Dental surgery in anticoagulated patients—stop the interruption

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In a literature review, the incidence and morbidity of bleeding complications after dental surgery in anticoagulated patients was compared with embolic complications when anticoagulation was interrupted. Over 99% of anticoagulated patients had no postoperative bleeding that required more than local hemostatic measures. Of more than 5431 patients undergoing more than 11,381 surgical procedures, with many patients at higher than present therapeutic intenational normalized ratio (INR) levels, only 31 (~0.6% of patients) required more than local hemostasis to control the hemorrhage; none died due to hemorrhage. Among at least 2673 patients whose warfarin dose was reduced or withdrawn for at least 2775 visits for dental procedures, there were 22 embolic complications (0.8% of cessations), including 6 fatal events (0.2% of cessations). The embolic morbidity risk in patients whose anticoagulation is interrupted for dental surgery exceeds that of significant bleeding complications in patients whose anticoagulation is continued, even when surgery is extensive. Warfarin anticoagulation, therefore, should not be interrupted for most dental surgery. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:136-157)

Vitamin K antagonists such as warfarin are commonly used in patients with atrial fibrillation, artificial heart valves, deep vein thrombosis, myocardial infarction, and pulmonary embolisms. Ever since the first report of excessive bleeding after dental extractions in 1957,[1] dental surgery in anticoagulated patients has been controversial and the subject of avid interest among physicians and dentists, who must weigh the bleeding risks in anticoagulated patients versus the risks of embolic complications in patients whose anticoagulation is reduced or withdrawn.

Dental surgery, including simple and surgical tooth extractions, is unlike surgery performed on most other parts of the body. Major blood vessels are unlikely to be encountered, and the surgical sites are easily accessible to local hemostatic methods, including pressure application (biting on gauze), cellulose, gelatin foams, hemcon dressing, microfibrillar collagen, sutures, hemostatic solutions (styptics), tannic acid, tranexamic acid, and fibrin glue.[2]

Sequential literature reviews in 1998[3] and 2000[4] demonstrated that bleeding complications requiring more than local hemostatic measures after dental surgery at therapeutic anticoagulation levels are exceedingly rare. On the other hand, sometimes fatal embolic complications can occur when anticoagulation is withdrawn or reduced for dental procedures. Of over 2400 dental surgical procedures in over 950 patients, only 12 patients (<1.3%) suffered bleeding complications requiring more than local hemostatic measures. Of 575 cessations of warfarin for dental procedures, there were 5 embolic complications (0.95%) and 1 fatal outcome. The conclusion was that continuous anticoagulation at therapeutic INR levels should not be interrupted for dental surgery with local hemostatic measures. The purpose of the present review is to update the previous findings with the inclusion of additional literature.

Since 2000, most authors have concurred that continuous therapeutic levels of anticoagulation (up to INR 3.5, or sometimes 4.0) should not be withdrawn or reduced or replaced with heparin for dental surgery.[5-12] Beirne concluded, "The risk of uncontrolled life-threatening bleeding is so low that it is not necessary to stop anticoagulation [INR 2.0 to 4.0] even for a short interval and risk thromboembolism in patients on oral anticoagulants."[13] Although not the subject of this article, the use of newer anticoagulants, including direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban), has not been studied as extensively as that of warfarin, but it does not appear

Statement of Clinical Relevance

The risk of postoperative bleeding complications in patients in whom anticoagulation is continued for dental surgery is exceedingly small and is outweighed by the small risk of serious and sometimes fatal embolic events when anticoagulation is interrupted for dental surgery.

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necessary to withdraw such medications for dental surgery.[14]

The inclusion criteria for article selection were English language peer-reviewed publications that reported on bleeding complications or thromboembolic events in human patients in whom warfarin therapy was continued unchanged, altered, or interrupted for a dental procedure. Literature searches were performed in NLM PubMed and Scopus for citations included in the databases up to October 10, 2013. Other retrieval methods included cited reference searching and manual searching of the literature. Search terms used included "oral surgical procedures," "oral surgery," "tooth extraction," "dental scaling," "dental procedures," "warfarin," "anticoagulant," "surgical blood loss," "oral hemorrhage," "postoperative hemorrhage," "hemostasis altering," "thromboembolism," "stroke," "adverse event," "risk assessment," and "treatment outcome."

DENTAL SURGERY IN PATIENTS WITH CONTINUOUS WARFARIN ANTICOAGULATION

We reviewed 83 clinical studies of dental surgery in more than 5431 patients who were continuously anticoagulated with vitamin K antagonists and underwent more than 11,381 dental surgical procedures, including more than 10,322 dental extractions (Table I).[1,15-96] Many of these studies showed similar incidences of postoperative bleeding or blood loss after dental surgery between continuously anticoagulated patients, patients whose anticoagulation was reduced or withdrawn, and nonanticoagulated patients.[17,18,22,23,37,53,65,95] Out of more than 5431 patients at greater than 5677 visits undergoing more than 11,381 surgical procedures, there were only 375 cases (~6.6% of patient visits) of minor postoperative bleeding that required additional local measures for hemostasis. Only 31 cases (~0.6% of patient visits) required more than local hemostatic measures to control hemorrhage. Thus, more than 99% of all patients had no postoperative bleeding that required more than local hemostatic measures. These studies confirm the earlier findings that for continuously anticoagulated dental patients, there is an exceedingly small risk of a significant postoperative bleeding complication (requiring more than local hemostatic measures).

Analysis of some cases of postoperative hemorrhage requiring more than local hemostatic measures

Cieślik-Bielecka et al.[45] studied 40 continuously anticoagulated patients undergoing 186 dental surgical procedures, including 181 extractions with local hemostatic measures. Two patients (undergoing 3 extractions at INR 3.5 and 6 extractions at INR 3.0) who had "minor bleeding" 2 and 3 days postoperatively were treated with new sutures and intravenous cyclonamine. Some patients were on additional medications, including aspirin, but it is unclear which patients or what local measures other than new sutures were attempted before administering cyclonamine.

