

# Delayed Complications of Tooth Extraction in Patients Taking Warfarin, Antibiotics, and Other Medications

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Current published data support treating patients taking warfarin (Coumadin) in a routine manner.<sup>1-3</sup> First, one should obtain an international normalized ratio (INR) level and then consider the use of enoxaparin (Lovenox) as interim anticoagulant therapy or simply maintain standard warfarin dosage, depending on the complexity of the treatment plan. Combined with intraoperative modalities such as local anesthesia, including epinephrine, oxidized cellulose, gelatin sponges, and primary closure, successful outcomes are common.

As the age of patients seeking oral surgery treatment has increased in the range of 55 to 95 years, so has the myriad of risks. This age group can have multiple medical diagnoses and comorbidities.<sup>4</sup> Cardiac conditions such as heart valve replacement and paroxysmal atrial fibrillation are common in this population and are often treated with warfarin.<sup>5</sup>

Even with the best of treatment plans, the combination of anticoagulation therapy in an older patient with comorbidities can result in challenges with routine exodontia procedures. This case report details 2 clinical cases with postoperative sequelae. The 2 patient scenarios occurred in a solo oral surgery practice in a county population of ~80,000. The complications occurred after routine mandibular extractions on the fifth (case 2) and eleventh (case 1) postoperative days.

These complications might have been related to the perioperative antibiotic therapy, potentiating the effects of warfarin. The judicious use of antibiotics is a never-ending consideration. However, warfarin has interpatient variability and multiple factors influencing its narrow therapeutic range. Also, considering the age of the patients, a natural slowing of the granulation process might have occurred, leading to a

tenuous clot. Therefore, the true scientific explanation for the complications could not be determined.

At a minimum, an appropriate consent should be reviewed with the patient and caretaker, explaining the possibility of delayed complications. Also, appropriate scheduling of the treatment should be used (eg, in case hemorrhage occurs later in the week). Communication with the warfarin-prescribing physician regarding guidance for transfusion, vitamin K therapy, and ceasing warfarin might be needed in the event of significant blood loss. Postoperative coagulation studies, although not standard care, are justifiable when patients are taking multiple medications, including antibiotics.

## Case Report

### CASE 1

A 64-year-old man was referred to the office by his general dentist. The patient was ambulatory but had multiple comorbidities (Table 1). He had been given amoxicillin for 7 days by the general dentist, whom he saw on an irregular basis. The dental diagnosis was an erupted and deeply carious mandibular right third molar (International Classification of Diseases code 9521.03). He had other mandibular teeth missing. No evidence was seen of vestibular edema or purulent exudate. No radiographic findings were noted other than severe decay.

On the morning of the extraction, the INR was 2.5, and the hemoglobin level was 12.5 g/dL (Table 2). His warfarin medication was not stopped, and the amoxicillin therapy was in progress (prescribed because of aortic valve replacement). The routine dosing schedule of warfarin was maintained at 7.5 mg, taken on Monday, Wednesday, and Friday. A conservative surgical extraction of the mandibular right third molar was performed with the patient under local anesthesia (2% lidocaine HCl with epinephrine 1:100,000). The mandibular right third molar required sectioning. A gelatin sponge and 3-0 chromic gut sutures were placed. At discharge, the patient had minimal bleeding noted on a gauze square. On postoperative day 1, a repeat INR was performed by the family physician and was 2.9. A routine postoperative examination was performed by myself on day 7 without significant findings.

On postoperative day 11, the patient's neighbor paged because the patient was hemorrhaging from the nose and mouth. He was transferred by the emergency medical service to a local hospital and then to a tertiary care center, where the hemorrhaging was managed with the transfusion of 2 U of fresh frozen plasma. No additional suturing or intervention was needed. He was kept in the hospital for 5

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0278-2391/11/6904-0012\$36.00/0  
doi:10.1016/j.joms.2010.05.012

**Table 1. PATIENT CHARACTERISTICS**

Characteristic	Patient 1	Patient 2
Gender	Male	Female
Age (yr)	64	82
Weight (lb)	235	121
Medical diagnosis	Aortic valve replacement Type 2 diabetes Obstructive sleep apnea Hypertension Atrial fibrillation Congestive heart failure Hyperlipidemia Stage IV renal disease	Aortic valve replacement Type 1 diabetes Anxiety Hypertension Dementia Hyperlipidemia
Prescription drugs at treatment	Warfarin Amoxicillin Simvastatin Clonidine Furosemide Iron Hydrochlorothiazide Terazosin Testosterone Diltiazem	Enoxaparin Clindamycin Atorvastatin Lotrel Donepezil Lithium Lorazepam Sertraline Insulin glargine
Alcohol use	Unknown	Unknown
Tobacco use	None	Smokeless

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days, closely monitored by physicians and a general practice resident (the author did not have privileges at the hospital) because of an elevated creatinine level. The admitting INR was 5.0, and the hemoglobin value was 8.3 g/dL (Table 2). The discharge INR was 1.1, and the hemoglobin level was 8.7 g/dL. For 48 hours before discharge, the patient was administered a heparin drip. Iron supplementation was started for 30 days, and he was instructed to use enoxaparin until seen by his outpatient family physician.

