by diet and other drugs, experts suggested to measure PT-INR within 24 [8,9,36,37] and 48 [38] hours before the procedure. The British Committee for Standards in Hematology recommended 72 hours before surgery [11]. Therefore, pre-extraction PT-INR values we utilized may not have accurately reflected the coagulation status immediately prior to the extraction, skewing the results of our analyses. To minimize the bias, we conducted another

PT-INR measurement in patients receiving warfarin who experienced clinically significant bleeding events soon after the event observation. In such patients, PT-INR values before and after the tooth extraction were 2.27 and 2.26, respectively, and not significantly changed. These data suggest that the possible bias derived from PT-INR values measured within 7 days in advance were minimal. Second, we performed all the analyses by tooth, not by patients. We hypothesized, based on previous studies that found no significant correlation between the numbers of tooth extracted and incidence of post extraction bleeding, [2,4,5,7] that risks for post-extraction bleeding may vary depending the position and/or conditions of the tooth extracted even in the same individual. In order for detecting possible influence of local factors, such as position of tooth extracted (foretooth vs. molar tooth) and gum conditions (presence of inflammation and/or inappropriate granulation) on risks for post-extraction bleeding, we chose to present our data by tooth, despite a possible bias of including some of the patient data multiple times when multiple teeth was extracted from a single patient. When analyzed by patient, clinically significant post-extraction bleeding occurred in 2.77 and 0.39% in warfarin and non-warfarin group, respectively, difference between which was 2.38% (95% CI, 0.65 – 4.10%). and was similar to that found in analysis by tooth. These data suggest that the bias that might arise from the analyses by tooth was minimal. Third, evaluation of the post-extraction bleeding events was not blinded and choice of secondary hemostasis means were left at the discretion by the operator in charge, which might have affected the outcome of our analyses. However, the definition of the clinically significant bleeding events was made clear, minimizing the influence by the person who evaluated the individual event. Lastly, we compared incidences of post-extraction bleeding in patients under warfarin therapy who underwent dental extraction without cessation of warfarin with those who are not receiving warfarin therapy. On the other hand, most of previous studies assessed post-extraction events in warfarinized patients with or without cessation of warfarin prior to dental extraction, Such

1
2
3 difference in study population might also have resulted in different finding in the present
4
5 study
6
7
8

9
10 **CONCLUSION**

11 The difference in incidence rates of post-extraction bleeding between warfarin and
12 non-warfarin group was 3.24% (95% CI, 1.49 – 4.99%). Age, PT-INR, and history of acute
13 inflammation at extraction site were risk factors for post-extraction bleeding in warfarin
14 receiving patients.
15
16
17
18
19

20
21
22
23 **Contributorship Statement:** H. Iwabuchi designed the study protocol and wrote the
24 manuscript. H. Imai analyzed the data and contributed to edition of the manuscript. H. Nakao
25 also participated in data analyses. Y. Imai is the Principle Investigator of the present study.
26 Rest of the authors participated in data collection.
27
28
29

30
31
32 **Competing interest;** None disclosed.
33

34 **Data sharing:** patient level data [and/or] full dataset [and/or] technical appendix [and/or]
35 statistical code [and/or] are available from the corresponding author upon request. Consent for
36 additional data sharing was not obtained but the presented data are anonymised and risk of
37 identification is low.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

- 1 Wahl MJ. Dental surgery in anticoagulated patients. *Arch Inter Med*1998;158:1610-16.
- 2 Evans IL, Sayers MS, Gibbons AJ, et al. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. *Br J Oral Maxillofac Surg*2002;40:248-252.
- 3 Sacco R, Sacco M, CarpenedoM, et al. Oral surgery in patients on oral anticoagulant therapy: A randomized comparison of different intensity targets. *Oral Surg Oral med Oral Pathol Oral RadiolEndod.* 2007;104:e18-21.
- 4 Al-Mubarak S, Al-Ali N, Rass MA, et al. Evaluation of dental extractions, suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. *Br Dent J.*2007;203:1-5.
- 5 Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery:Should the Anticoagulation regiment be altered? *J Oral Maxillofac Surg.*2000;58:131-5.
- 6 Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in patients on oral antithrombotic therapy. *J Oral Maxillofac Surg.*2008;66:51-7.
- 7 Barrero MV, Knezevic M, Martin MT, et al. Oral surgery in the patients undergoing oral anticoagulant therapy. *Med oral.*2002;7:63-70.
- 8 Aframian DJ, Lalla RV, Peterson DE. Management of dental patients taking common hemostasis –altering medications. *Oral Surg Oral med Oral Pathol Oral RadiolEndod.*2007;103(suppl 1):S45e1-11.
- 9 Goodchild JH, Donaldson M. An evidence-based dentistry challenge:Treating patients on warfarin(Coumadin). *Dental aimplantol Update*2009;20:1-8.
- 10 Nematullah A, Alabousi A, Blanas N, et al. Dental surgery for patients on anticoagulant therapy with warfarin:asystematic review and meta-analysis. *J can Dent Assoc.*2009;75:41-41i.

11 Perry DJ, Noakes TJC, Helliwell PS. Guidelines for the management of patients on oral anticoagulants requiring dental surgery. *Br Dent J.*2007;203:389-393.

12 Sasanuki H, et al: Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease. *Circ J.*2004;68suppl IV:1153-1219.

13 Jcs Joint Warking Group: Guidelines for pharmacotherapy of atrial fibrillation –Digest Version-. *Circ J.*2010;74:2479-2500.

14 Japanese Society of Dentistry for Medically Compromised Patient, Japanese Society of Oral and Maxillofacial Surgeons, Japanese Society of Gerodontology: The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction. 2010 version Gakujutsusha Corporation Tokyo 2010.

15 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Inter Med.* 2008;168:63-69.

16 Ogiuchi H, Ando T, Tanaka M, et al. Clinical reports on dental extraction from patients undergoing oral anticoagulant therapy. *Bull Tokyo Dent Coll.* 1985;26:205-212.

17 Balevi B. Should warfarin be discontinued before a dental extracion? A decision-tree analysis. *Oral Surg Oral Med Oral Pathol Oral RadiolEndod* 2010;110:691–697.

18 Balevi B.Should warfarin be discontinued before a dental extraction? *Oral Surg Oral Med Oral Pathol Oral RadiolEndod* 2012;113:150-152.

19 Gaspar R, Brenner B, Ardekian L, et al. Use of tranexamic acid mouthwash to prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication. *Quintessence Int* 1997;28:375-9.

20 Blinder D, Manor Y, Martinowitz U, et al. Dental extractions in patients maintained on oral anticoagulant therapy: comparison of INR value with occurrence of postoperative bleeding. *Int J Oral MaxillofacSurg* 2001;30(6):518-21.

21 Karsli ED, Erdogan O, Esen E, et al. Comparison of the effects of warfarin and heparin

- on bleeding caused by dental extraction: a clinical study. *J Oral Maxillofac Surg*. 2011;69:2500-7.
- 22 Devani P, Lavery KM, Howell CJT. Dental extractions in patients on warfarin –Is alternation of anticoagulant regime necessary? *Br J Oral Maxillofac Surg*. 1998;36:107-111.
- 23 Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy. *Oral Surg Oral Med Oral Pathol* 2002;94:57-64.
- 24 Toyoda K, Yasaka M, Iwade K, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease –A prospective, multicenter, observational study. *Stroke*. 2008;39:1740-45.
- 25 Maulaz AB, Bezerra DC, Michel P, et al. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. *Arch Neurol*. 2005;62:1217-1220.
- 26 Halfpenny W, Fraser JS, Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;92:257-259.
- 27 Carter G, Goss A, Lloyd J, et al. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. *J Oral Maxillofac Surg*. 2003;61:1432-1435.
- 28 Blinder D, Manor Y, Martinowitz U, et al. Dental extraction in patients maintained on continued oral anticoagulant. Comparison of local hemostatic modalities. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999;88:137-140.
- 29 Salam S, Yusuf H, Milosevic A. Bleeding after dental extractions in patients taking warfarin. *Br J Oral Maxillofac Surg*. 2007;45:463-466.
- 30 Al-Belasy FA, Amer MZ. Hemostatic effect of n-butyl-2-cyanoacrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. *J Oral Maxillofac Surg*. 2003; 61:

1405-1409.

31 Dunn AS,Alexander G,G Turpie. Perioperative management of patients receiving oral b
Anticoagulants A systemic review. Arch Intern Med. 2003;163:901-908.

32 Kovacs MJ, Kearon C, Rodger M, et al; Single-arm study of bridging therapy eith
low-molecular-weight heparin for patients at risk of arterial embolism who require
temporary interruption of warfarin. Circulation. 2004;110:1658-1663.

33 Bajkin BV, Popovic SL, Selakovic SDJ. Randomized prospective trial comparing
bridging therapy using low-molecular-weight heparin with maintenance of oral
anticoagulation during extraction of teeth. J Oral Maxillofac Surg. 2009; 67: 990-995.

34 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term
interruption of warfarin therapy. Arch Intern Med. 2008;168:63-69.

35 Bloomer CR. Excessive hemorrhage after dental extractions using low-molecular-
weight heparin (Lovenox) anticoagulation therapy. J Oral Maxillofac Surg.
2004;62:101-103.

36 Chugani V. Management of dental patients on warfarin therapy in a primary care setting.
Dental Update.2004;31:379-384.

37 Pototski M, Amenabar JM: Dental management of patients receiving anticoagulation or
antiplatelet treatment. J Oral Sci.2007;49:253-8.

38 Brennan MT, Hong C, Furney SL, et al. Utility of an international normalized ratio
testing device in a hospital-based dental practice. J Am Dent Assoc.2008;139:697-703.

Table 1. Breakdown of extracted teeth by important classification variables

No. of teeth by:		Warfarin n=496	No Warfarin n=2321	Total N = 2817	P value
Age (years)					
	< 65	124 (25.0)	1131 (48.7)	1255 (44.6)	< 0.0001
	≥ 65	372 (75.0)	1190 (51.3)	1562 (55.4)	
Sex					
	Male	320 (64.5)	1126 (48.5)	1446 (51.3)	< 0.0001
	Female	176 (35.5)	1195 (51.5)	1371 (48.7)	
Type					
	Foretooth	132 (26.6)	663 (28.6)	795 (28.2)	0.550
	Premolar	127 (25.6)	552 (23.8)	679 (24.1)	
	Molar	237 (47.8)	1106 (47.7)	1343 (47.7)	
Instrument					
	Forceps only	171 (34.5)	604 (26.0)	775 (27.5)	0.000
	Elevators only	226 (45.6)	919 (39.6)	1145 (40.6)	
	Forceps and elevators	99 (20.0)	798 (34.4)	897 (31.8)	
Cause for extraction					
	Periodontitis	160 (32.3)	533 (23.0)	693 (24.6)	< 0.0001
	Caries	87 (17.5)	477 (20.6)	564 (20.0)	
	Apical periodontitis	219 (44.2)	1002 (43.2)	1221 (46.6)	
	Wisdom tooth pericoronitis	23 (4.6)	192 (8.3)	215 (7.6)	
	Other	7 (1.4)	117 (5.0)	124 (4.4)	
Status of antiplatelet therapy					
	Yes	122 (24.6)	433 (18.7)	555 (19.7)	0.003
Use of local anesthetics containing vasoconstrictors					
	Yes	491 (99.0)	2265 (97.6)	2756 (97.8)	0.105
Use of inferior alveolar nerve block					
	Yes	14 (2.8)	82 (3.5)	96 (3.4)	0.429
Comorbidity possibly influencing hemostasis					
	Hypertension	267 (53.8)	715 (30.8)	982 (34.9)	< 0.0001
	Diabetes mellitus	89 (17.9)	267 (11.5)	356 (12.6)	
	Chronic hepatitis	21 (4.2)	110 (4.7)	131 (4.7)	
	Other	68 (13.7)	212 (9.1)	280 (9.9)	
	Multiple disorders	341 (68.8)	1039 (44.8)	1380 (49.0)	
History of acute inflammation at extraction site					
	Yes	216 (43.5)	829 (35.7)	1045 (37.1)	0.001
Gingival inflammation at extraction site					
	None	298 (60.1)	1266 (54.5)	1564 (55.5)	0.000
	Mild	95 (19.2)	264 (11.4)	359 (12.7)	
	Moderate	13 (2.6)	38 (1.6)	51 (1.8)	
	Severe	90 (18.1)	753 (32.4)	843 (29.9)	
Abnormal granulation tissue in extraction socket					

None	87 (17.5)	818 (35.2)	905 (32.1)	
Little	230 (46.4)	917 (39.5)	1147 (40.7)	
Medium	134 (27.0)	441 (19.0)	575 (20.4)	0.003
Much	45 (9.1)	145 (6.2)	190 (6.7)	
Severity of post-extraction bleeding				
G1	9 (1.8)	29 (1.2)	38 (1.3)	
G2-1	8 (1.6)	11 (0.5)	19 (0.7)	
G2-2	1 (0.2)	8 (0.3)	9 (0.3)	
G3	17 (3.4)	1 (0.04)	18 (0.6)	
total	35 (7.1)	49 (2.1)	84 (3.0)	< 0.0001
G2-2+G3	18 (3.6)	9 (0.4)	27 (1.0)	< 0.0001
PT-INR				
(mean ± SD)	1.90±0.49			

Table 2. Incidences of clinically significant post-extraction bleeding and their difference in patients receiving and not receiving warfarin

		Incidence over total numbers of teeth extracted (%)			
		Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence (%)	95% CL	
				Lower	Upper
Warfarin	3.63				
No			3.24	1.58	4.90
Warfarin	0.39				
		Incidence over total numbers of study subjects (%)			
		Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence (%)	95% CL	
				Lower	Upper
Warfarin	2.77				
No			2.38	0.65	4.10
Warfarin	0.39				

Table 3. Univariate analysis of post-extraction bleeding events by potential risk factors

		Incidence of post-extraction bleeding (%)	OR	95% CL		P-value
				Lower	Upper	
Age (years)						
	< 65	8.9	1 (Ref)			
	≥ 65	1.9	0.197	0.075	0.520	0.001*
Sex						
	Male	3.4	1 (Ref)			
	Female	4.0	1.164	0.443	3.057	0.759
Type						
	Foretooth or premolar	2.3	1 (Ref)			
	Molar	5.1	2.2249	0.830	6.091	0.111
Instrument						
	Forceps only	2.9	1 (Ref)			
	Elevators alone or with forceps	4	1.383	0.485	3.947	0.544
Cause for extraction						
	Caries, apical periodontitis, or other	2.6	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	5.5	2.204	0.854	5.688	0.102
Status of antiplatelet therapy						
	No	4.5	1 (Ref)			
	Yes	0.8	0.174	0.023	1.318	0.090
PT-INR						
			3.635	1.5640	8.448	0.003*
Use of vasoconstrictors						
	No	4.1	1 (Ref)			
	Yes	0				
Use of local anesthetics containing vasoconstrictors						
	No	0	1 (Ref)			
	Yes	3.7				
Use of inferior alveolar nerve block						
	No	3.3	1 (Ref)			
	Yes	14.3	4.854	1.002	23.513	0.050*
Comorbidity possibly influencing hemostatis						
	No	5.8	1 (Ref)			
	Yes	2.6	0.440	0.171	1.131	0.088
History of acute inflammation at extraction site						
	No	2.5	1 (Ref)			
	Yes	5.1	2.093	0.7970	5.492	0.134
Gingival inflammation at extraction site						
	None to mild	3.3	1 (Ref)			
	Moderate to severe	4.9	1.491	0.519	4.283	0.458
		23				

**Abnormal granulation tissue in
extraction socket**

None to little	2.2	1 (Ref)			
Medium to much	6.1	2.900	1.1040	7.619	0.031*

For peer review only

Table 4. Multivariate analysis of post-extraction bleeding events by potential risk factors

		OR	95% CL		P-Value
			Lower	Upper	
Age (years)					
	< 65	1 (Ref)			
	≥ 65	0.126	0.035	0.448	0.001*
Type					
	Foretooth or premolar	1 (Ref)			
	Molar	0.953	0.288	3.151	0.937
Cause for extraction					
	Caries, apical periodontitis, or other	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	2.301	0.742	7.142	0.149
Status of antiplatelet therapy					
	No	1 (Ref)			
	Yes	0.100	0.010	0.986	0.049*
PT-INR		7.797	2.2930	26.510	0.001*
Use of inferior alveolar nerve block					
	No	1 (Ref)			
	Yes	2.437	0.336	17.659	0.378
Comorbidity possibly influencing hemostatis					
	No	1 (Ref)			
	Yes	0.503	0.157	1.612	0.247
History of acute inflammation at extraction site					
	No	1 (Ref)			
	Yes	3.722	1.0850	12.773	0.037*
Abnormal granulation tissue in extraction socket					
	None to little	1 (Ref)			
	Medium to much	2.895	0.8940	9.369	0.076

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Hiroshi Iwabuchi¹⁾, Yutaka Imai²⁾, Soichiro Asanami³⁾, Masayori Shirakawa⁴⁾, Gen-yuki Yamane⁵⁾, Hideki Ogiuchi⁶⁾, Kenji Kurashina⁷⁾, Masaru Miyata⁸⁾, Hiroyuki Nakao⁹⁾, Hirohisa Imai⁹⁾

Department of Oral and Maxillofacial Surgery, Kanagawa Dental University¹⁾, Department of Oral & Maxillofacial Surgery, Dokkyo Medical University School of Medicine²⁾, Department of Dentistry and Implant Center, Sanno Hospital³⁾, Nippon Dental University⁴⁾, Tokyo Dental College⁵⁾, Tokyo Women's Medical University⁶⁾, Aizawa Hospital, Oral & Dental Center⁷⁾, Department of Dentistry and Oral Surgery, Ishikawa Prefectural Central Hospital⁸⁾, Department of Epidemiology, National Institute of Public Health of Japan⁹⁾

Corresponding author: Hiroshi Iwabuchi

Department of Oral and Maxillofacial Surgery, Kanagawa Dental University

82 Inaokamachi, Yokosuka-shi, Kanagawa 238-8580, Japan

TEL: 81-46-822-8810, ext 2395

e-mail: iwabuchi@kdu.ac.jp

Word count:

Keywords: tooth extraction, post-extraction bleeding, warfarin, risk factors

ABSTRACT

Objectives: We investigated incidence and risk factors for post-extraction bleeding in patients receiving warfarin and those not under anti-coagulation therapy.