Morimoto et al. studied three groups of 382 patients undergoing simple and surgical dental extractions on continuous antithrombotic therapy.[71,72] The first group was on warfarin monotherapy, the second group was on warfarin and antiplatelet combination therapy, and the third was on antiplatelet monotherapy. Hemostasis was achieved in all patients with local measures, but one patient on combined warfarin–antiplatelet therapy undergoing three extractions at INR 1.5 was also administered vitamin K because of an "excessively high" postoperative INR level that was impossible to measure.

Hong et al. studied 122 anticoagulated dental surgical patients,[63] some of whom were on additional medications thought to enhance anticoagulation. Only one patient (following liver transplantation, with end-stage renal disease and on hemodialysis) on combined warfarin–aspirin therapy required more than local hemostatic measures after 5 extractions at INR 2.2. His anticoagulation was INR 5.9 after hospital admission. Vitamin K and fresh frozen plasma were administered and local hemostatic measures applied.

All of the above four patients requiring more than local hemostatic measures underwent 3 or more extractions. The authors reported that at least 2 (and possibly all 4) patients had very high postoperative INR levels, possibly because of concomitant medications and/or medical history. These very high INR levels may have contributed to the bleeding complications, and in each study, the authors concluded that therapeutic levels of anticoagulation should not be interrupted for dental surgery.

ANTICOAGULATION WITHDRAWAL OR REDUCTION FOR DENTAL PROCEDURES

We reviewed 64 studies of more than 2673 patients whose anticoagulation was withdrawn or reduced for more than 2775 appointments for dental surgery.[1,17,18,20,25,31,35-37,40,48,49,51,53,57,58,61,65,71,74,79,82,83,86,87,91,94,96-132] There were 161 patients (~6% of patients and visits) with at least minor postoperative bleeding, including 4 patients (0.14% of visits) who were administered more than local measures for hemostasis. There were 22 embolic complications (0.8%), including 6 that were fatal (Table II).

Table I. Dental surgery in continuously anticoagulated patients

Source	*No. of patients (pts) treated (visits)*	*No. of surgical procedures*	*No. of extractions*	*International normalized ratio (INR)*	*Comment*	*Postoperative bleeding that required professional treatment at least with local measures (other than immediately postoperatively)*	*Bleeding complications requiring more than local measures*
Al Zoman et al. 2013[15]	2 (2)	2	0	4.1 and 4.0 on the days of the procedures		0	0
Al-Belasy & Amer 2003[16]	30 (30)	155	155	1.7-4.3		5	0
Al-Mubarak et al. 2006,[17] 2007[18]	110 (110)	>110	>110	Mean 2.4-2.7		8	0
Alexander et al. 2002[19]	15 (15)	28	27	1.9-3.6 (mean 2.57)	All 27 extractions were surgical	0	0
Anavi et al. 1981[20]	15 (15)	52	52	PT 19%-36%; mean 27.5% ***[INR <2.5 to INR >3.0]***		7	0
Askey & Cherry 1956[21]	6 (10)	14	14	Prothrombin concentration 14%-51% ***[INR <2.0 to INR >3.5]***		0	0
Bacci et al. 2010[22]	451 (451)	926	926	1.8-4.0 (mean 2.14)	379 extractions were surgical	7	0
Bacci et al. 2011[23]	50 (50)	159	0	1.8-4.0	All were single or multiple implant placement	2	0
Bailey & Fordyce 1983[24]	25 (25)	156	156	PT ratio 1.2 to 4.3; mean PT ratio 2.4		59	0
Bajkin et al. 2009[25]	109 (109)	194	194	1.68-4.0 (mean 2.45)		4	0
Bajkin et al. 2012[26]	213 (213)	142	235	Mean 2.43-2.45	71 were on combined warfarin−aspirin	5 (INR 2.32-3.45)	0
Bakathir 2009[27]	124 (124)	157	149	2.1-3.5 (mean 2.8)	26 extractions were surgical	6	0
Bal & Hardee 2000[28]	50 (50)	104	104	2-4.5	Tranexamic acid	0	0

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Table I. Continued

Source	*No. of patients (pts) treated (visits)*	*No. of surgical procedures*	*No. of extractions*	*International normalized ratio (INR)*	*Comment*	*Postoperative bleeding that required professional treatment at least with local measures (other than immediately postoperatively)*	*Bleeding complications requiring more than local measures*
Bandrowsky et al. 1996[29]	1 (1)	21	20	INR 3.51 preop; INR 9.03; 96 hr postop	tranexamic acid	0	1 pt with good hemostasis 72 hr after surgery. Amoxicillin 500 mg three times daily for 7 days after surgery was prescribed as prophylaxis. On 4th postoperative day, pt was bleeding and INR 9.03. Coumadin withheld, and pt transfused with fresh-frozen plasma, then packed red blood cells, and ultimately vitamin K. Authors conclude the elevated PT was from interaction with amoxicillin and that the amoxicillin was probably unnecessary.
Barrero et al. 2002[30]	125 (229)	367	367	2.0-3.0	Postoperative tranexamic acid mouthwash	1	1 required transfusion
Behrman & Wright 1961[31]	16 (16)	41	31	PT ratio 1.2-2.5		0	0
Benoliel et al. 1986[32]	$> 3 < 30$ (≥ 3)	87	87	PT ratio 1.3-2.5		1	0
Blinder et al. 1999[33]	150 (150)	359	359	1.5-4.0 (mean 2.19-2.7)	Some had tranexamic acid mouthwash	13	0
Blinder et al. 2001[34]	249 (249)	543	543	1.5->3.5 (mean $\sim$2.49)		30	0
Borea et al. 1993[35]	15 (15)	15	15	INR between 3.0 and 4.5; mean INR 3.09	Tranexamic acid	1	0
Brooks 2011[36]	1 (1)	1	1	2.5 (5.0 at hospital admission)	Pre- and postoperative amoxicillin also prescribed	1	1 fresh frozen plasma transfusion on 11th postoperative day