Design: Crossectional multicenter observational study

Setting: 26 hospitals where oral surgeon is available.

Participants: Data on 2,817 teeth (496: receiving warfarin, 2,321: not receiving warfarin; mean age (SD): 62.2 (17.6)) extracted from November 1, 2008 to March 31, 2010, were collected. Warfarin-receiving patients were eligible when PT-INR measured within 7days prior to the extraction was less than 3.0.

Interventions: Simple dental extraction was performed and incidence of post-extraction bleeding and comorbidities were recorded.

Primary and Secondary Outcome Measures: Post extraction bleeding not controlled by basic hemostatis procedure as clinically significant.

Results: Bleeding events were reported for 35 (7.1%) and 49 (2.1%) teeth, of which 18 (3.6%) and 9 (0.4%) teeth were considered as clinically significant, in warfarin and non-warfarin groups, respectively, the difference between which was 3.24% (confidence intervals 1.58 – 4.90%). The incidence rates by patients were 2.77 and 0.39%, in warfarinize- and non-warfarin group, respectively (incidence difference 2.38%, confidence intervals 0.65 – 4/10%). Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), mandibular foramen conduction anesthesia (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) significantly correlate with the bleeding incidence. Multivariate analysis revealed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding.

Conclusion: Our results suggest that there is slight but significant increase in incidences for the post-extraction bleeding in patients receiving warfarin. Although absolute incidence was low in both groups, the bleeding risk is not negligible.

Strength and Limitation of this Study

- The present study examined difference of the incidences for post-extraction bleeding between the patients receiving and not-receiving warfarin, which few previous studies to date have been reported.
- The study included dental facilities where at least one or more certified oral surgeons are available in order to standardize skills of the operators and capability of the facilities for providing advanced care in the event of significant bleeding.
- We also analyzed the risk factors for post-extraction bleeding events in patients receiving warfarin.
- Due to the study design, we may have underestimated the incidence of post-extraction bleeding that may occur in community dental clinics.
- Although we tried to standardize the dental extraction procedure, there might have been inter-facility differences.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

INTRODUCTION

Until recently, the common procedure for tooth extraction in patients continuously receiving warfarin or other antiplatelet therapy was to discontinue or reduce the dose to minimize the risks of odontorrhagia. However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1] Thereafter, many studies including randomized trials [2-4], Cohort studies [5-7] and meta-analyses [8-10] have been conducted, all of which reported no significant differences in incidences of post-extraction bleeding and/or other hemorrhagic complications, concluding that, in patients whose prothrombin time- international normalized ratio (PT-INR) is within desirable therapeutic range, dental extraction can be performed safely without cessation of warfarin. Clinical guidelines published after these studies advised that patients whose PT-INR values were within the recommended therapeutic ranges should continue warfarin when undergoing dental extraction.[11–13] However, there have been little studies that specifically addressed difference in the bleeding incidences and its 95% confidence interval comparing tooth extraction cases in patients receiving and not receiving warfarin.

Given these circumstances, we evaluated the difference in the post-extraction bleeding incidences in otherwise healthy control without warfarin administration (non-WF group) and in patients under reasonable coagulation control with warfarin (WF group). We selected the subjects for the latter group whose PT-INR was 3.0 or lower at the time of the procedure, as the PT-INR of 3.0 was indicated as the maximum safety threshold for tooth extraction in the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction in Japanese.[14] We also investigated the risk factors for the incidence of post-extraction bleeding in patients receiving warfarin therapy.

MATERIALS AND METHODS

This was a prospective multicenter observational study of post-extraction bleeding events in patients receiving and not receiving warfarin therapy.

Study Period and Eligibility Criteria

Twenty-six hospitals located across Japan participated. This study included patients who underwent simple tooth extraction from November 1, 2008 to March 31, 2010 at the department of oral surgery of these hospitals and who met the eligibility criteria listed below. Simple tooth extraction referred to a tooth removed without traumatizing the surrounding alveolar bone or elevating a mucoperiosteal flap.

Eligibility criteria included the following: 20 or more years of age at the time of tooth extraction; no contraindications for tooth extraction; surgery was performed by oral surgeon with a minimum of 3 years of experience in dental practice; the oral extraction procedure lasted for no longer than 15 minutes; and platelet count within 7 days prior to the procedure was normal. In addition, in patients receiving warfarin therapy, PT-INR measured within 7 days prior to the procedure should be less than 3.0. Patients receiving anti-platelet medication were not excluded but recorded as such. According to “The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction” [14], we instructed the participating hospitals that dental extraction should be performed without discontinuing or reducing the dose of warfarin in patients whose PT-INR was not exceeding 3.0 when measured within 7 days prior to the procedure.

Study Variables

The variables analyzed in this study were: bleeding events, patient’s age and sex, position of the removed tooth, instruments used for removal (forceps only, elevators only, forceps and elevators), reasons for extraction, use of antiplatelet drugs, PT-INR values measured within 7 days before exodontia (only for patients receiving chronic warfarin therapy), comorbidities possibly influencing hemostasis, use of vasoconstrictors, combined use of local anesthetics

and vasoconstrictors, use of inferior alveolar nerve block, severity of gingivitis after extraction (none, mild, moderate, severe), formation of abnormal granulation tissue in the extraction socket (none, little, medium, much), history of acute inflammation at extraction site, and post-extraction infection.

Hemostasis

The hemostatic methods for patients not receiving warfarin were chosen at the discretion of the dentist or oral surgeon performing the procedure. In patients on warfarin therapy, either absorbable oxidized cellulose or gelatin sponge was implanted into the alveolar socket, and wound margins were sutured. In both groups of patients, topical hemostatic agents other than epinephrine, systemic hemostatic agents, and splints were prohibited until primary hemostasis was observed. In patients who had multiple teeth extracted in one session, possible post-extraction bleeding was examined for each tooth. In a patient receiving warfarin, the post-extraction procedure defined above was performed each time after a tooth was removed.

Permitted Drugs

Use of local anesthetics containing vasoconstrictors (e.g., epinephrine and felypressin) was allowed at doses commonly practiced. In warfarin-treated patients, penicillins or cefems (e.g., cefcapenepivoxil and cefditoren pivoxil) was the primary choice of prophylactic antibiotics for their minimal interaction with warfarin. For those who were allergic to penicillins, clarithromycin was recommended. Use of analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors was allowed at ordinary doses.

Confirmation of Hemostasis

All patients were asked to bite down on a roll gauze for a maximum of 30 minutes for astriction of the wound. After release of the biting pressure, the wound was examined for hemostasis. Patients visited the hospital on the next day of surgery to check for possible bleeding, and were instructed to present at the hospital for treatment, if bleeding should occur later. The follow-up period was 7 days postoperatively.

Follow-up of Bleeding Events

If a patient had a bleeding event during the follow-up period, the severity of the hemorrhage and blood pressure were recorded. If the patient was on warfarin therapy, his or her PR-INR values were measured in addition.

Evaluation of Bleeding Events

In this study, bleeding events occurring in the follow-up period were classified into one of the following 5 grades: 0, no bleeding; 1, excessive blood clotting in the socket, no treatment required; 2-1, hemostasis achieved by compressing the wound longer than 30 minutes; 2-2, oozing hemorrhage observed on or after the next day of the procedure, which hemostasis was achieved by simple compression; 3, bleeding required treatments other than wound compression, such as application of compression brace and/or coagulation by electrotome was needed. Grade 2-2 and higher events were regarded as clinically significant, and were defined as post-extraction bleeds in this study.

Statistical Analysis

Data were collected by a tooth, but not by a patient. This means that patients who had multiple teeth extraction were counted multiple times for the number of extracted teeth. Data were then sorted and analyzed by the anatomical positions. The difference in post-extraction

bleeding incidence between patients receiving and not receiving warfarin therapy and its 95% confidence interval (CI) were calculated. In addition, a multivariate logistic regression analysis was conducted to identify risk factors for post-extraction bleeding in warfarin-treated patients. Adjusted odds ratios (ORs), their 95% CIs and *p*-values were calculated controlling for major confounders. Explanatory variables with a significance level of *P* < 0.20 on univariate analyses were included in the multivariate logistic regression model. Statistical analyses were performed using the SPSS software (version 15.0, SPSS Japan Inc., Tokyo, Japan).

Ethics

The objective of this study was explained in details to potential study participants so that they could make an informed decision. Informed consent was obtained orally or by a written document, according to the recommendation to the ethics committee of each participating facilities. Patients’ personal information was stored in a de-identified but linkable format during the 7-day follow-up period, and was rendered completely anonymous thereafter. This study was reviewed and approved by the ethics committee of the National Hospital Organization Tochigi Medical Center, Tochigi, Japan, prior to its conduct. The approved protocol was distributed to the participating hospitals to keep the uniformity of the study.

RESULTS

Totally, 3,515 case reports were submitted from the participating investigators. Of these, 698 cases were eliminated because of protocol deviations and/or insufficient data documentation, leaving 2,817 for further analysis.

Post-extraction Bleeding Incidence

Bleeding events including minor hemorrhagic episodes were reported for 35 out of 496 teeth (7.1%) of the warfarin group and for 49 out of 2,321 teeth (2.1%) of the non-warfarin group, with a total of 84 teeth. Clinically significant post-extraction bleeds (i.e., grade 2-2 or higher) were reported for 27 teeth, including 18 (3.6%) and 9 (0.4%) from the warfarin and non-warfarin groups, respectively (Table 1).

Breakdown of Removed Teeth by Sex and Study Group

The mean (SD) age of all study participants was 62.2 (17.6) years, and 1,446 and 1,371 teeth were removed from males (51.3%) and females (48.7%), respectively. The warfarin group had a mean (SD) age of 70.3 (10.9) years, and reported removal of 496 teeth, 320 from males (64.5%) and 176 from females (35.5%). Non-warfarin group had a mean (SD) age of 60.4 (18.3) years, and reported removal of 2321 teeth, 1126 from males (48.5%) and 1,195 from females (51.5%) (Table 1).

The difference in post-extraction bleeding incidence between the warfarin group and non-warfarin group was 3.24% and its 95% CI was 1.58% to 4.90%. When analyze by patient, clinically significant bleeding occurred in total of 361 out of 2,146 patients (2.77 and 0.39%, in warfarin- and non-warfarin group, respectively, incidence difference between which was 2.38% (95% CI, 0.65 – 4.10%; Table 2).

Risk Factors for Post-extraction Bleeding in Warfarin-Treated Patients

Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), inferior alveolar nerve block (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) were significantly correlated with post-extraction bleeding (Table 3). In addition to these variables, position of the removed tooth, reasons for extraction, antiplatelet drugs, comorbidities possibly influencing hemostasis,

and history of acute inflammation at extraction site were found to have P values smaller than 0.2 by univariate analysis. Consequently, these parameters were included as explanatory variables in the multivariate regression analysis. The results showed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding (Table 4).

DISCUSSION

Recent report brought attention to cases of potentially-lethal thromboembolic complication associated with dental extraction in patients under anti-coagulation therapy with warfarin when warfarin was temporarily discontinued in preparation for dental extraction.[1,15,16] On the other hand, multiple studies reported that dental extraction is safely performed and post-extraction bleeding can be sufficiently controlled by topical hemostasis only in patients receiving warfarin without discontinuing the mediation.[2-10] Based on these findings, the current guidelines recommend that dental extraction be performed with continuing maintenance dosage of warfarin.[11-13] In warfarinized patients, thromboembolic events were reported in varying frequency in literature raging as low as 0.059% [17, 18] to as high as 1% [1] when warfarin was discontinued prior to dental extraction, while few life-threatening bleeding complication have been reported. These findings have strongly suggested that warfarin should not be discontinued when performing dental extraction in warfarinized patients. [6,19-21].

The present study is a nation-wide, multi-institutional prospective study and evaluated frequency of clinically significant post-extraction bleeding and its difference between the non-warfarin and warfarin groups. Clinically significant post-extraction bleeding occurred in low rate in both study groups. Nonetheless, the difference between the two groups was 3.24%

with its 95% confidence interval between 1.58 – 4.90%.

Among the patients receiving warfarin, older patients showed lower risks for post-extraction bleeding in the present study. Few studies have addressed influence of patients' age on incidence of post-extraction bleeding. Mean PT-INR in the patients who experienced clinically significant post-extraction bleeding was 2.57 ± 0.62 in patients 65 years old or older, which was significantly higher compared to that in patients younger than 65 years old ($2.10 \pm 0.39, P = 0.048$). These results suggest that younger patients tend to experience clinically significant post-extraction bleeding at lower PT-INR, which might have contributed to the lower bleeding risks in the elderly patients in the present study.

Few studies reported to date examined the relationship between age and the incidence of post-extraction bleeding. Our finding indicated that extra caution should be taken when conducting exodontia in elderly patients receiving warfarin therapy, and the frequency of such situations would increase with aging population.

A study that investigated the impact of comorbid conditions on hemostasis suggested that patients with liver dysfunction are another group at high risk for post-extraction bleeding.[22] The present study did not identify liver dysfunction or other comorbid conditions that would affect hemostasis as a risk factor for increased incidence of post-extraction bleeding. The attribution of such condition may have been underestimated in the present study as only 4.2% of the study participants had chronic hepatitis.

Our results also showed that the incidence of post-extraction bleeding events increased with higher PT-INR, even though the values did not exceed 3.0. This finding suggests that a special attention would be needed in patients whose PT-INR are close to 3.0 or higher to prevent post-extraction hemorrhagic event. Because warfarin sensitivity may vary among individuals and different ethnic groups, further studies will be needed to verify if the current

findings are generalizable to other ethnic groups.

No randomized comparative trials that addressed incidences of post-extraction bleeding in patients receiving warfarin with or without anti-platelet medicine has so far been reported. An observational study by Morimoto et al found no significant difference in incidences of post-extraction bleeding between the patients receiving warfarin alone and those in combination with an anti-platelet medicine.[6] In contrast, Scully et al reported that, in patients with oral surgeries, post-operative bleeding incidence was higher in patients under the combination therapy of warfarin and an anti-platelet medicine.[23] Besides reports regarding the bleeding events associated with oral surgeries, increased incidence of hemorrhagic complications in patients receiving anti-platelet medicine in addition to warfarin compared to those receiving warfarin only was observed in a cohort study in Japanese patients under anti-coagulation therapies.[24]. The results from the present study suggested that incidence for post-extraction bleeding is lower in patients receiving both warfarin and an anti-platelet medicine. Although findings vary in those studies, anti-platelet medicine alone is in general considered to minimally affect incidences of post-operative bleeding in the cases of dental extraction[8] or of surgeries [25], and may as well in patients under the control of warfarin.

Suturing of wound and filling of the socket with oxidized cellulose or gelfoam have been widely recognized as efficient means of hemostasis after dental extraction.[26-28] However, some guidelines do not necessarily recommend suture of the wound, while supporting the use of oxidized cellulose, gelfoam or fibrin glue.[8] Several reports also found that suturing would could rather damage the tissue at the socket.[29,30]In the present study, incidences of post-extraction bleeding in patients not receiving warfarin were not significantly different between the patients whose wound was sutured and those without suture (0.6 and 0.2%, respectively). However, we were unable to tell whether suturing increased the incidence of post-extraction bleeding in the patients receiving warfarin as wounds were sutured in all the

patients receiving warfarin in the present study. Evaluation of the outcome of suturing in patients receiving warfarin would be worthy of future study. Heparin bridging is another effective means to prevent thromboembolism and to reduce risk for post-operative bleeding.[31,32], application of which is primarily limited to a major surgery that topical hemostasis is not applicable. Efficacy of heparin bridging was evaluated by a randomized comparative study,[33] which found no significant differences in incidences of post-extraction bleeding or thromboembolic complications with and without addition of heparin bridging with continuing warfarin therapy, concluding that heparin bridging is not required when dental extraction is performed as long as topical hemostasis is applicable. On the other hand, comparative studies examined cases of minor surgeries performed with cessation of warfarin with or without additional heparin bridging reported severe hemorrhagic event in cases receiving heparin bridging, though no thromboembolic complication had occurred.[34,35] Furthermore, heparin needs to be continuously administered intravenously when performing heparin bridging, necessitating hospital admission with resulting higher cost and demands for medical personnel. The results from the present study further supported the notion that topical hemostasis provides sufficient hemostasis in cases of simple tooth extraction without discontinuing warfarin, and therefore heparin bridging is not necessary. Several aspects of our study design that may have affected the outcome of the present study should be noted. First,, we included PT-INR values measured within 7 days prior to tooth extraction, considering the availability of measurement results. However, because effects of warfarin can be affected by diet and other drugs, experts suggested to measure PT-INR within 24 [8,9,36,37] and 48 [38] hours before the procedure. The British Committee for Standards in Hematology recommended 72 hours before surgery [11]. Therefore, pre-extraction PT-INR values we utilized may not have accurately reflected the coagulation status immediately prior to the extraction, skewing the results of our analyses. To minimize the bias, we conducted another

PT-INR measurement in patients receiving warfarin who experienced clinically significant bleeding events soon after the event observation. In such patients, PT-INR values before and after the tooth extraction were 2.27 and 2.26, respectively, and not significantly changed. These data suggest that the possible bias derived from PT-INR values measured within 7 days in advance were minimal. Second, we performed all the analyses by tooth, not by patients. We hypothesized, based on previous studies that found no significant correlation between the numbers of tooth extracted and incidence of post extraction bleeding, [2,4,5,7] that risks for post-extraction bleeding may vary depending the position and/or conditions of the tooth extracted even in the same individual. In order for detecting possible influence of local factors, such as position of tooth extracted (foretooth vs. molar tooth) and gum conditions (presence of inflammation and/or inappropriate granulation) on risks for post-extraction bleeding, we chose to present our data by tooth, despite a possible bias of including some of the patient data multiple times when multiple teeth was extracted from a single patient. When analyzed by patient, clinically significant post-extraction bleeding occurred in 2.77 and 0.39% in warfarin and non-warfarin group, respectively, difference between which was 2.38% (95% CI, 0.65 – 4.10%).and was similar to that found in analysis by tooth. These data suggest that the bias that might arise from the analyses by tooth was minimal. Third, evaluation of the post-extraction bleeding events was not blinded and choice of secondary hemostasis means were left at the discretion by the operator in charge, which might have affected the outcome of our analyses. However, the definition of the clinically significant bleeding events was made clear, minimizing the influence by the person who evaluated the individual event. Lastly, we compared incidences of post-extraction bleeding in patients under warfarin therapy who underwent dental extraction without cessation of warfarin with those who are not receiving warfarin therapy. On the other hand, most of previous studies assessed post-extraction events in warfarinized patients with or without cessation of warfarin prior to dental extraction, Such

difference in study population might also have resulted in different finding in the present study.

CONCLUSION

The difference in incidence rates of post-extraction bleeding between warfarin and non-warfarin group was 3.24% (95% CI, 1.49 – 4.99%). Age, PT-INR, and history of acute inflammation at extraction site were risk factors for post-extraction bleeding in warfarin receiving patients.

Competing interest; None disclosed.

H. Iwabuchi designed the study protocol and wrote the manuscript. H. Imai analyzed the data and contributed to edition of the manuscript. H. Nakao also participated in data analyses. Y. Imai is the Principle Investigator of the present study. Rest of the authors participated in data collection.

REFERENCES

1 Wahl MJ. Dental surgery in anticoagulated patients. Arch Inter Med1998;158:1610-16.

2 Evans IL, Sayers MS, Gibbons AJ, et al. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. Br J Oral Maxillofac Surg2002;40:248-252.

3 Sacco R, Sacco M, CarpenedoM, et al. Oral surgery in patients on oral anticoagulant therapy: A randomized comparison of different intensity targets. Oral Surg Oral med Oral Pathol Oral RadiolEndod. 2007;104:e18-21.

4 Al-Mubarak S, Al-Ali N, Rass MA, et al. Evaluation of dental extractions, suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. Br Dent J.2007;203:1-5.

5 Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery:Should the Anticoagulation regiment be altered? J Oral Maxillofac Surg.2000;58:131-5.

6 Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in patients on oral antithrombotic therapy. J Oral Maxillofac Surg.2008;66:51-7.

7 Barrero MV, Knezevic M, Martin MT, et al. Oral surgery in the patients undergoing oral anticoagulant therapy. Med oral.2002;7:63-70.

8 Aframian DJ, Lalla RV, Peterson DE. Management of dental patients taking common hemostasis –altering medications. Oral Surg Oral med Oral Pathol Oral RadiolEndod.2007;103(suppl 1):S45e1-11.

9 Goodchild JH, Donaldson M. An evidence-based dentistry challenge:Treating patients on warfarin(Coumadin). Dental aimplantol Update2009;20:1-8.

10 Nematullah A, Alabousi A, Blanas N, et al. Dental surgery for patients on anticoagulant therapy with warfarin:asystematic review and meta-analysis. J can Dent Assoc.2009;75:41-41i.

- 11 Perry DJ, Noakes TJC, Helliwell PS. Guidelines for the management of patients on oral anticoagulants requiring dental surgery. *Br Dent J*.2007;203:389-393.
- 12 Sasanuki H, et al: Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease. *Circ J*.2004;68suppl IV:1153-1219.
- 13 Jcs Joint Warking Group: Guidelines for pharmacotherapy of atrial fibrillation –Digest Version-. *Circ J*.2010;74:2479-2500.
- 14 Japanese Society of Dentistry for Medically Compromised Patient, Japanese Society of Oral and Maxillofacial Surgeons, Japanese Society of Gerodontology: The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction. 2010 version Gakujutsusha Corporation Tokyo 2010.
- 15 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Inter Med*. 2008;168:63-69.
- 16 Ogiuchi H, Ando T, Tanaka M, et al. Clinical reports on dental extraction from patients undergoing oral anticoagulant therapy. *Bull Tokyo Dent Coll*. 1985;26:205-212.
- 17 Balevi B. Should warfarin be discontinued before a dental extracion? A decision-tree analysis. *Oral Surg Oral Med Oral Pathol Oral RadiolEndod* 2010;110:691–697.
- 18 Balevi B.Should warfarin be discontinued before a dental extraction? *Oral Surg Oral Med Oral Pathol Oral RadiolEndod* 2012;113:150-152.
- 19 Gaspar R, Brenner B, Ardekian L, Peled M. Use of tranexamic acid mouthwash to prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication. *Quintessence Int* 1997;28:375-9.
- 20 Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on oral anticoagulant therapy: comparison of INR value with occurrence of postoperative bleeding. *Int J Oral MaxillofacSurg* 2001;30(6):518-21.
- 21 Karsli ED, Erdogan O, Esen E, Acartürk E. Comparison of the effects of warfarin and

heparin on bleeding caused by dental extraction: a clinical study. *J Oral Maxillofac Surg*. 2011;69:2500-7.

22 Devani P, Lavery KM, Howell CJT. Dental extractions in patients on warfarin –Is alternation of anticoagulant regime necessary? *Br J Oral Maxillofac Surg*.1998;36:107-111.

23 Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy. *Oral Surg Oral Med Oral Pathol* 2002;94:57-64.

24 Toyoda K, Yasaka M, Iwade K, et al. Dualantithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease –A prospective,multicenter,observational study. *Stroke*.2008;39:1740-45.

25 Maulaz AB, BezerraDC, Michel P, et al. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. *Arch Neurol*.2005;62:1217-1220.

26 Halfpenny W, Fraser JS,Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. *Oral Surg Oral Med Oral Phthol Oral Radiol Endnd*.2001;92:257-259.

27 Carter G, Goss A, Lloyd J, et al. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. *J Oral Maxillofac Surg*.2003;61:1432-1435.

28 Blinder D, Manor Y, Martinowitz U, et al. Dental extraction in patients maintained on continued oral anticoagulant. Comparison of local hemostatic modalities.*Oral Surg Oral Med Oral Phthol Oral Radiol Endnd*.1999;88:137-140.

29 Salam S, Yusuf H, Milosevic A. Bleeding after dental extractions in patients taking warfarin. *Br J Oral Maxillofac Surg*. 2007;45:463-466.

30 Al-Belasy FA, Amer MZ. Hemostatic effect of n-butyl-2-cyano- acrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. *J Oral Maxillofac Surg*. 2003; 61:

- 1405-1409.
- 31 Dunn AS, Alexander G, G Turpie. Perioperative management of patients receiving oral b
Anticoagulants A systemic review. Arch Intern Med. 2003;163:901-908.
- 32 Kovacs MJ, Kearon C, Rodger M, et al; Single-arm study of bridging therapy with
low-molecular-weight heparin for patients at risk of arterial embolism who require
temporary interruption of warfarin. Circulation. 2004;110:1658-1663.
- 33 Bajkin BV, Popovic SL, Selakovic SDJ. Randomized prospective trial comparing
bridging therapy using low-molecular-weight heparin with maintenance of oral
anticoagulation during extraction of teeth. J Oral Maxillofac Surg. 2009; 67: 990-995.
- 34 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term
interruption of warfarin therapy. Arch Intern Med. 2008;168:63-69.
- 35 Bloomer CR. Excessive hemorrhage after dental extractions using low-molecular-
weight heparin (Lovenox) anticoagulation therapy. J Oral Maxillofac Surg.
2004;62:101-103.
- 36 Chugani V. Management of dental patients on warfarin therapy in a primary care setting.
Dental Update. 2004;31:379-384.
- 37 Pototski M, Amenabar JM: Dental management of patients receiving anticoagulation or
antiplatelet treatment. J Oral Sci. 2007;49:253-8.
- 38 Brennan MT, Hong C, Furney SL, et al. Utility of an international normalized ratio
testing device in a hospital-based dental practice. J Am Dent Assoc. 2008;139:697-703.

Table 1. Breakdown of extracted teeth by important classification variables

No. of teeth by:		Warfarin	No Warfarin	Total	P value
		n=496	n=2321	N = 2817	
Age (years)					
	< 65	124 (25.0)	1131 (48.7)	1255 (44.6)	< 0.0001
	≥ 65	372 (75.0)	1190 (51.3)	1562 (55.4)	
Sex					
	Male	320 (64.5)	1126 (48.5)	1446 (51.3)	< 0.0001
	Female	176 (35.5)	1195 (51.5)	1371 (48.7)	
Type					
	Foretooth	132 (26.6)	663 (28.6)	795 (28.2)	0.550
	Premolar	127 (25.6)	552 (23.8)	679 (24.1)	
	Molar	237 (47.8)	1106 (47.7)	1343 (47.7)	
Instrument					
	Forceps only	171 (34.5)	604 (26.0)	775 (27.5)	0.000
	Elavators only	226 (45.6)	919 (39.6)	1145 (40.6)	
	Forceps and elevators	99 (20.0)	798 (34.4)	897 (31.8)	
Cause for extraction					
	Periodontitis	160 (32.3)	533 (23.0)	693 (24.6)	< 0.0001
	Caries	87 (17.5)	477 (20.6)	564 (20.0)	
	Apical periodontitis	219 (44.2)	1002 (43.2)	1221 (46.6)	
	Wisdom tooth pericoronitis	23 (4.6)	192 (8.3)	215 (7.6)	
	Other	7 (1.4)	117 (5.0)	124 (4.4)	
Status of antiplatelet therapy					
	Yes	122 (24.6)	433 (18.7)	555 (19.7)	0.003
Use of local anesthetics containing vasoconstrictors					
	Yes	491 (99.0)	2265 (97.6)	2756 (97.8)	0.105
Use of inferior alveolar nerve block					
	Yes	14 (2.8)	82 (3.5)	96 (3.4)	0.429
Comorbidity possibly influencing hemostatis					
	Hypertension	267 (53.8)	715 (30.8)	982 (34.9)	< 0.0001
	Diabetes mellitus	89 (17.9)	267 (11.5)	356 (12.6)	
	Chronic hepatitis	21 (4.2)	110 (4.7)	131 (4.7)	
	Other	68 (13.7)	212 (9.1)	280 (9.9)	
	Multiple disorders	341 (68.8)	1039 (44.8)	1380 (49.0)	
History of acute inflammation at extraction site					
	Yes	216 (43.5)	829 (35.7)	1045 (37.1)	0.001
Gingival inflammation at extraction site					
	None	298 (60.1)	1266 (54.5)	1564 (55.5)	0.000
	Mild	95 (19.2)	264 (11.4)	359 (12.7)	
	Moderate	13 (2.6)	38 (1.6)	51 (1.8)	
	Severe	90 (18.1)	753 (32.4)	843 (29.9)	
Abnormal granulation tissue in extraction socket					

None	87 (17.5)	818 (35.2)	905 (32.1)	
Little	230 (46.4)	917 (39.5)	1147 (40.7)	
Medium	134 (27.0)	441 (19.0)	575 (20.4)	0.003
Much	45 (9.1)	145 (6.2)	190 (6.7)	
Severity of post-extraction bleeding				
G1	9 (1.8)	29 (1.2)	38 (1.3)	
G2-1	8 (1.6)	11 (0.5)	19 (0.7)	
G2-2	1 (0.2)	8 (0.3)	9 (0.3)	
G3	17 (3.4)	1 (0.04)	18 (0.6)	
total	35 (7.1)	49 (2.1)	84 (3.0)	< 0.0001
G2-2+G3	18 (3.6)	9 (0.4)	27 (1.0)	< 0.0001
PT-INR				
(mean ± SD)	1.90±0.49			

Table 2. Incidences of clinically significant post-extraction bleeding and their difference in patients receiving and not receiving warfarin

Incidence over total numbers of teeth extracted (%)				
95% CL				
	Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence (%)	Lower	Upper
Warfarin	3.63	3.24	1.58	4.90
No Warfarin	0.39			

Incidence over total numbers of study subjects (%)				
95% CL				
	Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence (%)	Lower	Upper
Warfarin	2.77	2.38	0.65	4.10
No Warfarin	0.39			