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Table I. Continued

Source	*No. of patients (pts) treated (visits)*	*No. of surgical procedures*	*No. of extractions*	*International normalized ratio (INR)*	*Comment*	*Postoperative bleeding that required professional treatment at least with local measures (other than immediately postoperatively)*	*Bleeding complications requiring more than local measures*
Campbell et al. 2000[37]	12 (12)	40	38	1.2-2.9 (mean 2.0)		0	0
Candemir et al. 2010[38]	1 (1)	1	1	4.4; 10 days after procedure		0	0
Cañigral et al. 2010[39]	19 (19)	19	19	Not reported		1	0
Cannon & Dharmar 2003[40]	25 (25)	72	70	2.1-4.0 (average 3.4)		3	0
Carter & Goss 2003[41]	85 (85)	152	152	2.0-4.0 (average 2.75)		3	0
Carter et al. 2003[42]	1 (1)	1	1	3.8	Fibrin glue used for surgery extraction	0	0
Carter et al. 2003[43]	49 (49)	152	152	2.1-4.0 (mean 3.0-3.1)		2 (1 pt INR 3.6 day of surgery and 5.9, 7th postoperative day; 1 pt INR 2.2 day of surgery and 7.9, 3rd postoperative day)	0
Cesar & Itturiaga 2007[44]	1 (1)	1	1	2.6	Tranexamic mouthwashes	1	1 transfused with packed red blood cells and administered vitamin K and full anticoagulation with enoxaparin started, and bleeding continued. Finally controlled with desmopressin. The authors theorize that the LMWH caused the bleeding.
Cieślik-Bielecka et al. 2005[45]	40 (≥42)	186	181	1.0-4.0		2	2 described as "minor bleeding complications" treated with additional sutures and cyclonamine. 1 pt had 3 teeth removed at INR 3.5; 1 pt had 6 teeth removed at INR 3.0
Cone 1993[46]	1 (1)	1	1	INR 1.5		0	0

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Table I. Continued

Source	*No. of patients (pts) treated (visits)*	*No. of surgical procedures*	*No. of extractions*	*International normalized ratio (INR)*	*Comment*	*Postoperative bleeding that required professional treatment at least with local measures (other than immediately postoperatively)*	*Bleeding complications requiring more than local measures*
Dantas et al. 2009[47]	26 (26)	47	46	1.8-3.8		1	0
Davies 2003[48]	~24 (~24)	~≥24	~≥24	Not reported		0	0
Devani et al. 1998[49]	33 (33)	69	69	INR 2.2-3.9 (mean 2.7)		1	0
Eichhorn et al. 2012[50]	637 (637)	934	88	1.2-4.2 (mean 2.44)		47	2 (anticoagulant changed for 6 days)
Elad & Findler 2008[51]	≥ 2 ≤ 498 (≥2)	≥2	≥2	Not reported	Periodontal surgery	2 INR ≥3.5	0
Elad et al. 2010[52]	2 (2)	2	2	1.88-2.0		0	0
Evans et al. 2002[53]	57 (57)	114	114	1.2-4.7 (mean 2.5)		5	0
Ferrieri et al. 2007[54]	255 (334)	≥1197	≥1177	1.3-5.4 (mean 1.4-3.4)	81 were "complicated"	5	0
Frank et al. 1963[55]	11 (11)	51	51	PT activity from 35% to 15% ***[INR <2.5 to INR 3.5]***		0	0
Gagneja et al. 2007[56]	1 (1)	6	6	2.97	Clindamycin prophylaxis	0	0
Gaspar et al. 1997[57]	32 (32)	≥57	≥57	INR 1.9-3.5 (mean 2.5)	Tranexamic acid mouthwash	2	0
Giuffrè et al. 2006[58]	156 (156)	~≥156	~≥156	2.0-3.5	Amoxicillin + clavulanic acid prophylaxis; 104 given platelet-rich plasma, 52 given tranexamic acid soaked gauze for hemostasis	40	6 pts in the tranexamic acid group required vitamin K for hemostasis
Goodchild & Donaldson 2013[59]	1 (1)	6	6	2.8		1	0
Greenberg et al. 1972[60]	13 (13)	27	27	PT activity 28%-14% ***[INR >2.5 to INR >3.5]***		0	0
Hadziabdic et al. 2011[61]	50 (50)	≥50	≥50	0.96-2.89		2	1 anticoagulant withdrawn for 1 day postoperatively
Halfpenny et al. 2001[62]	46 (46)	79	79	2.0-4.1, mean 2.7-2.9	13 were surgical; 1 pt with intermittent bleeding admitted to hospital	3	0

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Table I. Continued

Source	*No. of patients (pts) treated (visits)*	*No. of surgical procedures*	*No. of extractions*	*International normalized ratio (INR)*	*Comment*	*Postoperative bleeding that required professional treatment at least with local measures (other than immediately postoperatively)*	*Bleeding complications requiring more than local measures*
Hong et al. 2012[63]	~105 (105)	252	248	1.1-3.3, mean 2.0	≥ 1 surgical	5	1 pt (post–liver transplantation, end-stage renal disease, and hemodialysis) on combined warfarin–aspirin therapy, who had undergone 5 extractions at INR 2.2. At hospital admission, anticoagulation was INR 5.9. Vitamin K and fresh frozen plasma were administered, and local measures for hemostasis were applied.
Inchingolo et al. 2011[64]	193 (193)	≥193	~≥193	Not reported	Tranexamic acid	0	0
Karsli et al. 2011[65]	13 (13)	13	13	Mean 2.6		0	0
Kovács et al. 1976[66]	31 (31)	56	53	Prothrombin level 19 to 49% (average 33.3%) ***[INR <2.0 to INR >3.0 average INR <2.5]***		0	0
Kusafuka et al. 2013[67]	18 (18)	35	35	1.08-2.91 (mean 1.75)	1 extraction surgical	0	0
Kwapis 1963[68]	60 (60)	>85	>82	PT ratios not given		0	3 pts (2 with single extractions and PT less than 1.5 the control) had "prolonged bleeding" and administered vitamin K. (Not known if local measures to control hemostasis were attempted.)
Martinowitz et al. 1990[69]	40 (40)	63	63	INR 2.5-4.29; average INR 3.25		1	0
McIntyre 1966[70]	106 (106)	636	636	Thrombotest generally 15% to 7% ***[INR 2.1 to INR 3.6]***		1	1 pt whose thrombotest was 5% ***[INR 4.8]*** bled for 12 hr after 9 extractions and administered vitamin K.