Table 3. Univariate analysis of post-extraction bleeding events by potential risk factors

		Incidence of post-extraction bleeding (%)	OR	95% CL		P-value
				Lower	Upper	
Age (years)						
	< 65	8.9	1 (Ref)			
	≥ 65	1.9	0.197	0.075	0.520	0.001*
Sex						
	Male	3.4	1 (Ref)			
	Female	4.0	1.164	0.443	3.057	0.759
Type						
	Foretooth or premolar	2.3	1 (Ref)			
	Molar	5.1	2.2249	0.830	6.091	0.111
Instrument						
	Forceps only	2.9	1 (Ref)			
	Elevators alone or with forceps	4	1.383	0.485	3.947	0.544
Cause for extraction						
	Caries, apical periodontitis, or other	2.6	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	5.5	2.204	0.854	5.688	0.102
Status of antiplatelet therapy						
	No	4.5	1 (Ref)			
	Yes	0.8	0.174	0.023	1.318	0.090
PT-INR						
			3.635	1.5640	8.448	0.003*
Use of vasoconstrictors						
	No	4.1	1 (Ref)			
	Yes	0				
Use of local anesthetics containing vasoconstrictors						
	No	0	1 (Ref)			
	Yes	3.7				
Use of inferior alveolar nerve block						
	No	3.3	1 (Ref)			
	Yes	14.3	4.854	1.002	23.513	0.050*
Comorbidity possibly influencing hemostatis						
	No	5.8	1 (Ref)			
	Yes	2.6	0.440	0.171	1.131	0.088
History of acute inflammation at extraction site						
	No	2.5	1 (Ref)			
	Yes	5.1	2.093	0.7970	5.492	0.134
Gingival inflammation at extraction site						
	None to mild	3.3	1 (Ref)			
	Moderate to severe	4.9	1.491	0.519	4.283	0.458
		23				

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abnormal granulation tissue in extraction socket					
None to little	2.2	1 (Ref)			
Medium to much	6.1	2.900	1.1040	7.619	0.031*

For peer review only

Table 4. Multivariate analysis of post-extraction bleeding events by potential risk factors

		OR	95% CL		P-Value
			Lower	Upper	
Age (years)					
	< 65	1 (Ref)			
	≥ 65	0.126	0.035	0.448	0.001*
Type					
	Foretooth or premolar	1 (Ref)			
	Molar	0.953	0.288	3.151	0.937
Cause for extraction					
	Caries, apical periodontitis, or other	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	2.301	0.742	7.142	0.149
Status of antiplatelet therapy					
	No	1 (Ref)			
	Yes	0.100	0.010	0.986	0.049*
PT-INR		7.797	2.2930	26.510	0.001*
Use of inferior alveolar nerve block					
	No	1 (Ref)			
	Yes	2.437	0.336	17.659	0.378
Comorbidity possibly influencing hemostasis					
	No	1 (Ref)			
	Yes	0.503	0.157	1.612	0.247
History of acute inflammation at extraction site					
	No	1 (Ref)			
	Yes	3.722	1.0850	12.773	0.037*
Abnormal granulation tissue in extraction socket					
	None to little	1 (Ref)			
	Medium to much	2.895	0.8940	9.369	0.076

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

		Item No	Recommendation
Title and Abstract	✓	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
	✓		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	✓	2	Explain the scientific background and rationale for the investigation being reported
Objectives	✓	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	✓	4	Present key elements of study design early in the paper
Setting	✓	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	✓	6	(a) Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants
	N/A		(b) Cohort study
Variables	✓	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effects modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	✓	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	✓	9	Describe any efforts to address potential sources of bias
Study size	✓	10	Explain how the study size was arrived at
	✓	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	✓	12	(a) Describe all statistical methods, including those used to control for confounding
	✓		(b) Describe any methods used to examine subgroups and interactions
	✓		(c) Explain how missing data were addressed
	✓		(d) Cross-sectional study – If applicable, describe analytical methods taking accounting of sampling strategy
	✓		(e) Describe any sensitivity analyses
Results			
	✓	13	(a) Report numbers of individuals at each stage of study – e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed
	N/A		(b) Give reasons for non-participation at each stage
	N/A		(c) Consider use of a flow diagram
Descriptive data	✓	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
	✓		(b) Indicate numbers of participants with missing data for each variable of interest
	N/A		(c) Cohort study
Outcome data	✓	15	Cross-sectional study – Report numbers of outcomes events or summary measures
Main results	✓	16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (e.g. 95 confidence interval). Make clear which confounders were adjusted for and why they were included
	✓		(b) Report category boundaries when continuous variable were categorized
	✓		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	✓	17	Report other analyses done – e.g. analyses of subgroups, and sensitivity analyses

Discussion		
✓	18	Summarize key results with reference to study objectives
		Discuss limitations of the study, taking into account sources of potential bias or imprecision.
✓	19	Discuss both direction and magnitude of any potential bias
		Give a cautious overall interpretations of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
✓	20	
✓	21	Discuss the generalizability (external validity) or the study results
Other information		
Funding		
✓	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

BMJ Open

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005777.R3
Article Type:	Research
Date Submitted by the Author:	01-Oct-2014
Complete List of Authors:	Iwabuchi, Hiroshi; Kanagawa Dental University, Department of Oral and Maxillofacial Surgery Imai, Yutaka; Dokkyo Medical University School of Medicine, Department of Oral & Maxillofacial Surgery Asanami, Soichiro; Sanno Hospital, Department of Dentistry and Implant Center Shirakawa, Masayori; Nippon Dental University, Yamane, Gen-yuki; Tokyo Dental College, Ogiuchi, Hideki; Tokyo Women's Medical University, Kurashina, Kenji; Aizawa Hospital, Oral & Dental Center Miyata, Masaru; Ishikawa Prefectural Central Hospital, Department of Dentistry and Oral Surgery Nakao, Hiroyuki; National Institute of Public Health, Department of Epidemiology Imai, Hirohisa; National Institute of Public Health, Department of Epidemiology
Primary Subject Heading:	Dentistry and oral medicine
Secondary Subject Heading:	Dentistry and oral medicine
Keywords:	ORAL & MAXILLOFACIAL SURGERY, ORAL MEDICINE, Oral & maxillofacial surgery < SURGERY

SCHOLARONE™
Manuscripts

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Hiroshi Iwabuchi¹⁾, Yutaka Imai²⁾, Soichiro Asanami³⁾, Masayori Shirakawa⁴⁾, Gen-yuki Yamane⁵⁾, Hideki Ogiuchi⁶⁾, Kenji Kurashina⁷⁾, Masaru Miyata⁸⁾, Hiroyuki Nakao⁹⁾, Hirohisa Imai⁹⁾

Department of Oral and Maxillofacial Surgery, Kanagawa Dental University¹⁾, Department of Oral & Maxillofacial Surgery, Dokkyo Medical University School of Medicine²⁾, Department of Dentistry and Implant Center, Sanno Hospital³⁾, Nippon Dental University⁴⁾, Tokyo Dental College⁵⁾, Tokyo Women's Medical University⁶⁾, Aizawa Hospital, Oral & Dental Center⁷⁾, Department of Dentistry and Oral Surgery, Ishikawa Prefectural Central Hospital⁸⁾, Department of Epidemiology, National Institute of Public Health of Japan⁹⁾

Corresponding author: Hiroshi Iwabuchi
Department of Oral and Maxillofacial Surgery, Kanagawa Dental University
82 Inaokamachi, Yokosuka-shi, Kanagawa 238-8580, Japan
TEL: 81-46-822-8810, ext 2395
e-mail: Hiroshi Iwabuchi : iwabuchi@kdu.ac.jp

Word count: 3145

Keywords: tooth extraction, post-extraction bleeding, warfarin, risk factors

ABSTRACT

Objectives: We investigated incidence and risk factors for post-extraction bleeding in patients receiving warfarin and those not under anti-coagulation therapy.

Design: Crossover multicenter observational study

Setting: 26 hospitals where oral surgeon is available.

Participants: Data on 2,817 teeth (496: receiving warfarin, 2,321: not receiving warfarin; mean age (SD): 62.2 (17.6)) extracted from November 1, 2008 to March 31, 2010, were collected. Warfarin-receiving patients were eligible when PT-INR measured within 7 days prior to the extraction was less than 3.0.

Interventions: Simple dental extraction was performed and incidence of post-extraction bleeding and comorbidities were recorded.

Primary and Secondary Outcome Measures: Post extraction bleeding not controlled by basic hemostatic procedure as clinically significant.

Results: Bleeding events were reported for 35 (7.1%) and 49 (2.1%) teeth, of which 18 (3.6%) and 9 (0.4%) teeth were considered as clinically significant, in warfarin and non-warfarin groups, respectively, the difference between which was 3.24% (confidence intervals 1.58 – 4.90%). The incidence rates by patients were 2.77 and 0.39%, in warfarinized- and non-warfarin group, respectively (incidence difference 2.38%, confidence intervals 0.65 – 4.10%). Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), mandibular foramen conduction anesthesia (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) significantly correlate with the bleeding incidence. Multivariate analysis revealed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding.

Conclusion: Our results suggest that there is slight but significant increase in incidences for the post-extraction bleeding in patients receiving warfarin. Although absolute incidence was low in both groups, the bleeding risk is not negligible.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Strength and Limitation of this Study

- The present study examined difference of the incidences for post-extraction bleeding between the patients receiving and not-receiving warfarin, which few previous studies to date have been reported.
- The study included dental facilities where at least one or more certified oral surgeons are available in order to standardize skills of the operators and capability of the facilities for providing advanced care in the event of significant bleeding.
- We also analyzed the risk factors for post-extraction bleeding events in patients receiving warfarin.
- Due to the study design, we may have underestimated the incidence of post-extraction bleeding that may occur in community dental clinics.
- Although we tried to standardize the dental extraction procedure, there might have been inter-facility differences.

INTRODUCTION

Until recently, the common procedure for tooth extraction in patients continuously receiving warfarin or other antiplatelet therapy was to discontinue or reduce the dose to minimize the risks of odontorrhagia. However, the procedure has been re-evaluated since cases of thromboembolic complications after dental extraction with warfarin (WF) cessation were reported [1-3]. Thereafter, many studies including randomized trials [4-6], Cohort studies [7-9] and meta-analyses [10-12] have been conducted, all of which reported no significant differences in incidences of post-extraction bleeding and/or other hemorrhagic complications, concluding that, in patients whose prothrombin time- international normalized ratio (PT-INR) is within desirable therapeutic range, dental extraction can be performed safely without cessation of warfarin. Clinical guidelines published after these studies advised that patients whose PT-INR values were within the recommended therapeutic ranges should continue warfarin when undergoing dental extraction.[13-15] However, there have been little studies that specifically addressed difference in the bleeding incidences and its 95% confidence interval comparing tooth extraction cases in patients receiving and not receiving warfarin.

Given these circumstances, we evaluated the difference in the post-extraction bleeding incidences in otherwise healthy control without warfarin administration (non-WF group) and in patients under reasonable coagulation control with warfarin (WF group). We selected the subjects for the latter group whose PT-INR was 3.0 or lower at the time of the procedure, as the PT-INR of 3.0 was indicated as the maximum safety threshold for tooth extraction in the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction in Japanese.[16] We also investigated the risk factors for the incidence of post-extraction bleeding in patients receiving warfarin therapy.

MATERIALS AND METHODS

This was a prospective multicenter observational study of post-extraction bleeding events in patients receiving and not receiving warfarin therapy.

Study Period and Eligibility Criteria

Twenty-six hospitals located across Japan participated. This study included patients who underwent simple tooth extraction from November 1, 2008 to March 31, 2010 at the department of oral surgery of these hospitals and who met the eligibility criteria listed below. Simple tooth extraction referred to a tooth removed without traumatizing the surrounding alveolar bone or elevating a mucoperiosteal flap.

Eligibility criteria included the following: 20 or more years of age at the time of tooth extraction; no contraindications for tooth extraction; surgery was performed by oral surgeon with a minimum of 3 years of experience in dental practice; the oral extraction procedure lasted for no longer than 15 minutes; and platelet count within 7 days prior to the procedure was normal. In addition, in patients receiving warfarin therapy, PT-INR measured within 7 days prior to the procedure should be less than 3.0. Patients receiving anti-platelet medication were not excluded but recorded as such. According to “The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction”[14], we instructed the participating hospitals that dental extraction should be performed without discontinuing or reducing the dose of warfarin in patients whose PT-INR was not exceeding 3.0 when measured within 7 days prior to the procedure.

Study Variables

The variables analyzed in this study were: bleeding events, patient’s age and sex, position of the removed tooth, instruments used for removal (forceps only, elevators only, forceps and elevators), reasons for extraction, use of antiplatelet drugs, PT-INR values measured within 7 days before exodontia (only for patients receiving chronic warfarin therapy), comorbidities possibly influencing hemostasis, use of vasoconstrictors, combined use of local anesthetics

and vasoconstrictors, use of inferior alveolar nerve block, severity of gingivitis after extraction (none, mild, moderate, severe), formation of abnormal granulation tissue in the extraction socket (none, little, medium, much), history of acute inflammation at extraction site, and post-extraction infection.

Hemostasis

The hemostatic methods for patients not receiving warfarin were chosen at the discretion of the dentist or oral surgeon performing the procedure. In patients on warfarin therapy, either absorbable oxidized cellulose or gelatin sponge was implanted into the alveolar socket, and wound margins were sutured. In both groups of patients, topical hemostatic agents other than epinephrine, systemic hemostatic agents, and splints were prohibited until primary hemostasis was observed. In patients who had multiple teeth extracted in one session, possible post-extraction bleeding was examined for each tooth. In a patient receiving warfarin, the post-extraction procedure defined above was performed each time after a tooth was removed.

Permitted Drugs

Use of local anesthetics containing vasoconstrictors (e.g., epinephrine and felypressin) was allowed at doses commonly practiced. In warfarin-treated patients, penicillins or cefems (e.g., cefcapenepivoxil and cefditoren pivoxil) was the primary choice of prophylactic antibiotics for their minimal interaction with warfarin. , For those who were allergic to penicillins, clarithromycin was recommended. Use of analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors was allowed at ordinary doses.

Confirmation of Hemostasis

All patients were asked to bite down on a roll gauze for a maximum of 30 minutes for astriction of the wound. After release of the biting pressure, the wound was examined for hemostasis. Patients visited the hospital on the next day of surgery to check for possible bleeding, and were instructed to present at the hospital for treatment, if bleeding should occur later. The follow-up period was 7 days postoperatively.

Follow-up of Bleeding Events

If a patient had a bleeding event during the follow-up period, the severity of the hemorrhage and blood pressure were recorded. If the patient was on warfarin therapy, his or her PR-INR values were measured in addition.

Evaluation of Bleeding Events

In this study, bleeding events occurring in the follow-up period were classified into one of the following 5 grades: 0, no bleeding; 1, excessive blood clotting in the socket, no treatment required; 2-1, hemostasis achieved by compressing the wound longer than 30 minutes; 2-2, oozing hemorrhage observed on or after the next day of the procedure, which hemostasis was achieved by simple compression; 3, bleeding required treatments other than wound compression, such as application of compression brace and/or coagulation by electrotome was needed. Grade 2-2 and higher events were regarded as clinically significant, and were defined as post-extraction bleeds in this study.

Statistical Analysis

Data were collected by a tooth, but not by a patient. This means that patients who had multiple teeth extraction were counted multiple times for the number of extracted teeth. Data were then sorted and analyzed by the anatomical positions. The difference in post-extraction

bleeding incidence between patients receiving and not receiving warfarin therapy and its 95% confidence interval (CI) were calculated. In addition, a multivariate logistic regression analysis was conducted to identify risk factors for post-extraction bleeding in warfarin-treated patients. Adjusted odds ratios (ORs), their 95% CIs and *p*-values were calculated controlling for major confounders. Explanatory variables with a significance level of $P < 0.20$ on univariate analyses were included in the multivariate logistic regression model. Statistical analyses were performed using the SPSS software (version 15.0, SPSS Japan Inc., Tokyo, Japan).