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Table I. Continued

Source	*No. of patients (pts) treated (visits)*	*No. of surgical procedures*	*No. of extractions*	*International normalized ratio (INR)*	*Comment*	*Postoperative bleeding that required professional treatment at least with local measures (other than immediately postoperatively)*	*Bleeding complications requiring more than local measures*
Morimoto et al. 2008,[71] 2011[72]	254 (292)	533	533	1.5-2.96 in the 15 pts with postoperative hemorrhage	18 pt were on combined warfarin-antiplatelet therapy; 68 extractions were surgical	15	1 pt (INR 1.50) on warfarin−antiplatelet combination therapy administered vitamin K because of "markedly prolonged" INR level that was unable to be measured 5 days after 3 extractions
Morimoto et al. 2009[73]	≥36 (≤52)	52	0	≤2.97	11 pts on combined warfarin−antiplatelet	1	0
Nakasato et al. 1989[74]	23 (23)	≥23	≥23	Not reported		0	0
Pereira et al. 2011[75]	107 (107)	~214	~214	0.8-4.9, mean 3.15	9 pts on combined warfarin−aspirin	1	0
Raborn et al. 1990[76]	17 (17)	17	17	Average (7 pts): PT 15/11.5; (10 pts): 18.4/11.5		0	0
Ramli & Rahman 2005[77]	21 (30)	44	44	1.89-3.5	Tranexamic acid mouthwash	1	0
Ramstrom et al. 1993[78]	89 (89)	~137	~133	INR 2.1-4.0	Tranexamic acid or placebo mouthwash	9	1 administered vitamin K (5 mg) after local measures. INR not given.
Sacco et al. 2007[79]	65 (65)	>100	>100	Mean 2.89		6	0
Salam et al. 2007[80]	150 (150)	279	279	0.9-4.2 (mean 2.5)	30 extractions were surgical	10	0
Sammartino et al. 2011[81]	50 (50)	168	168	Mean 3.16		2	0
Sammartino et al. 2012[82]	53 (≥53)	173	173	2.0-4.0	Tranexamic acid	2	0
Schmitt 1961[83]	1 (1)	6	6	PT 39 seconds (~40%)		0 (hematoma)	0
Shira RB et al. 1962[84]	18 (18)	50	45	PT 16.8 seconds to 50.7 seconds [PT ratio 1.4 to 4.225]	Gelfoam and sutures placed for most extractions	6	1: PT 12.5% 35.4 seconds [PT ratio 2.95] (extraction with suture but no Gelfoam) given vitamin K.

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Table I. Continued

Source	*No. of patients (pts) treated (visits)*	*No. of surgical procedures*	*No. of extractions*	*International normalized ratio (INR)*	*Comment*	*Postoperative bleeding that required professional treatment at least with local measures (other than immediately postoperatively)*	*Bleeding complications requiring more than local measures*
Sindet-Pederson et al. 1989[85]	39 (39)	119	112	INR 2.5-4.8	Tranexamic acid or placebo mouthwash	10	1 pt required hospitalization and fresh-frozen plasma. INR not reported
Souto et al. 1996[86]	153 (156)	$\geq 153 \leq 163$	$\geq 153 \leq 163$	INR 1.5-5.25	tranexamic acid mouthwash for some pts	7	0 (Souto JC, Fontcuberta J. Personal correspondence. August 21, 1996.)
Street & Leung 1990[87]	12 (12)	12	12	INR not reported	Tranexamic acid mouthwash	1	0 although 1 pt not compliant with mouthwash who had an impacted infected tooth extraction was admitted to the hospital for observation but not treatment
Svensson et al. 2013[88]	124 (124)	194	194	Mean INR 2.4 (1.0-3.5)		5	0
Throndson & Walstad 1999[89]	1 (1)	1	1	3.8	Tranexamic mouthwash postoperatively	1	1 transfusion and argon beam coagulator
Tomasi & Wolf 1974[90]	1 (1)	2	1	PT ratio 1.2		0	0
Tulloch & Wright 1954[91]	1 (1-2)	1?	1?	PT ratio 3.3		0	0
Waldrep & McKelvey 1968[92]	20 (20)	76	60	Prothrombin activity rate 30% or less; average 20.3% ***[INR 2.5 or more; average INR 3.0]***		3	2 pts had postop anticoagulation withdrawn to control postop bleeding

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Table I. Continued

Source	*No. of patients (pts) treated (visits)*	*No. of surgical procedures*	*No. of extractions*	*International normalized ratio (INR)*	*Comment*	*Postoperative bleeding that required professional treatment at least with local measures (other than immediately postoperatively)*	*Bleeding complications requiring more than local measures*
Wood & Deeble 1993[93]	2 (2)	7	7	INR 2.3-2.9 preop; INR 4.3-9.1 postop	Sutures and surgicel	2	2: After bleeding control with local measures, 1 pt (preop INR 2.3) bled 2 days after extraction when his INR was 4.3, possibly from interaction with concomitant erythromycin. Given fresh frozen plasma and blood. 1 pt (preop INR 2.9 for 6 extractions) no bleeding problem until 1 week later (oozing from one socket) when INR was 9.1. Given fresh frozen plasma, blood, and vitamin K.
Yoshimura et al. 1987[94]	13-16 (19)	19	19	PT ratio 1.05-2.1 when reported		6	0
Zanon et al. 2003[95]	250 (250)	525	525	1.8-4.0	236 extractions surgical	4	0
Ziffer et al. 1957[1]	2 (3)	3	3	PT ratio 2.35 to 2.8		2	2 (3 episodes: PT ratio 2.8 for one pt; PT ratio 2.35 and 2.4 for other pt): vitamin K administered
Zusman et al. 1992[96]	23 (23)	61	61	PT 50% to 19% ***[INR <2.0 to INR 3.2]***		3	0
TOTALS	>5431 (>5677)	>11,381	>10,322			375 (7% of pts and visits)	31 (0.6% of pts, 0.5% of visits)

Table II. Anticoagulation interruption for dental procedures

Source	*No. of patients (pts)*	*No. of interruptions for dental procedures*	*Presurgical days of cessation or reduction*	*International normalized ratio (INR) after withdrawal*	*Bleeding complications treated with local measures by doctor*	*Thromboembolic complications*
Akbarian et al. 1968[97]	1	1	Not reported	Not reported	0	1 fatal embolism
Akopov et al. 2005[98]	2	2	4-6	Not reported	Not reported	2: 1 pt withdrawn for 4 days before dental procedure; 1 pt withdrawn for 3 days before cataract surgery and did not restart for the upcoming dental procedure On the 6th day after withdrawal, a cerebral infarction developed
Al-Mubarak et al. 2006,[17] 2007[18]	104	104	2	Mean 1.8-.9	7 had postoperative bleeding on day 3	0
Aldous and Olson 2001[99]	1	1	Warfarin withdrawn for 2 days and replaced with heparin	Preop INR not reported, but on postop day 15 INR was 3.5 and on day 18 it was INR 13	1 on postop day 15 and eventually on day 18, when INR was 13, transfusion and vitamin K given	0
Alexander R 2003[100]	4	4	1-5	Not reported	Not reported	4; 2 fatal
Anavi 1981[20]	15	15	until prothrombin time (PT) level was 50%-60%		3	0
Bajkin et al. 2009[25]	105	105	Warfarin or acenocoumarol withdrawn 3-4 days (with low-molecular-weight heparin [LMWH] nadroparin-calcium replacement) until INR <1.5	INR 1.06-1.47 (mean 1.26)	3	0
Baykul et al. 2010[101]	2	2	INR reduced, but not reported how	1.3-1.4	1	0
Behrman & Wright 1961[31]	1	1	Anticoagulation withdrawn before dental surgery (number of days unreported)	Not reported	0	1 fatal massive cerebral thrombosis 17 days after discontinuing warfarin
Behrman and Wright 1961[31]	4	4	Warfarin withdrawn day of surgery or 1 day preoperatively	Not reported	1	0

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Table II. Continued

Source	*No. of patients (pts)*	*No. of interruptions for dental procedures*	*Presurgical days of cessation or reduction*	*International normalized ratio (INR) after withdrawal*	*Bleeding complications treated with local measures by doctor*	*Thromboembolic complications*
Bloomer 2004[102]	1	1	5 (with enoxaparin substitution but no anticoagulation at all for 12 hours)	1.5 one day before surgery	1 (vitamin K administered also)	0
Borea et al. 1993[35]	15	15	Anticoagulation withdrawn or reduced in artificial heart valve patients	Preop INR 1.5-2.5 (mean 1.69) in artificial heart valve patients	2	0
Broderick et al. 2011[103]	1	1	Not reported	Not reported	Not reported	1 after warfarin cessation for a dental procedure
Brooks 2011[36]	1	1	14 (with enoxaparin substitution)	1.2 (1.4 at hospital admission)	1 (fresh frozen plasma transfusion)	0
Campbell et al. 2000[37]	13	13	3-4	1.1-3.0 (mean 2.0)	0	0
Cannon & Dharmar 2003[40]	32	32	2-4	<2.0	2	0
Crean et al. 2000[104]	1	1	3 (with heparin substitution on the 3rd day)	1.3	0	0
Davies D 2003[48]	1	1	2 (anticoagulant reduced)	Not reported	0	1 transient ischemic attack (TIA)
Davis & Sczupak 1979[105]	28	28?	Up to 2 weeks for "dental or surgical procedures"	Not reported	Not reported	0
Della Valle et al. 2003[106]	40	40	1.5	1.5-3.0	17	0
Devani et al. 1998[49]	32	32	Warfarin withdrawn 2 days preoperatively until INR 1.5-2.1	INR 1.2-2.1 (mean 1.6)	1	0
Douketis et al. 2004[107]	3	3	5-6 days (LMWH dalteparin replacement); stop dalteparin at least 12 hr before surgery	Not reported	0 (but rectus sheath hematoma)	0
Dunn et al. 2007[108]	22	≥22	5 days (LMWH enoxaparin replacement; stop enoxaparin day of procedure)	<1.8	0	0
Elad & Findler 2008[51]	2	2	Not reported; warfarin replaced with LMWH	Not reported	2	0
Evans et al. 2002[53]	52	52	2	1.2-2.3 (mean 1.6)	0	0
Finn & Schow 1993[109]	1	1	4 (with heparin substitution)	PT 12.8 seconds (INR not reported)	0	0
Garcia et al. 2008[110]	257	323	1-10 in larger study	Not reported	Not reported	1 after a 7 day interruption for oral surgery
Gaspar et al. 1997[57]	15	15	Warfarin withdrawn for 3 days	INR 1.25-1.9 (mean 1.45)	1	0