Ethics

The objective of this study was explained in details to potential study participants so that they could make an informed decision. Informed consent was obtained orally or by a written document, according to the recommendation to the ethics committee of each participating facilities. Patients' personal information was stored in a de-identified but linkable format during the 7-day follow-up period, and was rendered completely anonymous thereafter. This study was reviewed and approved by the ethics committee of the National Hospital Organization Tochigi Medical Center, Tochigi, Japan, prior to its conduct. The approved protocol was distributed to the participating hospitals to keep the uniformity of the study.

RESULTS

Totally, 3,515 case reports were submitted from the participating investigators. Of these, 698 cases were eliminated because of protocol deviations and/or insufficient datadocumentation, leaving 2,817 for further analysis.

Post-extraction Bleeding Incidence

Bleeding events including minor hemorrhagic episodes were reported for 35 out of 496 teeth (7.1%) of the warfarin group and for 49 out of 2,321 teeth (2.1%) of the non-warfarin group, with a total of 84 teeth. Clinically significant post-extraction bleeds (i.e., grade 2-2 or higher) were reported for 27 teeth, including 18 (3.6%) and 9 (0.4%) from the warfarin and non-warfarin groups, respectively (Table 1).

Breakdown of Removed Teeth by Sex and Study Group

The mean (SD) age of all study participants was 62.2 (17.6) years, and 1,446 and 1,371 teeth were removed from males (51.3%) and females (48.7%), respectively. The warfarin group had a mean (SD) age of 70.3 (10.9) years, and reported removal of 496 teeth, 320 from males (64.5%) and 176 from females (35.5%). Non-warfarin group had a mean (SD) age of 60.4 (18.3) years, and reported removal of 2321 teeth, 1126 from males (48.5%) and 1,195 from females (51.5%) (Table 1).

The difference in post-extraction bleeding incidence between the warfarin group and non-warfarin group was 3.24% and its 95% CI was 1.58% to 4.90%. When analyze by patient, clinically significant bleeding occurred in total of 361 out of 2,146 patients (2.77 and 0.39%, in warfarin- and non-warfarin group, respectively, incidence difference between which was 2.38% (95% CI, 0.65 – 4.10%; Table 2),

Risk Factors for Post-extraction Bleeding in Warfarin-Treated Patients

Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), inferior alveolar nerve block (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) were significantly correlated with post-extraction bleeding (Table 3). In addition to these variables, position of the removed tooth, reasons for extraction, antiplatelet drugs, comorbidities possibly influencing hemostasis,

and history of acute inflammation at extraction site were found to have P values smaller than 0.2 by univariate analysis. Consequently, these parameters were included as explanatory variables in the multivariate regression analysis. The results showed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding (Table 4).

DISCUSSION

In warfarinized patients, thromboembolic events were reported in varying frequency in literature ranging as low as 0.059% [17, 18] to as high as 1% [1] when warfarin was discontinued prior to dental extraction, while little reports serious post-extraction bleeding associated with dental extraction. Based on those data, literature now suggest that WF should not be discontinued when performing dental extraction in warfarinized patients, regardless of incidences of thromboembolic events associated with dental procedure.[5, 19-21]. . Majority of previous studies assessed safety of dental procedure comparing incidence of complications in patients receiving WF when the WF was discontinued or not. Now that dental extraction without WF cessation has become a standard procedure in patients receiving WF, we now conducted the present study to evaluate incidences of post-extraction bleeding in comparison with patients who are not receiving anti-coagulation therapy.

The present study is a nation-wide, multi-institutional prospective study and evaluated frequency of clinically significant post-extraction bleeding and its difference between the non-warfarin and warfarin groups. Clinically significant post-extraction bleeding occurred in low rate in both study groups. Nonetheless, the difference between the two groups was 3.24% with its 95% confidence interval between 1.58 – 4.90%..

Among the patients receiving warfarin, older patients showed lower risks for

1
2
3 post-extraction bleeding in the present study. Few studies have addressed influence of patients'
4
5 age on incidence of post-extraction bleeding. Mean PT-INR in the patients who experienced
6
7 clinically significant post-extraction bleeding was 2.57 ± 0.62 in patients 65 years old or older,
8
9 which was significantly higher compared to that in patients younger than 65 years old (2.10
10
11 ± 0.39 , $P = 0.048$). These results suggest that younger patients tend to experience clinically
12
13 significant post-extraction bleeding at lower PT-INR, which might have contributed to the
14
15 lower bleeding risks in the elderly patients in the present study.
16
17

18
19 Few studies reported to date examined the relationship between age and the incidence of
20
21 post-extraction bleeding. Our finding indicated that extra caution should be taken when
22
23 conducting exodontia in elderly patients receiving warfarin therapy, and the frequency of such
24
25 situations would increase with aging population.
26

27
28 A study that investigated the impact of comorbid conditions on hemostasis suggested that
29
30 patients with liver dysfunction are another group at high risk for post-extraction bleeding.[22]
31
32 The present study did not identify liver dysfunction or other comorbid conditions that would
33
34 affect hemostasis as a risk factor for increased incidence of post-extraction bleeding. The
35
36 attribution of such condition may have been underestimated in the present study as only 4.2%
37
38 of the study participants had chronic hepatitis.
39
40

41
42
43 Our results also showed that the incidence of post-extraction bleeding events increased
44
45 with higher PT-INR, even though the values did not exceed 3.0. This finding suggests that a
46
47 special attention would be needed in patients whose PT-INR are close to 3.0 or higher to
48
49 prevent post-extraction hemorrhagic event. Because warfarin sensitivity may vary among
50
51 individuals and different ethnic groups, further studies will be needed to verify if the current
52
53 findings are generalizable to other ethnic groups.
54
55

56
57 No randomized comparative trials that addressed incidences of post-extraction bleeding
58
59

in patients receiving warfarin with or without anti-platelet medicine has so far been reported. An observational study by Morimoto et al found no significant difference in incidences of post-extraction bleeding between the patients receiving warfarin alone and those in combination with an anti-platelet medicine.[6] In contrast, Scully et al reported that, in patients with oral surgeries, post-operative bleeding incidence was higher in patients under the combination therapy of warfarin and an anti-platelet medicine.[23] Besides reports regarding the bleeding events associated with oral surgeries, increased incidence of hemorrhagic complications in patients receiving anti-platelet medicine in addition to warfarin compared to those receiving warfarin only was observed in a cohort study in Japanese patients under anti-coagulation therapies.[24]. The results from the present study suggested that incidence for post-extraction bleeding is lower in patients receiving both warfarin and an anti-platelet medicine. Although findings vary in those studies, anti-platelet medicine alone is in general considered to minimally affect incidences of post-operative bleeding in the cases of dental extraction[8] or of surgeries [25], and may as well in patients under the control of warfarin.

Suturing of wound and filling of the socket with oxidized cellulose or gelfoam have been widely recognized as efficient means of hemostasis after dental extraction.[26-28] However, some guidelines do not necessarily recommend suture of the wound, while supporting the use of oxidized cellulose, gelfoam or fibrin glue.[8] Several reports also found that suturing would could rather damage the tissue at the socket.[29,30] In the present study, incidences of post-extraction bleeding in patients not receiving warfarin were not significantly different between the patients whose wound was sutured and those without suture (0.6 and 0.2%, respectively). However, we were unable to tell whether suturing increased the incidence of post-extraction bleeding in the patients receiving warfarin as wounds were sutured in all the patients receiving warfarin in the present study. Evaluation of the outcome of suturing in patients receiving warfarin would be worthy of future study. Heparin bridging is another

effective means to prevent thromboembolism and to reduce risk for post-operative bleeding.[31,32], application of which is primarily limited to a major surgery that topical hemostasis is not applicable. Efficacy of heparin bridging was evaluated by a randomized comparative study,[33] which found no significant differences in incidences of post-extraction bleeding or thromboembolic complications with and without addition of heparin bridging with continuing warfarin therapy, concluding that heparin bridging is not required when dental extraction is performed as long as topical hemostasis is applicable. On the other hand, comparative studies examined cases of minor surgeries performed with cessation of warfarin with or without additional heparin bridging reported severe hemorrhagic event in cases receiving heparin bridging, though no thromboembolic complication had occurred.[34,35] Furthermore, heparin needs to be continuously administered intravenously when performing heparin bridging, necessitating hospital admission with resulting higher cost and demands for medical personnel. The results from the present study further supported the notion that topical hemostasis provides sufficient hemostasis in cases of simple tooth extraction without discontinuing warfarin, and therefore heparin bridging is not necessary. Several aspects of our study design that may have affected the outcome of the present study should be noted. First,, we included PT-INR values measured within 7 days prior to tooth extraction, considering the availability of measurement results. However, because effects of warfarin can be affected by diet and other drugs, experts suggested to measure PT-INR within 24 [8,9,36,37] and 48 [38] hours before the procedure. The British Committee for Standards in Hematology recommended 72 hours before surgery [11]. Therefore, pre-extraction PT-INR values we utilized may not have accurately reflected the coagulation status immediately prior to the extraction, skewing the results of our analyses. To minimize the bias, we conducted another PT-INR measurement in patients receiving warfarin who experienced clinically significant bleeding events soon after the event observation. In such patients, PT-INR values before and

after the tooth extraction were 2.27 and 2.26, respectively, and not significantly changed. These data suggest that the possible bias derived from PT-INR values measured within 7 days in advance were minimal. Second, we performed all the analyses by tooth, not by patients. We hypothesized, based on previous studies that found no significant correlation between the numbers of tooth extracted and incidence of post extraction bleeding,[2,4,5,7] that risks for post-extraction bleeding may vary depending the position and/or conditions of the tooth extracted even in the same individual. In order for detecting possible influence of local factors, such as position of tooth extracted (foretooth vs. molar tooth) and gum conditions (presence of inflammation and/or inappropriate granulation) on risks for post-extraction bleeding, we chose to present our data by tooth, despite a possible bias of including some of the patient data multiple times when multiple teeth was extracted from a single patient. When analyzed by patient, clinically significant post-extraction bleeding occurred in 2.77 and 0.39% in warfarin and non-warfarin group, respectively, difference between which was 2.38% (95% CI, 0.65 – 4.10%).and was similar to that found in analysis by tooth. These data suggest that the bias that might arise from the analyses by tooth was minimal. Third, evaluation of the post-extraction bleeding events was not blinded and choice of secondary hemostasis means were left at the discretion by the operator in charge, which might have affected the outcome of our analyses. However, the definition of the clinically significant bleeding events was made clear, minimizing the influence by the person who evaluated the individual event. Indeed, there was little difference in post-extraction bleeding incidence in patients whose wound was sutured or not (0.6% and 0.2%, respectively), further supporting the notion that means of hemostasis have minimally affected the present findings.

CONCLUSION

The difference in incidence rates of post-extraction bleeding between warfarin and non-warfarin group was 3.24% (95% CI, 1.49 – 4.99%). Age, PT-INR, and history of acute inflammation at extraction site were risk factors for post-extraction bleeding in warfarin receiving patients.

CONTRIBUTORSHIP STATEMENT

H. Iwabuchi designed the study protocol and wrote the manuscript. H. Imai analyzed the data and contributed to edition of the manuscript. H. Iwabuchi, Y Imai, S Asanami, M Shirakawa, G Yamane, H Ogiuchi, K Kurashina, M Miyata contributed to data collection. H. Nakao also participated in data analyses. Y. Imai is the Principle Investigator of the present study. All the authors have approved the final version of the manuscript to be published. All the authors also agreed upon their accountability for its accuracy and integrity of any part of the present work.

COMPETING INTEREST

I/We have read and understood BMJ policy on declaration of interests and declare the following interests.

Copyright and license for the publication:

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located;

and, vi) licence any third party to do any or all of the above.”

FUNDING

There is no involvement of funding sources in this research.

DATA SHARING

Data sharing: patient level data [and/or] full dataset [and/or] technical appendix [and/or] statistical code [and/or] are available from the corresponding author upon request. Consent for additional data sharing was not obtained but the presented data are anonymised and risk of identification is low.

REFERENCES

1 Wahl MJ. Dental surgery in anticoagulated patients. Arch Inter Med1998;158:1610-16.

2 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Inter Med. 2008;168:63-69.

3 Ogiuchi H, Ando T, Tanaka M, et al. Clinical reports on dental extraction from patients undergoing oral anticoagulant therapy. Bull Tokyo Dent Coll. 1985;26:205-212.

4 Evans IL, Sayers MS, Gibbons AJ, et al. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. Br J Oral Maxillofac Surg2002;40:248-252.

5 Sacco R, Sacco M, CarpenedoM,et al.Oral surgery in patients on oral anticoagulant therapy: A randomized comparison of different intensity targets. Oral Surg Oral med Oral Pathol Oral RadiolEndod.2007;104:e18-21.

6 Al-Mubarak S, Al-Ali N, Rass MA, et al.Evaluation of dental extractions,suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. Br Dent J.2007;203:1-5.

7 Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery:Should the Anticoagulation regiment be altered? J Oral Maxillofac Surg.2000;58:131-5.

8 Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in patients on oral antithrombotic therapy. J Oral Maxillofac Surg.2008;66:51-7.

9 Barrero MV, Knezevic M, Martin MT, et al. Oral surgery in the patients undergoing oral anticoagulant therapy. Med oral.2002;7:63-70.

10 Aframian DJ, Lalla RV, Peterson DE. Management of dental patients taking common hemostasis –altering medications. Oral Surg Oral med Oral Pathol Oral RadiolEndod.2007;103(suppl 1):S45e1-11.

11 Goodchild JH, Donaldson M. An evidence-based dentistry challenge:Treating patients on

- warfarin(Coumadin). Dental aimplantol Update2009;20:1-8.
- 12 Nematullah A, Alabousi A, Blanas N, et al. Dental surgery for patients on anticoagulant therapy with warfarin:asystematic review and meta-analysis. J can Dent Assoc.2009;75:41-41i.
- 13 Perry DJ, Noakes TJC, Helliwell PS. Guidelines for the management of patients on oral anticoagulants requiring dental surgery. Br Dent J.2007;203:389-393.
- 14 Sasanuki H, et al: Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease. Circ J.2004;68suppl IV:1153-1219.
- 15 Jcs Joint Warking Group: Guidelines for pharmacotherapy of atrial fibrillation –Digest Version-. Circ J.2010;74:2479-2500.
- 16 Japanese Society of Dentistry for Medically Compromised Patient,Japanese Society of Oral and Maxillofacial Surgeons, Japanese Society ofGerodontology:The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction.2010 versionGakujutsusha CorporationTokyo 2010.
- 17 Balevi B. Should warfarin be discontinued before a dental extracion? A decision-tree analysis. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2010;110:691–697.
- 18 Balevi B.Should warfarin be discontinued before a dental extraction? Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2012;113:150-152.
- 19 Gaspar R, Brenner B, Ardekian L, Peled M. Use of tranexamic acid mouthwash to prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication. Quintessence Int 1997;28:375-9.
- 20 Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on oral anticoagulant therapy: comparison of INR value with occurrence of postoperative bleeding. Int J Oral MaxillofacSurg 2001;30(6):518-21.
- 21 Karsli ED, Erdogan O, Esen E, Acartürk E. Comparison of the effects of warfarin and

heparin on bleeding caused by dental extraction: a clinical study. J Oral Maxillofac Surg. 2011;69:2500-7.

22 Devani P, Lavery KM, Howell CJT. Dental extractions in patients on warfarin –Is alternation of anticoagulant regime necessary? Br J Oral Maxillofac Surg.1998;36:107-111.

23 Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy.Oral Surg Oral Med Oral Pathol 2002;94:57-64.

24 Toyoda K, Yasaka M, Iwade K, et al.Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease –A prospective,multicenter,observational study. Stroke.2008;39:1740-45.

25 Maulaz AB, Bezerra DC, Michel P, et al. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol.2005;62:1217-1220.

26 Halfpenny W, Fraser JS,Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod.2001;92:257-259.

27 Carter G, Goss A, Lloyd J,et al. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. J Oral Maxillofac Surg.2003;61:1432-1435.