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Table II. Continued

Source	*No. of patients (pts)*	*No. of interruptions for dental procedures*	*Presurgical days of cessation or reduction*	*International normalized ratio (INR) after withdrawal*	*Bleeding complications treated with local measures by doctor*	*Thromboembolic complications*
Giuffrè et al. 2006[58]	52	52	Until PT, partial thromboplastin time (PTT), and INR values reached 50% (heparin replacement)	1.0-1.75	0	0
Hadziabdic et al. 2011[61]	21	21	For 1 day, anticoagulation reduced in 4 and withdrawn in 17 patients	Not reported	0	0
Johnson-Leong & Rada 2002[111]	1	1	4 (with enoxaparin substitution but no anticoagulation at all for 24 hours)	1.1	0	0
Karsli et al. 2011[65]	21	26	3 days with LMWH or unfractionated heparin (UFH) bridging	Mean 1.6	0	0
Lund et al. 2002[112]	6	≥6	Heparin replacement to reach PTT 55-65 seconds (all patients were on mechanical circulatory support)	Not reported	3 patients had minor hemorrhage 4 days after surgery	2 transient ischemic events
Marshall 1963[113]	1	1	Anticoagulation withdrawn 9 days preoperatively	Not reported	0	1 fatal myocardial infarction 19 days after interruption of therapy of 9 days duration
Mehra et al. 2000[114]	20	20	1-2 days with heparin replacement	Not reported	1	0
Milligan et al. 2003[115]	≥1	1	4 to 5	1.2-1.8 (mean INR 1.5 for entire study, which included nondental surgeries)	Not reported	0
Morimoto et al. 2008[71]	4	7	2 days warfarin reduction with LMWH (dalteparin) replacement	1.2-2.36	1 (compression and warfarin discontinuation 6 days postop due to high INR and oozing)	0
Mulligan 1987[116]	17	44	Anticoagulation withdrawn 2-7 days preoperatively	PTR 1.13-1.93	0	0
Nakasato et al. 1989[74]	28	28	Warfarin discontinued until thrombin test level raised from 40%-50%	Mean thrombin test value 49.8% ± 14.5%	0	0

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Table II. Continued

Source	*No. of patients (pts)*	*No. of interruptions for dental procedures*	*Presurgical days of cessation or reduction*	*International normalized ratio (INR) after withdrawal*	*Bleeding complications treated with local measures by doctor*	*Thromboembolic complications*
Ogiuchi et al. 1985[117]	128	128	Warfarin dose decreased 3 to 7 days preoperatively, then discontinued the day of the procedure and restarted afterward	Thrombotest values 10%-100%	0	1 fatal cerebral thromboembolism 5 days postoperatively.
Pávek & Bigl 1993[118]	11	11	Anticoagulation reduced for one day and then withdrawn for 1 day with heparin replacement	≤1.87	0	0
Pearce et al. 1975[118]	1	1	Warfarin withdrawn for unknown days	Not reported	0	0
Prudoff & Stratigos 1972[120]	2	2	Warfarin withdrawn 2 days preoperatively	Protime 13/13 and 22/14	0	0
Roberts 1961[121]	3	3	3-4	PT 25-33 seconds; 24; 21	1 after 2 days of postoperative bleeding, intravenous estrogen was administered for hemostasis	0
Roberts 1966[122]	≥40	≥40	3 days	PT up to 25 seconds	0	0
Russo et al. 2000[123]	104	104	2	1.18-3.4 (mean INR 1.87)	2	0
Sacco et al. 2007[79]	66	66	3 (dosages reduced until for target INR 1.8)	Mean 1.77	10	0
Sammartino et al. 2012[82]	31	≥31	Warfarin withdrawn "some days" before procedure until INR <2.0	Preop INR <2.0	4 treated with local measures 2-4 days postoperatively	0
Saour et al. 1994[124]	212	212	Warfarin withdrawn 2 days or until INR ≤1.5	INR ≤1.5	0	0
Scheitler et al. 1988[125]	1	1	1 day; heparin replacement until 6 hours before surgery	PT 13.0/10.2 seconds	0	0
Schofield 1984[126]	~168	~168	Warfarin withdrawn 6 days pre-operatively	Thrombotest >25%	0	0
Sheller & Tong 1994[127]	1	1	Warfarin withdrawn for 2 days	Not reported	0	0
Somma et al. 2010[128]	80	≥80	3 days	Not reported	0	2 thromboembolic complications
Somma et al. 2010[128]	800	≥800	Warfarin dosage adjusted	1.6-1.8	82	0
Souto et al. 1996[86]	39	39	Anticoagulation reduced for 2 days and replaced with heparin	INR 1.25-5.0	13	0

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Table II. Continued

Source	*No. of patients (pts)*	*No. of interruptions for dental procedures*	*Presurgical days of cessation or reduction*	*International normalized ratio (INR) after withdrawal*	*Bleeding complications treated with local measures by doctor*	*Thromboembolic complications*
Street & Leung 1990[87]	2	2	Not reported	Not reported	0	0
Todd 2001[129]	1	1	Anticoagulant withdrawn until INR normalized	Not reported	0	0
Tulloch & Wright 1954[91]	12	13	Anticoagulant withdrawn for 4 days in most cases	Not reported	0	1 pt whose therapy was withdrawn for 8 days developed cerebral and brachial nonfatal emboli
Wilson et al. 2001[130]	6	6	Warfarin discontinued 5 days before procedure with LMWH (dalteparin) substitution	≤1.5	1	0
Wood & Conn 1954[131]	5	5	Anticoagulation withdrawn "dental extraction or surgical procedure" 7 to 37 days	Not reported	0	0
Yasaka et al. 2006[132]	4	4	3-6	0.94-2.5 on admission	Not reported	4 cardioembolic strokes: Interrupted at 3, 4, 5, and 6 days before dental extractions
Yoshimura et al. 1987[94]	4	4	Anticoagulant withdrawn or reduced 1-2 days preoperatively	Not reported	0	0
Ziffer et al. 1957[1]	1	1	9 days		0	0
Zusman et al. 1993[96]	23	23	2	Not reported	0	0
TOTALS	≥2673	≥2775			161 (6% of pts and visits), including 5 (0.2%) administered more than local measures	15 (0.6% of pts, 0.5% of visits); 6 (0.2% of pts or visits) fatal

Analysis of some cases of embolic complications after anticoagulation withdrawal or reduction for dental procedures

Alexander reported four cases of catastrophic embolic complications in patients whose anticoagulation was withdrawn before dental extractions after the dentists consulted with physicians. Two cases were fatal, and all four ended in lawsuits—presumably both the dentist and physician were sued for inappropriately recommending anticoagulation interruption without good reason in each of these cases.[100] In one case, the plan was to substitute low-molecular-weight heparin (LMWH) for warfarin once the INR level fell below 2.0 in a patient with anticardiolipin, but the patient suffered a fatal pulmonary embolism after warfarin withdrawal and before LMWH could be started. In another case of a patient with atrial fibrillation, the dentist consulted with the patient's cardiologist before a single extraction. The cardiologist recommended a 3- to 5-day withdrawal of warfarin. On day 4 of warfarin interruption, the extraction was done, and that evening the patient suffered a fatal pulmonary embolism. In the other two cases, the patients' physicians recommended interruption of warfarin for single extractions. After INR levels fell below 2.0, both patients suffered major strokes.

Akopov et al. reported thrombotic events in five patients with INR between 1.5 and 2.0 at hospital admission after anticoagulation withdrawal for medical procedures.[98] Two of these patients were dental patients, one whose anticoagulation was withdrawn for 4 days preoperatively and the other whose anticoagulation was withdrawn for 3 days before cataract surgery; however, anticoagulation was not immediately restarted due to an upcoming dental appointment. On postoperative day 6, the second patient suffered a cerebral infarct. The authors noted that withdrawal of warfarin for dental procedures was based on a "mostly theoretical risk of hemorrhage…which may be controlled with local measures should it occur at all." They concluded, "[T]emporary discontinuation of warfarin for invasive procedures in patients with established high-risk for cardioembolic cerebral infarction may lead to a devastating cerebral infarction. These events constitute an unacceptably large percentage of hospital admissions for cardioembolic cerebral infarctions."

Garcia et al. studied 1293 cases of warfarin interruption in 1024 patients, including 323 warfarin interruptions in 257 oral or dental surgery patients.[110] Only 8.3% of warfarin interruptions included patients receiving bridge therapy with heparin, and this bridge therapy was associated with a higher risk of postoperative hemorrhage compared with no bridge therapy. Interestingly, of all 1293 cases of mostly nondental surgical procedures, 23 patients whose warfarin was interrupted (of whom 14 were on periprocedural heparin bridge therapy) sustained major or significant hemorrhage after the procedure anyway. Overall, there were 7 thromboembolic events (none in patients receiving bridge therapy), including a stroke suffered by a dental patient whose warfarin was withdrawn for 7 days for a dental procedure.

Of the 2197 cases of ischemic stroke identified through hospital discharge records, Broderick et al. determined that 114 (5.2%) occurred within 60 days of antithrombotic agent withdrawal, about half of which were withdrawn by a physician in the periprocedural period.[103] One of the cases of stroke was after warfarin cessation for a dental procedure.

EVALUATION AND DISCUSSION OF THE EVIDENCE

The reviewed literature indicates that withdrawing or reducing therapeutic levels of warfarin for dental procedures is associated with a small but real risk of embolic complications, such as stroke, and pulmonary embolism. Although the risk may be low, embolic complications after warfarin withdrawal for dental surgery can lead to permanent morbidity or even be fatal. On the other hand, there are no documented cases of permanent morbidity or fatalities from bleeding complications when anticoagulation is continued for dental surgery, and most such bleeding complications are easily treated with local hemostatic measures. Although most authorities assert that anticoagulation should be continued for dental surgery, some still recommend anticoagulation withdrawal or reduction, based on one or more of the positions discussed below.

Position 1: Bleeding complications can be disconcerting to patients and dentists

The American College of Chest Physicians (ACCP) states that postoperative bleeding after dental surgery can cause "anxiety and distress."[133] Todd stated, "My experience and that of many of my colleagues is that even though bleeding is never life threatening, it can be difficult to control at therapeutic levels of anticoagulation and can be troublesome, especially for elderly patients."[134] While minor postoperative bleeding can be disconcerting to both patients and dentists, it is also true that postoperative bleeding in anticoagulated dental patients is rare and usually amenable to management with local hemostatic measures. In fact, most studies have shown that minor bleeding complications occur at a rate similar to those in patients whose anticoagulation was withdrawn or reduced for dental surgery.

In our series (Tables I and II), the incidence of minor bleeding in the anticoagulation group (~7%) was about

the same as in the anticoagulation withdrawal group or the reduction group (~6%). Even though the incidence of bleeding requiring more than local measures was higher in the anticoagulation group (0.5% of visits), five patients (0.2% of visits) in the anticoagulation withdrawal or reduction group also required more than local measures to control hemorrhage. On the other hand, embolic complications in dental patients whose anticoagulation is withdrawn or reduced, while also infrequent, can be devastating and even fatal. Surely, after a dental procedure, an embolic complication after anticoagulation withdrawal or reduction is more disconcerting than a bleeding complication when anticoagulation is continued.