28 Blinder D, Manor Y, Martinowitz U, et al. Dental extraction in patients maintained on continued oral anticoagulant. Comparison of local hemostatic modalities.Oral Surg Oral Med Oral Pathol Oral Radiol Endod.1999;88:137-140.

29 Salam S, Yusuf H, Milosevic A. Bleeding after dental extractions in patients taking warfarin. Br J Oral Maxillofac Surg. 2007;45:463-466.

30 Al-Belasy FA, Amer MZ. Hemostatic effect of n-butyl-2-cyano- acrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. J Oral Maxillofac Surg. 2003; 61:

- 1405-1409.
- 31 Dunn AS, Alexander G, G Turpie. Perioperative management of patients receiving oral b
Anticoagulants A systemic review. Arch Intern Med. 2003;163:901-908.
- 32 Kovacs MJ, Kearon C, Rodger M, et al; Single-arm study of bridging therapy with
low-molecular-weight heparin for patients at risk of arterial embolism who require
temporary interruption of warfarin. Circulation. 2004;110:1658-1663.
- 33 Bajkin BV, Popovic SL, Selakovic SDJ. Randomized prospective trial comparing
bridging therapy using low-molecular-weight heparin with maintenance of oral
anticoagulation during extraction of teeth. J Oral Maxillofac Surg. 2009; 67: 990-995.
- 34 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term
interruption of warfarin therapy. Arch Intern Med. 2008;168:63-69.
- 35 Bloomer CR. Excessive hemorrhage after dental extractions using low-molecular-
weight heparin (Lovenox) anticoagulation therapy. J Oral Maxillofac Surg.
2004;62:101-103.
- 36 Chugani V. Management of dental patients on warfarin therapy in a primary care setting.
Dental Update. 2004;31:379-384.
- 37 Pototski M, Amenabar JM: Dental management of patients receiving anticoagulation or
antiplatelet treatment. J Oral Sci. 2007;49:253-8.
- 38 Brennan MT, Hong C, Furney SL, et al. Utility of an international normalized ratio
testing device in a hospital-based dental practice. J Am Dent Assoc. 2008;139:697-703.

Table 1. Breakdown of extracted teeth by important classification variables

No. of teeth by:		Warfarin n=496	No Warfarin n=2321	Total N = 2817	P value
Age (years)					
	< 65	124 (25.0)	1131 (48.7)	1255 (44.6)	< 0.0001
	≥ 65	372 (75.0)	1190 (51.3)	1562 (55.4)	
Sex					
	Male	320 (64.5)	1126 (48.5)	1446 (51.3)	< 0.0001
	Female	176 (35.5)	1195 (51.5)	1371 (48.7)	
Type					
	Foretooth	132 (26.6)	663 (28.6)	795 (28.2)	0.550
	Premolar	127 (25.6)	552 (23.8)	679 (24.1)	
	Molar	237 (47.8)	1106 (47.7)	1343 (47.7)	
Instrument					
	Forceps only	171 (34.5)	604 (26.0)	775 (27.5)	0.000
	Elavators only	226 (45.6)	919 (39.6)	1145 (40.6)	
	Forceps and elevators	99 (20.0)	798 (34.4)	897 (31.8)	
Cause for extraction					
	Periodontitis	160 (32.3)	533 (23.0)	693 (24.6)	< 0.0001
	Caries	87 (17.5)	477 (20.6)	564 (20.0)	
	Apical periodontitis	219 (44.2)	1002 (43.2)	1221 (46.6)	
	Wisdom tooth pericoronitis	23 (4.6)	192 (8.3)	215 (7.6)	
	Other	7 (1.4)	117 (5.0)	124 (4.4)	
Status of antiplatelet therapy					
	Yes	122 (24.6)	433 (18.7)	555 (19.7)	0.003
Use of local anesthetics containing vasoconstrictors					
	Yes	491 (99.0)	2265 (97.6)	2756 (97.8)	0.105
Use of inferior alveolar nerve block					
	Yes	14 (2.8)	82 (3.5)	96 (3.4)	0.429
Comorbidity possibly influencing hemostatis					
	Hypertension	267 (53.8)	715 (30.8)	982 (34.9)	< 0.0001
	Diabetes mellitus	89 (17.9)	267 (11.5)	356 (12.6)	
	Chronic hepatitis	21 (4.2)	110 (4.7)	131 (4.7)	
	Other	68 (13.7)	212 (9.1)	280 (9.9)	
	Multiple disorders	341 (68.8)	1039 (44.8)	1380 (49.0)	
History of acute inflammation at extraction site					
	Yes	216 (43.5)	829 (35.7)	1045 (37.1)	0.001
Gingival inflammation at extraction site					
	None	298 (60.1)	1266 (54.5)	1564 (55.5)	0.000
	Mild	95 (19.2)	264 (11.4)	359 (12.7)	
	Moderate	13 (2.6)	38 (1.6)	51 (1.8)	
	Severe	90 (18.1)	753 (32.4)	843 (29.9)	
Abnormal granulation tissue in extraction socket					

None	87 (17.5)	818 (35.2)	905 (32.1)	
Little	230 (46.4)	917 (39.5)	1147 (40.7)	
Medium	134 (27.0)	441 (19.0)	575 (20.4)	0.003
Much	45 (9.1)	145 (6.2)	190 (6.7)	
Severity of post-extraction bleeding				
G1	9 (1.8)	29 (1.2)	38 (1.3)	
G2-1	8 (1.6)	11 (0.5)	19 (0.7)	
G2-2	1 (0.2)	8 (0.3)	9 (0.3)	
G3	17 (3.4)	1 (0.04)	18 (0.6)	
total	35 (7.1)	49 (2.1)	84 (3.0)	< 0.0001
G2-2+G3	18 (3.6)	9 (0.4)	27 (1.0)	< 0.0001
PT-INR				
(mean ± SD)	1.90±0.49			

Table 2. Incidences of clinically significant post-extraction bleeding and their difference in patients receiving and not receiving warfarin

		Incidence over total numbers of teeth extracted (%)			
		Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence (%)	95% CL	
				Lower	Upper
Warfarin	3.63				
No Warfarin	0.39		3.24	1.58	4.90

		Incidence over total numbers of study subjects (%)			
		Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence (%)	95% CL	
				Lower	Upper
Warfarin	2.77				
No Warfarin	0.39		2.38	0.65	4.10

Table 3. Univariate analysis of post-extraction bleeding events by potential risk factors

		Incidence of post-extraction bleeding (%)	OR	95% CL		P-value
				Lower	Upper	
Age (years)						
	< 65	8.9	1 (Ref)			
	≥ 65	1.9	0.197	0.075	0.520	0.001*
Sex						
	Male	3.4	1 (Ref)			
	Female	4.0	1.164	0.443	3.057	0.759
Type						
	Foretooth or premolar	2.3	1 (Ref)			
	Molar	5.1	2.2249	0.830	6.091	0.111
Instrument						
	Forceps only	2.9	1 (Ref)			
	Elevators alone or with forceps	4	1.383	0.485	3.947	0.544
Cause for extraction						
	Caries, apical periodontitis, or other	2.6	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	5.5	2.204	0.854	5.688	0.102
Status of antiplatelet therapy						
	No	4.5	1 (Ref)			
	Yes	0.8	0.174	0.023	1.318	0.090
PT-INR						
			3.635	1.5640	8.448	0.003*
Use of vasoconstrictors						
	No	4.1	1 (Ref)			
	Yes	0				
Use of local anesthetics containing vasoconstrictors						
	No	0	1 (Ref)			
	Yes	3.7				
Use of inferior alveolar nerve block						
	No	3.3	1 (Ref)			
	Yes	14.3	4.854	1.002	23.513	0.050*
Comorbidity possibly influencing hemostatis						
	No	5.8	1 (Ref)			
	Yes	2.6	0.440	0.171	1.131	0.088
History of acute inflammation at extraction site						
	No	2.5	1 (Ref)			
	Yes	5.1	2.093	0.7970	5.492	0.134
Gingival inflammation at extraction site						
	None to mild	3.3	1 (Ref)			
	Moderate to severe	4.9	1.491	0.519	4.283	0.458

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abnormal granulation tissue in extraction socket					
None to little	2.2	1 (Ref)			
Medium to much	6.1	2.900	1.1040	7.619	0.031*

For peer review only

Table 4. Multivariate analysis of post-extraction bleeding events by potential risk factors

		OR	95% CL		P-Value
			Lower	Upper	
Age (years)					
	< 65	1 (Ref)			
	≥ 65	0.126	0.035	0.448	0.001*
Type					
	Foretooth or premolar	1 (Ref)			
	Molar	0.953	0.288	3.151	0.937
Cause for extraction					
	Caries, apical periodontitis, or other	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	2.301	0.742	7.142	0.149
Status of antiplatelet therapy					
	No	1 (Ref)			
	Yes	0.100	0.010	0.986	0.049*
PT-INR		7.797	2.2930	26.510	0.001*
Use of inferior alveolar nerve block					
	No	1 (Ref)			
	Yes	2.437	0.336	17.659	0.378
Comorbidity possibly influencing hemostasis					
	No	1 (Ref)			
	Yes	0.503	0.157	1.612	0.247
History of acute inflammation at extraction site					
	No	1 (Ref)			
	Yes	3.722	1.0850	12.773	0.037*
Abnormal granulation tissue in extraction socket					
	None to little	1 (Ref)			
	Medium to much	2.895	0.8940	9.369	0.076

Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study

Hiroshi Iwabuchi¹⁾, Yutaka Imai²⁾, Soichiro Asanami³⁾, Masayori Shirakawa⁴⁾, Gen-yuki Yamane⁵⁾, Hideki Ogiuchi⁶⁾, Kenji Kurashina⁷⁾, Masaru Miyata⁸⁾, Hiroyuki Nakao⁹⁾, Hirohisa Imai⁹⁾

Department of Oral and Maxillofacial Surgery, Kanagawa Dental University¹⁾, Department of Oral & Maxillofacial Surgery, Dokkyo Medical University School of Medicine²⁾, Department of Dentistry and Implant Center, Sanno Hospital³⁾, Nippon Dental University⁴⁾, Tokyo Dental College⁵⁾, Tokyo Women's Medical University⁶⁾, Aizawa Hospital, Oral & Dental Center⁷⁾, Department of Dentistry and Oral Surgery, Ishikawa Prefectural Central Hospital⁸⁾, Department of Epidemiology, National Institute of Public Health of Japan⁹⁾

Corresponding author: Hiroshi Iwabuchi
Department of Oral and Maxillofacial Surgery, Kanagawa Dental University
82 Inaokamachi, Yokosuka-shi, Kanagawa 238-8580, Japan
TEL: 81-46-822-8810, ext 2395
e-mail: Hiroshi Iwabuchi : iwabuchi@kdu.ac.jp

Word count: 3145

Keywords: tooth extraction, post-extraction bleeding, warfarin, risk factors

ABSTRACT

Objectives: We investigated incidence and risk factors for post-extraction bleeding in patients receiving warfarin and those not under anti-coagulation therapy.

Design: Crossover multicenter observational study

Setting: 26 hospitals where oral surgeon is available.

Participants: Data on 2,817 teeth (496: receiving warfarin, 2,321: not receiving warfarin; mean age (SD): 62.2 (17.6)) extracted from November 1, 2008 to March 31, 2010, were collected. Warfarin-receiving patients were eligible when PT-INR measured within 7 days prior to the extraction was less than 3.0.

Interventions: Simple dental extraction was performed and incidence of post-extraction bleeding and comorbidities were recorded.

Primary and Secondary Outcome Measures: Post extraction bleeding not controlled by basic hemostatis procedure as clinically significant.

Results: Bleeding events were reported for 35 (7.1%) and 49 (2.1%) teeth, of which 18 (3.6%) and 9 (0.4%) teeth were considered as clinically significant, in warfarin and non-warfarin groups, respectively, the difference between which was 3.24% (confidence intervals 1.58 – 4.90%). The incidence rates by patients were 2.77 and 0.39%, in warfarinized- and non-warfarin group, respectively (incidence difference 2.38%, confidence intervals 0.65 – 4.10%). Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), mandibular foramen conduction anesthesia (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) significantly correlate with the bleeding incidence. Multivariate analysis revealed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding.

Conclusion: Our results suggest that there is slight but significant increase in incidences for the post-extraction bleeding in patients receiving warfarin. Although absolute incidence was low in both groups, the bleeding risk is not negligible.

Strength and Limitation of this Study

- The present study examined difference of the incidences for post-extraction bleeding between the patients receiving and not-receiving warfarin, which few previous studies to date have been reported.
- The study included dental facilities where at least one or more certified oral surgeons are available in order to standardize skills of the operators and capability of the facilities for providing advanced care in the event of significant bleeding.
- We also analyzed the risk factors for post-extraction bleeding events in patients receiving warfarin.
- Due to the study design, we may have underestimated the incidence of post-extraction bleeding that may occur in community dental clinics.
- Although we tried to standardize the dental extraction procedure, there might have been inter-facility differences.

INTRODUCTION

Until recently, the common procedure for tooth extraction in patients continuously receiving warfarin or other antiplatelet therapy was to discontinue or reduce the dose to minimize the risks of odontorrhagia. ~~However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1]~~ However, the procedure has been re-evaluated since cases of thromboembolic complications after dental extraction with warfarin (WF) cessation were reported [1-3]. Thereafter, many studies including randomized trials [2-44-6], Cohort studies [5-77-9] and meta-analyses [8-1010-12] have been conducted, all of which reported no significant differences in incidences of post-extraction bleeding and/or other hemorrhagic complications, concluding that, in patients whose prothrombin time- international normalized ratio (PT-INR) is within desirable therapeutic range, dental extraction can be performed safely without cessation of warfarin. Clinical guidelines published after these studies advised that patients whose PT-INR values were within the recommended therapeutic ranges should continue warfarin when undergoing dental extraction.[11-1313-15] However, there have been little studies that specifically addressed difference in the bleeding incidences and its 95% confidence interval comparing tooth extraction cases in patients receiving and not receiving warfarin.

Given these circumstances, we evaluated the difference in the post-extraction bleeding incidences in otherwise healthy control without warfarin administration (non-WF group) and in patients under reasonable coagulation control with warfarin (WF group). We selected the subjects for the latter group whose PT-INR was 3.0 or lower at the time of the procedure, as the PT-INR of 3.0 was indicated as the maximum safety threshold for tooth extraction in the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction in Japanese.[1416] We also investigated the risk factors for the incidence of post-extraction bleeding in patients receiving warfarin therapy.

MATERIALS AND METHODS

This was a prospective multicenter observational study of post-extraction bleeding events

in patients receiving and not receiving warfarin therapy.

Study Period and Eligibility Criteria

Twenty-six hospitals located across Japan participated. This study included patients who underwent simple tooth extraction from November 1, 2008 to March 31, 2010 at the department of oral surgery of these hospitals and who met the eligibility criteria listed below. Simple tooth extraction referred to a tooth removed without traumatizing the surrounding alveolar bone or elevating a mucoperiosteal flap.

Eligibility criteria included the following: 20 or more years of age at the time of tooth extraction; no contraindications for tooth extraction; surgery was performed by oral surgeon with a minimum of 3 years of experience in dental practice; the oral extraction procedure lasted for no longer than 15 minutes; and platelet count within 7 days prior to the procedure was normal. In addition, in patients receiving warfarin therapy, PT-INR measured within 7 days prior to the procedure should be less than 3.0. Patients receiving anti-platelet medication were not excluded but recorded as such. According to “The Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction”[14], we instructed the participating hospitals that dental extraction should be performed without discontinuing or reducing the dose of warfarin in patients whose PT-INR was not exceeding 3.0 when measured within 7 days prior to the procedure.

Study Variables

The variables analyzed in this study were: bleeding events, patient’s age and sex, position of the removed tooth, instruments used for removal (forceps only, elevators only, forceps and elevators), reasons for extraction, use of antiplatelet drugs, PT-INR values measured within 7

days before exodontia (only for patients receiving chronic warfarin therapy), comorbidities possibly influencing hemostasis, use of vasoconstrictors, combined use of local anesthetics and vasoconstrictors, use of inferior alveolar nerve block, severity of gingivitis after extraction (none, mild, moderate, severe), formation of abnormal granulation tissue in the extraction socket (none, little, medium, much), history of acute inflammation at extraction site, and post-extraction infection.

Hemostasis

The hemostatic methods for patients not receiving warfarin were chosen at the discretion of the dentist or oral surgeon performing the procedure. In patients on warfarin therapy, either absorbable oxidized cellulose or gelatin sponge was implanted into the alveolar socket, and wound margins were sutured. In both groups of patients, topical hemostatic agents other than epinephrine, systemic hemostatic agents, and splints were prohibited until primary hemostasis was observed. In patients who had multiple teeth extracted in one session, possible post-extraction bleeding was examined for each tooth. In a patient receiving warfarin, the post-extraction procedure defined above was performed each time after a tooth was removed.

Permitted Drugs

Use of local anesthetics containing vasoconstrictors (e.g., epinephrine and felypressin) was allowed at doses commonly practiced. In warfarin-treated patients, penicillins or cefems (e.g., cefcapenepivoxil and cefditoren pivoxil) was the primary choice of prophylactic antibiotics for their minimal interaction with warfarin. For those who were allergic to penicillins, clarithromycin was recommended. Use of analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors was allowed at ordinary doses.

Confirmation of Hemostasis

All patients were asked to bite down on a roll gauze for a maximum of 30 minutes for astriction of the wound. After release of the biting pressure, the wound was examined for hemostasis. Patients visited the hospital on the next day of surgery to check for possible bleeding, and were instructed to present at the hospital for treatment, if bleeding should occur later. The follow-up period was 7 days postoperatively.

Follow-up of Bleeding Events

If a patient had a bleeding event during the follow-up period, the severity of the hemorrhage and blood pressure were recorded. If the patient was on warfarin therapy, his or her PR-INR values were measured in addition.

Evaluation of Bleeding Events

In this study, bleeding events occurring in the follow-up period were classified into one of the following 5 grades: 0, no bleeding; 1, excessive blood clotting in the socket, no treatment required; 2-1, hemostasis achieved by compressing the wound longer than 30 minutes; 2-2, oozing hemorrhage observed on or after the next day of the procedure, which hemostasis was achieved by simple compression; 3, bleeding required treatments other than wound compression, such as application of compression brace and/or coagulation by electrotome was needed. Grade 2-2 and higher events were regarded as clinically significant, and were defined as post-extraction bleeds in this study.

Statistical Analysis

Data were collected by a tooth, but not by a patient. This means that patients who had

multiple teeth extraction were counted multiple times for the number of extracted teeth. Data were then sorted and analyzed by the anatomical positions. The difference in post-extraction bleeding incidence between patients receiving and not receiving warfarin therapy and its 95% confidence interval (CI) were calculated. In addition, a multivariate logistic regression analysis was conducted to identify risk factors for post-extraction bleeding in warfarin-treated patients. Adjusted odds ratios (ORs), their 95% CIs and *p*-values were calculated controlling for major confounders. Explanatory variables with a significance level of $P < 0.20$ on univariate analyses were included in the multivariate logistic regression model. Statistical analyses were performed using the SPSS software (version 15.0, SPSS Japan Inc., Tokyo, Japan).

Ethics

The objective of this study was explained in details to potential study participants so that they could make an informed decision. Informed consent was obtained orally or by a written document, according to the recommendation to the ethics committee of each participating facilities. Patients' personal information was stored in a de-identified but linkable format during the 7-day follow-up period, and was rendered completely anonymous thereafter. This study was reviewed and approved by the ethics committee of the National Hospital Organization Tochigi Medical Center, Tochigi, Japan, prior to its conduct. The approved protocol was distributed to the participating hospitals to keep the uniformity of the study.

RESULTS

Totally, 3,515 case reports were submitted from the participating investigators. Of these, 698 cases were eliminated because of protocol deviations and/or insufficient datadocumentation, leaving 2,817 for further analysis.

Post-extraction Bleeding Incidence

Bleeding events including minor hemorrhagic episodes were reported for 35 out of 496 teeth (7.1%) of the warfarin group and for 49 out of 2,321 teeth (2.1%) of the non-warfarin group, with a total of 84 teeth. Clinically significant post-extraction bleeds (i.e., grade 2-2 or higher) were reported for 27 teeth, including 18 (3.6%) and 9 (0.4%) from the warfarin and non-warfarin groups, respectively (Table 1).

Breakdown of Removed Teeth by Sex and Study Group

The mean (SD) age of all study participants was 62.2 (17.6) years, and 1,446 and 1,371 teeth were removed from males (51.3%) and females (48.7%), respectively. The warfarin group had a mean (SD) age of 70.3 (10.9) years, and reported removal of 496 teeth, 320 from males (64.5%) and 176 from females (35.5%). Non-warfarin group had a mean (SD) age of 60.4 (18.3) years, and reported removal of 2321 teeth, 1126 from males (48.5%) and 1,195 from females (51.5%) (Table 1).

The difference in post-extraction bleeding incidence between the warfarin group and non-warfarin group was 3.24% and its 95% CI was 1.58% to 4.90%. When analyze by patient, clinically significant bleeding occurred in total of 361 out of 2,146 patients (2.77 and 0.39%, in warfarin- and non-warfarin group, respectively, incidence difference between which was 2.38% (95% CI, 0.65 – 4.10%; Table 2),

Risk Factors for Post-extraction Bleeding in Warfarin-Treated Patients

Univariate analyses showed that age (OR: 0.197, $P = 0.001$), PT-INR (OR: 3.635, $P = 0.003$), inferior alveolar nerve block (OR: 4.854, $P = 0.050$), and formation of abnormal granulation tissue in extraction socket (OR: 2.900, $P = 0.031$) were significantly correlated

with post-extraction bleeding (Table 3). In addition to these variables, position of the removed tooth, reasons for extraction, antiplatelet drugs, comorbidities possibly influencing hemostasis, and history of acute inflammation at extraction site were found to have P values smaller than 0.2 by univariate analysis. Consequently, these parameters were included as explanatory variables in the multivariate regression analysis. The results showed that age (OR: 0.126, $P = 0.001$), antiplatelet drugs (OR: 0.100, $P = 0.049$), PT-INR (OR: 7.797, $P = 0.001$), and history of acute inflammation at extraction site (OR: 3.722, $P = 0.037$) were significant risk factors for post-extraction bleeding (Table 4).

DISCUSSION

~~Recent report brought attention to cases of potentially lethal thromboembolic complication associated with dental extraction in patients under anti-coagulation therapy with warfarin when warfarin was temporarily discontinued in preparation for dental extraction.[1,15,16] On the other hand, multiple studies reported that dental extraction is safely performed and post-extraction bleeding can be sufficiently controlled by topical hemostasis only in patients receiving warfarin without discontinuing the medication.[2-10] Based on these findings, the current guidelines recommend that dental extraction be performed with continuing maintenance dosage of warfarin.[11-13] In warfarinized patients, thromboembolic events were reported in varying frequency in literature ranging as low as 0.059% [17, 18] to as high as 1% [1] when warfarin was discontinued prior to dental extraction, while little reports serious post-extraction bleeding associated with dental extraction. Based on those data, literature now suggest that WF should not be discontinued when performing dental extraction in warfarinized patients, regardless of incidences of thromboembolic events associated with dental procedure.[5, 19-21]. while few life-threatening bleeding complication have been reported. These findings have strongly suggested that warfarin should not be discontinued~~

~~when performing dental extraction in warfarinized patients. [6,19-21].~~ Majority of previous studies assessed safety of dental procedure comparing incidence of complications in patients receiving WF when the WF was discontinued or not. Now that dental extraction without WF cessation has become a standard procedure in patients receiving WF, we now conducted the present study to evaluate incidences of post-extraction bleeding in comparison with patients who are not receiving anti-coagulation therapy.

The present study is a nation-wide, multi-institutional prospective study and evaluated frequency of clinically significant post-extraction bleeding and its difference between the non-warfarin and warfarin groups. Clinically significant post-extraction bleeding occurred in low rate in both study groups. Nonetheless, the difference between the two groups was 3.24% with its 95% confidence interval between 1.58 – 4.90%.

Among the patients receiving warfarin, older patients showed lower risks for post-extraction bleeding in the present study. Few studies have addressed influence of patients' age on incidence of post-extraction bleeding. Mean PT-INR in the patients who experienced clinically significant post-extraction bleeding was 2.57 ± 0.62 in patients 65 years old or older, which was significantly higher compared to that in patients younger than 65 years old ($2.10 \pm 0.39, P = 0.048$). These results suggest that younger patients tend to experience clinically significant post-extraction bleeding at lower PT-INR, which might have contributed to the lower bleeding risks in the elderly patients in the present study.

Few studies reported to date examined the relationship between age and the incidence of post-extraction bleeding. Our finding indicated that extra caution should be taken when conducting exodontia in elderly patients receiving warfarin therapy, and the frequency of such situations would increase with aging population.

A study that investigated the impact of comorbid conditions on hemostasis suggested that patients with liver dysfunction are another group at high risk for post-extraction bleeding.[22]

The present study did not identify liver dysfunction or other comorbid conditions that would affect hemostasis as a risk factor for increased incidence of post-extraction bleeding. The attribution of such condition may have been underestimated in the present study as only 4.2% of the study participants had chronic hepatitis.

Our results also showed that the incidence of post-extraction bleeding events increased with higher PT-INR, even though the values did not exceed 3.0. This finding suggests that a special attention would be needed in patients whose PT-INR are close to 3.0 or higher to prevent post-extraction hemorrhagic event. Because warfarin sensitivity may vary among individuals and different ethnic groups, further studies will be needed to verify if the current findings are generalizable to other ethnic groups.

No randomized comparative trials that addressed incidences of post-extraction bleeding in patients receiving warfarin with or without anti-platelet medicine has so far been reported. An observational study by Morimoto et al found no significant difference in incidences of post-extraction bleeding between the patients receiving warfarin alone and those in combination with an anti-platelet medicine.[6] In contrast, Scully et al reported that, in patients with oral surgeries, post-operative bleeding incidence was higher in patients under the combination therapy of warfarin and an anti-platelet medicine.[23] Besides reports regarding the bleeding events associated with oral surgeries, increased incidence of hemorrhagic complications in patients receiving anti-platelet medicine in addition to warfarin compared to those receiving warfarin only was observed in a cohort study in Japanese patients under anti-coagulation therapies.[24]. The results from the present study suggested that incidence for post-extraction bleeding is lower in patients receiving both warfarin and an anti-platelet medicine. Although findings vary in those studies, anti-platelet medicine alone is in general considered to minimally affect incidences of post-operative bleeding in the cases of dental

extraction[8] or of surgeries [25], and may as well in patients under the control of warfarin.

Suturing of wound and filling of the socket with oxidized cellulose or gelfoam have been widely recognized as efficient means of hemostasis after dental extraction.[26-28] However, some guidelines do not necessarily recommend suture of the wound, while supporting the use of oxidized cellulose, gelfoam or fibrin glue.[8] Several reports also found that suturing would could rather damage the tissue at the socket.[29,30]In the present study, incidences of post-extraction bleeding in patients not receiving warfarin were not significantly different between the patients whose wound was sutured and those without suture (0.6 and 0.2%, respectively). However, we were unable to tell whether suturing increased the incidence of post-extraction bleeding in the patients receiving warfarin as wounds were sutured in all the patients receiving warfarin in the present study. Evaluation of the outcome of suturing in patients receiving warfarin would be worthy of future study. Heparin bridging is another effective means to prevent thromboembolism and to reduce risk for post-operative bleeding.[31,32], application of which is primarily limited to a major surgery that topical hemostasis is not applicable. Efficacy of heparin bridging was evaluated by a randomized comparative study,[33] which found no significant differences in incidences of post-extraction bleeding or thromboembolic complications with and without addition of heparin bridging with continuing warfarin therapy, concluding that heparin bridging is not required when dental extraction is performed as long as topical hemostasis is applicable. On the other hand, comparative studies examined cases of minor surgeries performed with cessation of warfarin with or without additional heparin bridging reported severe hemorrhagic event in cases receiving heparin bridging, though no thromboembolic complication had occurred.[34,35] Furthermore, heparin needs to be continuously administered intravenously when performing heparin bridging, necessitating hospital admission with resulting higher cost and demands for medical personnel. The results from the present study further supported the notion that topical

hemostasis provides sufficient hemostasis in cases of simple tooth extraction without discontinuing warfarin, and therefore heparin bridging is not necessary. Several aspects of our study design that may have affected the outcome of the present study should be noted. First, we included PT-INR values measured within 7 days prior to tooth extraction, considering the availability of measurement results. However, because effects of warfarin can be affected by diet and other drugs, experts suggested to measure PT-INR within 24 [8,9,36,37] and 48 [38] hours before the procedure. The British Committee for Standards in Hematology recommended 72 hours before surgery [11]. Therefore, pre-extraction PT-INR values we utilized may not have accurately reflected the coagulation status immediately prior to the extraction, skewing the results of our analyses. To minimize the bias, we conducted another PT-INR measurement in patients receiving warfarin who experienced clinically significant bleeding events soon after the event observation. In such patients, PT-INR values before and after the tooth extraction were 2.27 and 2.26, respectively, and not significantly changed. These data suggest that the possible bias derived from PT-INR values measured within 7 days in advance were minimal. Second, we performed all the analyses by tooth, not by patients. We hypothesized, based on previous studies that found no significant correlation between the numbers of tooth extracted and incidence of post extraction bleeding,[2,4,5,7] that risks for post-extraction bleeding may vary depending the position and/or conditions of the tooth extracted even in the same individual. In order for detecting possible influence of local factors, such as position of tooth extracted (foretooth vs. molar tooth) and gum conditions (presence of inflammation and/or inappropriate granulation) on risks for post-extraction bleeding, we chose to present our data by tooth, despite a possible bias of including some of the patient data multiple times when multiple teeth was extracted from a single patient. When analyzed by patient, clinically significant post-extraction bleeding occurred in 2.77 and 0.39% in warfarin and non-warfarin group, respectively, difference between which was 2.38% (95% CI,

0.65 – 4.10%).and was similar to that found in analysis by tooth. These data suggest that the bias that might arise from the analyses by tooth was minimal. Third, evaluation of the post-extraction bleeding events was not blinded and choice of secondary hemostasis means were left at the discretion by the operator in charge, which might have affected the outcome of our analyses. However, the definition of the clinically significant bleeding events was made clear, minimizing the influence by the person who evaluated the individual event. ~~Lastly, we compared incidences of post extraction bleeding in patients under warfarin therapy who underwent dental extraction without cessation of warfarin with those who are not receiving warfarin therapy. On the other hand, most of previous studies assessed post extraction events in warfarinized patients with or without cessation of warfarin prior to dental extraction. Such difference in study population might also have resulted in different finding in the present study..~~ Indeed, there was little difference in post-extraction bleeding incidence in patients whose wound was sutured or not (0.6\$ and 0.2%, respectively), further supporting the notion that means of hemostasis have minimally affected the present findings.

CONCLUSION

The difference in incidence rates of post-extraction bleeding between warfarin and non-warfarin group was 3.24% (95% CI, 1.49 – 4.99%). Age, PT-INR, and history of acute inflammation at extraction site were risk factors for post-extraction bleeding in warfarin receiving patients.

CONTRIBUTORSHIP STATEMENT

H. Iwabuchi designed the study protocol and wrote the manuscript. H. Imai analyzed the data and contributed to edition of the manuscript. ~~H. Nakao also participated in data analyses. Y. Imai is the Principle Investigator of the present study.~~ H. Iwabuchi, Y Imai, S Asanami, M

Shirakawa, G Yamane, H Ogiuchi, K Kurashina, M Miyata contributed to data collection. H. Nakao also participated in data analyses. Y. Imai is the Principle Investigator of the present study. All the authors have approved the final version of the manuscript to be published. All the authors also agreed upon their accountability for its accuracy and integrity of any part of the present work.

COMPETING INTEREST

I/We have read and understood BMJ policy on declaration of interests and declare the following interests.

Copyright and license for the publication:

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.”

FUNDING

There is no involvement of funding sources in this research.