Position 2: Embolic complications are rare when anticoagulation is reduced or withdrawn for dental procedures, and those documented cases of embolic complications for dental procedures have very long warfarin cessation periods

In 2010, Balevi stated that recommendations for continuing anticoagulation for dental extractions "were made despite the fact that there has been no reported case of a dental extraction causing a cardiovascular accident (CVA) in a patient whose warfarin was temporarily discontinued."[135] In a letter responding to this assertion "Bleed or die? A bloody simple decision,"[136] it was pointed out that there had been at least five serious embolic complications (one fatal) reported in the literature after warfarin withdrawal for dental procedures.[31,91,97,113,117] Todd points out that in these five cases of embolic events after warfarin cessation, the cessation period was either unknown or ranged from 5 to 19 days of withdrawal, so he advocates a brief discontinuation of anticoagulation for some oral surgical procedures, partly based on the lack of cases in the literature of thrombotic events in patients whose INR levels fell to 1.5 to 2.0.[134,137] Russo et al. advocated warfarin interruption for prosthetic valve patients undergoing dental surgery, calling a 2-day interruption "simple and safe."[123]

Our current review documenting 22 cases (6 fatal) of embolic complications after anticoagulation, demonstrated that embolic complications have been reported with warfarin interruption for as few as 2, 3, or 4 days (Table II). Yasaka et al. reported cases of cardioembolic stroke in four patients whose warfarin was withdrawn for 3 to 6 days before dental extractions. INR levels in these patients ranged from 0.94 to 2.5 on admission.[132]

On the other hand, postoperative bleeding complications that require more than local hemostatic measures are rare, and there have been no fatal cases of hemorrhage documented after dental surgery in continuously anticoagulated patients.

The recommended therapeutic INR range for most patients, including patients with mechanical aortic valves is INR levels of 2.0 to 3.0, although the INR level is 2.5 to 3.5 for those with mechanical mitral valves.[138] There are no patients whose recommended optimal levels are lower than INR 2.0 or higher than INR 3.5. Even a brief interruption of warfarin would reduce the INR to a *suboptimal* level, exposing these patients to a higher risk of stroke or even death for little or no benefit in prevention of postoperative hemorrhage. If postoperative hemorrhage occurs at all, it can usually be treated with local measures. Although embolic events are infrequent when warfarin anticoagulation is briefly interrupted, when an embolic event, such as a stroke, occurs, it is often catastrophic and sometimes fatal.

Position 3: The 2012 ACCP statement provides an option to discontinue anticoagulation for dental procedures

The ACCP consensus statements issued in 2001,[139] 2004,[140] and 2008[141] have recognized that the risk of hemorrhage after dental surgery in anticoagulated patients was outweighed by the morbidity of the risk of embolic complications from reducing or withdrawing anticoagulation and recommended continuing anticoagulation for dental surgery. In 2012,[133] the ACCP recommended dental surgery without warfarin interruption and with a prohemostatic mouthwash but gave an additional option to withdraw anticoagulation for 2 to 3 days before the dental procedure, citing four prospective studies as references for this option. None of these studies (discussed below) supports warfarin interruption—on the contrary, they confirm that continuous warfarin is safe and appropriate for dental surgery.

Campbell et al. studied anticoagulated dental surgical patients divided into three groups: (1) 12 patients whose anticoagulation was continued, (2) 13 whose anticoagulation was interrupted for 3 to 4 days before surgery, and (3) an additional control group of patients who had never been on anticoagulant therapy.[37] There was no difference in blood loss in any of the groups, and no patient suffered any bleeding complications. The authors concluded, "The data suggest that many patients can safely undergo routine outpatient oral surgical procedures without alteration of their regular therapeutic anticoagulation regimens and without additional medical intervention." Beirne, in an accompanying discussion, stated that "this study strongly supports the recommendation" for continuing therapeutic anticoagulation before dental extractions.[142]

Devani et al. studied 65 anticoagulated patients undergoing dental extractions,[49] divided into a control group whose warfarin was interrupted and a study group

whose warfarin was continued. With no bleeding complications requiring more than local hemostatic measures, the authors concluded there is "no justification in altering warfarin treatment (between INR 2.0 and 4.0) before dental extractions in these patients, and thereby exposing them to the risk of thromboembolism."

Gaspar et al. studied 47 continuously anticoagulated oral surgical patients, divided into two groups.[57] Anticoagulation was reduced in the control group, and there was no change in the test group. The incidence of bleeding in the two groups was not significantly different, and the authors concluded that "patients taking anticoagulant therapy should not discontinue their medication before ambulatory oral surgery."

Blinder et al. divided 249 patients undergoing dental extractions into five groups, based on lowest to highest INR levels.[34] There was no significant difference in the incidence of postoperative bleeding between the groups, and the INR value did not significantly affect the incidence of postoperative bleeding. No patient required more than local hemostatic measures. The authors concluded that "dental extractions can be performed without modification of oral anticoagulant treatment."

In each of these cases, there were no bleeding complications that required more than local hemostatic measures whether anticoagulation was reduced, withdrawn, or continued, and in each case the authors concluded that anticoagulation should be continued for dental surgery with local hemostatic measures. Although there were no embolic complications reported in any of these studies, patients were exposed to a life-threatening, although low, risk of embolism with suboptimal levels of anticoagulation without a concomitant decreased risk of hemorrhage, which if it occurred would probably not have been life threatening anyway.

CONCLUSION

Potential bleeding complications in anticoagulated patients undergoing dental surgery must be weighed against possible embolic complications when anticoagulation is withdrawn or reduced for dental surgery. This review of the literature has confirmed earlier findings that there is an exceedingly low risk (0.6%) of bleeding complications that require more than local hemostatic measures in continuously anticoagulated patients, with no cases of permanent morbidity or fatality. On the other hand, there is a similarly low (0.8%) but highly significant risk of serious embolic complications in patients whose anticoagulation is reduced or withdrawn for dental procedures. In some cases, these embolic complications resulted in permanent morbidity and even fatality. The evidence reviewed indicates that therapeutic anticoagulation with warfarin should not be interrupted for most dental surgery.

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