DATA SHARING

Data sharing: patient level data [and/or] full dataset [and/or] technical appendix [and/or] statistical code [and/or] are available from the corresponding author upon request. Consent for

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

additional data sharing was not obtained but the presented data are anonymised and risk of identification is low.

For peer review only

REFERENCES

- 1 Wahl MJ. Dental surgery in anticoagulated patients. Arch Inter Med 1998;158:1610-16.
- 2 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Inter Med. 2008;168:63-69.
- 3 Ogiuchi H, Ando T, Tanaka M, et al. Clinical reports on dental extraction from patients undergoing oral anticoagulant therapy. Bull Tokyo Dent Coll. 1985;26:205-212.
- 4 Evans IL, Sayers MS, Gibbons AJ, et al. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. Br J Oral Maxillofac Surg 2002;40:248-252.
- 5 Sacco R, Sacco M, Carpenedo M, et al. Oral surgery in patients on oral anticoagulant therapy: A randomized comparison of different intensity targets. Oral Surg Oral med Oral Pathol Oral Radiol Endod. 2007;104:e18-21.
- 6 Al-Mubarak S, Al-Ali N, Rass MA, et al. Evaluation of dental extractions, suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. Br Dent J. 2007;203:1-5.
- 7 Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery: Should the Anticoagulation regiment be altered? J Oral Maxillofac Surg. 2000;58:131-5.
- 8 Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in patients on oral antithrombotic therapy. J Oral Maxillofac Surg. 2008;66:51-7.
- 9 Barrero MV, Knezevic M, Martin MT, et al. Oral surgery in the patients undergoing oral anticoagulant therapy. Med oral. 2002;7:63-70.
- 10 Aframian DJ, Lalla RV, Peterson DE. Management of dental patients taking common hemostasis –altering medications. Oral Surg Oral med Oral Pathol Oral Radiol Endod. 2007;103(suppl 1):S45e1-11.
- 11 Goodchild JH, Donaldson M. An evidence-based dentistry challenge: Treating patients on

warfarin(Coumadin). Dental aimplantol Update2009;20:1-8.

1012 Nematullah A, Alabousi A, Blanas N, et al. Dental surgery for patients on
anticoagulant therapy with warfarin: a systematic review and meta-analysis. J can Dent
Assoc.2009;75:41-41i.

1013 Perry DJ, Noakes TJC, Helliwell PS. Guidelines for the management of patients on
oral anticoagulants requiring dental surgery. Br Dent J.2007;203:389-393.

1014 Sasanuki H, et al: Guidelines for management of anticoagulant and antiplatelet
therapy in cardiovascular disease. Circ J.2004;68suppl IV:1153-1219.

1015 Jcs Joint Warking Group: Guidelines for pharmacotherapy of atrial fibrillation –
Digest Version-. Circ J.2010;74:2479-2500.

1016 Japanese Society of Dentistry for Medically Compromised Patient, Japanese Society
of Oral and Maxillofacial Surgeons, Japanese Society of Gerodontology: The Guidelines
for Patients on Antithrombotic Therapy Requiring Dental Extraction. 2010
version Gakujutsusha Corporation Tokyo 2010.

~~15 Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short term
interruption of warfarin therapy. Arch Inter Med. 2008;168:63-69.~~

~~16 Ogiuchi H, Ando T, Tanaka M, et al. Clinical reports on dental extraction from patients
undergoing oral anticoagulant therapy. Bull Tokyo Dent Coll. 1985;26:205-212.~~

17 Balevi B. Should warfarin be discontinued before a dental extracion? A decision-tree
analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:691-697.

18 Balevi B. Should warfarin be discontinued before a dental extraction? Oral Surg Oral Med
Oral Pathol Oral Radiol Endod 2012;113:150-152.

19 Gaspar R, Brenner B, Ardekian L, Peled M. Use of tranexamic acid mouthwash to
prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication.
Quintessence Int 1997;28:375-9.

- 20 Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on oral anticoagulant therapy: comparison of INR value with occurrence of postoperative bleeding. *Int J Oral Maxillofac Surg* 2001;30(6):518-21.
- 21 Karsli ED, Erdogan O, Esen E, Acartürk E. Comparison of the effects of warfarin and heparin on bleeding caused by dental extraction: a clinical study. *J Oral Maxillofac Surg* 2011;69:2500-7.
- 22 Devani P, Lavery KM, Howell CJT. Dental extractions in patients on warfarin –Is alternation of anticoagulant regime necessary? *Br J Oral Maxillofac Surg*.1998;36:107-111.
- 23 Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy. *Oral Surg Oral Med Oral Pathol* 2002;94:57-64.
- 24 Toyoda K, Yasaka M, Iwade K, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease –A prospective, multicenter, observational study. *Stroke*.2008;39:1740-45.
- 25 Maulaz AB, Bezerra DC, Michel P, et al. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. *Arch Neurol*.2005;62:1217-1220.
- 26 Halfpenny W, Fraser JS, Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*.2001;92:257-259.
- 27 Carter G, Goss A, Lloyd J, et al. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. *J Oral Maxillofac Surg*.2003;61:1432-1435.
- 28 Blinder D, Manor Y, Martinowitz U, et al. Dental extraction in patients maintained on continued oral anticoagulant. Comparison of local hemostatic modalities. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*.1999;88:137-140.

29 Salam S, Yusuf H, Milosevic A. Bleeding after dental extractions in patients taking warfarin. *Br J Oral Maxillofac Surg.* 2007;45:463-466.

30 Al-Belasy FA, Amer MZ. Hemostatic effect of n-butyl-2-cyano- acrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. *J Oral Maxillofac Surg.* 2003; 61: 1405-1409.

31 Dunn AS,Alexander G,G Turpie. Perioperative management of patients receiving oral b Anticoagulants A systemic review. *Arch Intern Med.* 2003;163:901-908.

32 Kovacs MJ, Kearon C, Rodger M, et al; Single-arm study of bridging therapy eith low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. *Circulation.* 2004;110:1658-1663.

33 Bajkin BV, Popovic SL, Selakovic SDJ. Randomized prospective trial comparing bridging therapy using low-molecular-weight heparin with maintenance of oral anticoagulation during extraction of teeth. *J Oral Maxillofac Surg.* 2009; 67: 990-995.

34 Garcia DA, Regan S, Henault LE, etal.Risk of thromboembolism with short-term interruption of warfarin therapy.*Arch Intern Med.* 2008;168:63-69.

35 Bloomer CR. Excessive hemorrhage after dental extractions using low-molecular-weight heparin(Lovenox) anticoagulation therapy. *J Oral Maxillofac Surg.* 2004;62:101-103.

36 Chugani V. Management of dental patients on warfarin therapy in a primary care setting. *Dental Update.*2004;31:379-384.

37 Pototski M, Amenabar JM: Dental management of patients receiving anticoagulation or antiplatelet treatment. *J Oral Sci.*2007;49:253-8.

38 Brennan MT, Hong C, Furney SL, et al. Utility of an international normalized ratio testing device in a hospital-based dental practice. *J Am Dent Assoc.*2008;139:697-703.

Table 1. Breakdown of extracted teeth by important classification variables

No. of teeth by:		Warfarin n=496	No Warfarin n=2321	Total N = 2817	P value
Age (years)					
	< 65	124 (25.0)	1131 (48.7)	1255 (44.6)	< 0.0001
	≥ 65	372 (75.0)	1190 (51.3)	1562 (55.4)	
Sex					
	Male	320 (64.5)	1126 (48.5)	1446 (51.3)	< 0.0001
	Female	176 (35.5)	1195 (51.5)	1371 (48.7)	
Type					
	Foretooth	132 (26.6)	663 (28.6)	795 (28.2)	0.550
	Premolar	127 (25.6)	552 (23.8)	679 (24.1)	
	Molar	237 (47.8)	1106 (47.7)	1343 (47.7)	
Instrument					
	Forceps only	171 (34.5)	604 (26.0)	775 (27.5)	0.000
	Elevators only	226 (45.6)	919 (39.6)	1145 (40.6)	
	Forceps and elevators	99 (20.0)	798 (34.4)	897 (31.8)	
Cause for extraction					
	Periodontitis	160 (32.3)	533 (23.0)	693 (24.6)	< 0.0001
	Caries	87 (17.5)	477 (20.6)	564 (20.0)	
	Apical periodontitis	219 (44.2)	1002 (43.2)	1221 (46.6)	
	Wisdom tooth pericoronitis	23 (4.6)	192 (8.3)	215 (7.6)	
	Other	7 (1.4)	117 (5.0)	124 (4.4)	
Status of antiplatelet therapy					
	Yes	122 (24.6)	433 (18.7)	555 (19.7)	0.003
Use of local anesthetics containing vasoconstrictors					
	Yes	491 (99.0)	2265 (97.6)	2756 (97.8)	0.105
Use of inferior alveolar nerve block					
	Yes	14 (2.8)	82 (3.5)	96 (3.4)	0.429
Comorbidity possibly influencing hemostasis					
	Hypertension	267 (53.8)	715 (30.8)	982 (34.9)	< 0.0001
	Diabetes mellitus	89 (17.9)	267 (11.5)	356 (12.6)	
	Chronic hepatitis	21 (4.2)	110 (4.7)	131 (4.7)	
	Other	68 (13.7)	212 (9.1)	280 (9.9)	
	Multiple disorders	341 (68.8)	1039 (44.8)	1380 (49.0)	
History of acute inflammation at extraction site					
	Yes	216 (43.5)	829 (35.7)	1045 (37.1)	0.001
Gingival inflammation at extraction site					
	None	298 (60.1)	1266 (54.5)	1564 (55.5)	0.000
	Mild	95 (19.2)	264 (11.4)	359 (12.7)	
	Moderate	13 (2.6)	38 (1.6)	51 (1.8)	
	Severe	90 (18.1)	753 (32.4)	843 (29.9)	
Abnormal granulation tissue in extraction socket					

None	87 (17.5)	818 (35.2)	905 (32.1)	0.003
Little	230 (46.4)	917 (39.5)	1147 (40.7)	
Medium	134 (27.0)	441 (19.0)	575 (20.4)	
Much	45 (9.1)	145 (6.2)	190 (6.7)	
Severity of post-extraction bleeding				
G1	9 (1.8)	29 (1.2)	38 (1.3)	< 0.0001
G2-1	8 (1.6)	11 (0.5)	19 (0.7)	
G2-2	1 (0.2)	8 (0.3)	9 (0.3)	
G3	17 (3.4)	1 (0.04)	18 (0.6)	
total	35 (7.1)	49 (2.1)	84 (3.0)	
G2-2+G3	18 (3.6)	9 (0.4)	27 (1.0)	< 0.0001
PT-INR				
(mean ± SD)	1.90±0.49			

Table 2. Incidences of clinically significant post-extraction bleeding and their difference in patients receiving and not receiving warfarin

		Incidence over total numbers of teeth extracted (%)			
		Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence (%)	95% CL	
				Lower	Upper
Warfarin	3.63				
No			3.24	1.58	4.90
Warfarin	0.39				
		Incidence over total numbers of study subjects (%)			
		Post-extraction bleeding incidences (%)	Difference in post-extraction bleeding incidence (%)	95% CL	
				Lower	Upper
Warfarin	2.77				
No			2.38	0.65	4.10
Warfarin	0.39				

Table 3. Univariate analysis of post-extraction bleeding events by potential risk factors

		Incidence of post-extraction bleeding (%)	OR	95% CL		P-value
				Lower	Upper	
Age (years)						
	< 65	8.9	1 (Ref)			
	≥ 65	1.9	0.197	0.075	0.520	0.001*
Sex						
	Male	3.4	1 (Ref)			
	Female	4.0	1.164	0.443	3.057	0.759
Type						
	Foretooth or premolar	2.3	1 (Ref)			
	Molar	5.1	2.2249	0.830	6.091	0.111
Instrument						
	Forceps only	2.9	1 (Ref)			
	Elevators alone or with forceps	4	1.383	0.485	3.947	0.544
Cause for extraction						
	Caries, apical periodontitis, or other	2.6	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	5.5	2.204	0.854	5.688	0.102
Status of antiplatelet therapy						
	No	4.5	1 (Ref)			
	Yes	0.8	0.174	0.023	1.318	0.090
PT-INR						
			3.635	1.5640	8.448	0.003*
Use of vasoconstrictors						
	No	4.1	1 (Ref)			
	Yes	0				
Use of local anesthetics containing vasoconstrictors						
	No	0	1 (Ref)			
	Yes	3.7				
Use of inferior alveolar nerve block						
	No	3.3	1 (Ref)			
	Yes	14.3	4.854	1.002	23.513	0.050*
Comorbidity possibly influencing hemostasis						
	No	5.8	1 (Ref)			
	Yes	2.6	0.440	0.171	1.131	0.088
History of acute inflammation at extraction site						
	No	2.5	1 (Ref)			
	Yes	5.1	2.093	0.7970	5.492	0.134
Gingival inflammation at extraction site						
	None to mild	3.3	1 (Ref)			
	Moderate to severe	4.9	1.491	0.519	4.283	0.458

**Abnormal granulation tissue in
extraction socket**

None to little	2.2	1 (Ref)			
Medium to much	6.1	2.900	1.1040	7.619	0.031*

For peer review only

Table 4. Multivariate analysis of post-extraction bleeding events by potential risk factors

		OR	95% CL		P-Value
			Lower	Upper	
Age (years)					
	< 65	1 (Ref)			
	≥ 65	0.126	0.035	0.448	0.001*
Type					
	Foretooth or premolar	1 (Ref)			
	Molar	0.953	0.288	3.151	0.937
Cause for extraction					
	Caries, apical periodontitis, or other	1 (Ref)			
	Periodontitis or wisdom tooth pericoronitis	2.301	0.742	7.142	0.149
Status of antiplatelet therapy					
	No	1 (Ref)			
	Yes	0.100	0.010	0.986	0.049*
PT-INR		7.797	2.2930	26.510	0.001*
Use of inferior alveolar nerve block					
	No	1 (Ref)			
	Yes	2.437	0.336	17.659	0.378
Comorbidity possibly influencing hemostatis					
	No	1 (Ref)			
	Yes	0.503	0.157	1.612	0.247
History of acute inflammation at extraction site					
	No	1 (Ref)			
	Yes	3.722	1.0850	12.773	0.037*
Abnormal granulation tissue in extraction socket					
	None to little	1 (Ref)			
	Medium to much	2.895	0.8940	9.369	0.076

		Item No	Recommendation
Title and Abstract	✓	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
	✓		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	✓	2	Explain the scientific background and rationale for the investigation being reported
Objectives	✓	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	✓	4	Present key elements of study design early in the paper
Setting	✓	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	✓	6	(a) Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants
	N/A		(b) Cohort study
Variables	✓	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effects modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	✓	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	✓	9	Describe any efforts to address potential sources of bias
Study size	✓	10	Explain how the study size was arrived at
Statistical methods	✓	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
	✓	12	(a) Describe all statistical methods, including those used to control for confounding
	✓		(b) Describe any methods used to examine subgroups and interactions
	✓		(c) Explain how missing data were addressed
	✓		(d) Cross-sectional study – If applicable, describe analytical methods taking accounting of sampling strategy
	✓		(e) Describe any sensitivity analyses
Results			
	✓	13	(a) Report numbers of individuals at each stage of study – e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed
	N/A		(b) Give reasons for non-participation at each stage
	N/A		(c) Consider use of a flow diagram
Descriptive data	✓	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
	✓		(b) Indicate numbers of participants with missing data for each variable of interest
	N/A		(c) Cohort study
Outcome data	✓	15	Cross-sectional study – Report numbers of outcomes events or summary measures
Main results	✓	16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (e.g. 95 confidence interval). Make clear which confounders were adjusted for and why they were included
	✓		(b) Report category boundaries when continuous variable were categorized
	✓		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	✓	17	Report other analyses done – e.g. analyses of subgroups, and sensitivity analyses

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Discussion		
✓	18	Summarize key results with reference to study objectives
✓	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
✓	20	Give a cautious overall interpretations of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
✓	21	Discuss the generalizability (external validity) or the study results
Other information		
Funding	✓ 22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based