#### CASE 2

An 82-year-old woman was referred by her family physician to the author's office for the extraction of 3 decayed teeth (the mandibular left third molar, mandibular left lateral incisor, and mandibular right second premolar). The patient was ambulatory and had other medical diagnoses (Table 1). She had not received routine dental care but had been successfully treated 5 years earlier by myself when 4 teeth were extracted while she had been taking warfarin. The current teeth were erupted and showed severe dental caries (International Classification of Diseases code 9521.06). Moderate alveolar bone loss was associated with all her teeth.

Because of the dermato-chondromas to be excised by a dermatologist before the dental extractions, the family physician switched the patient to enoxaparin nearly 14 days before the extractions were performed. On the morning of the extractions, the INR was 1.2 and the hemoglobin level was 11.3 g/dL. Owing to an aortic valve replacement and penicillin allergy, she was premedicated with 600 mg clindamycin. A conservative approach was again used to ex-

tract the mandibular left third molar, mandibular left lateral incisor, and mandibular right second premolar with the patient under local anesthesia (2% lidocaine HCl and 1:100,000 epinephrine). The mandibular left lateral incisor required sectioning. Gelatin sponges and 3-0 chromic gut sutures were placed in each socket. The patient had minimal to no bleeding on gauze at discharge.

On postoperative day 5, the family physician resumed a warfarin dosage of 10 mg in the morning. By the evening on the same day, the emergency room paged the author concerning admission of the patient to the intensive care unit for blood loss. She was stabilized with 2 U of fresh frozen plasma and 2 U of packed red blood cells. The admitting INR was 1.4, and the hemoglobin value was 9.5 g/dL (Table 2). The author examined the patient after the transfusions, and no further oral surgery care was necessary. The patient reported most of the bleeding had been from the region of the mandibular left lateral incisor. She stayed in the hospital for 3 days under a family physician's care, who was also monitoring her insulin therapy. A discharge INR was not done, but the hemoglobin level was 13.4 g/dL.

#### Discussion

The number of warfarin prescriptions filled in 2004 was 31 million.<sup>6</sup> The data collected from hospital emergency departments concerning warfarin with the Food and Drug Administration's Advance Event Reporting System led to the "black box" labeling about the risk of bleeding. Warfarin has been approved for preventing thromboembolic complications with atrial fibrillation and cardiac valve replacement and for the prevention of venous thrombosis. Despite the labeling, medication guidelines and educational brochures provided to patients taking warfarin, adverse events still occur. Between 1993 and mid-July 2006, 999 patients died of fatal bleeding caused by warfarin.<sup>6</sup>

Warfarin is a synthetic derivative of coumarin found in many plants and in low levels of licorice and lavender.<sup>7</sup> It inhibits vitamin K epoxide reductase, diminishing available vitamin K. Coagulation factors II, VII, IX, and X (dependent on vitamin K) are incapable of binding to the endothelial surface of blood vessels, preventing clot formation primarily through the extrinsic pathway. The half-life of warfarin is 36 hours, and it is metabolized in the liver.

**Table 2. INTERNATIONAL NORMALIZED RATIO AND HEMOGLOBIN LEVELS**

Patient	Preoperative INR	Preoperative Hgb	Admission INR	Admission Hgb
1	2.5	12.5	5	8.3
2	1.2	11.3	1.4	9.5

Abbreviations: Hgb, hemoglobin; INR, international normalized ratio.

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Because of the drug and food interactions, the prothrombin time and INR should be closely checked for patients taking warfarin.<sup>8</sup> In theory, antibiotics can potentiate the effects of warfarin by slowing the hepatic metabolism of warfarin and by inhibiting intestinal flora that produce vitamin K. Clinical trials evaluating warfarin and antibiotic combinations have had mixed results. Mean changes and supratherapeutic INR values have been documented in patients taking azithromycin, levofloxacin, and trimethoprim/sulfamethoxazole.<sup>9</sup> However, in the latter study, only trimethoprim/sulfamethoxazole was related to adverse bleeding events, and the median follow-up was 6 days.

Because no specific studies have related warfarin and penicillin or clindamycin with overanticoagulation, it is difficult to know the reason for the hemorrhage in the 2 presented patients. Evidence has been positively linked to the degree of surgical intervention (multiple extractions) with increased postoperative INR results.<sup>10</sup> Both presented cases involved the mandible and only 1 to 3 teeth. In the future, controlled studies might elucidate the potentiation of warfarin from penicillin, amoxicillin, or clindamycin.

What is known is that our patient population is aging, and, thus, more medications are being prescribed. The variables affecting warfarin such as drug-food interactions and patient metabolism will continue to be a health care concern, requiring significant intervention on rare occasions. Both presented patients were treated appropriately to the level of care described by the current data. Adding additional layers of postoperative surveillance with more immediate examinations and INR tests would be helpful in management but they do not always work with a patient with multiple comorbidities.

A recently treated 75-year-old woman with obesity, type 2 diabetes mellitus, hypertension, congestive heart failure, hyperlipidemia, and chronic obstructive pulmonary disease received an immediate postoperative examination on day 4, after extraction of the maxillary left second premolar and first molar with the patient under local anesthesia. Although the patient had not been experiencing uncontrollable hemorrhaging, her INR was more than 9.0 in the family physician's office and 11.2 at the emergency room. The family physician had begun treating a urinary tract infection on postoperative day 2 with ciprofloxacin and was aware of the recent dental extractions. The emergency room physician transfused 4 U of fresh frozen plasma and diagnosed the patient with warfarin poisoning.

These cases should act as a red flag for the postoperative management after simple exodontia proce-

dures involving warfarin therapy and other medications. Because multiple medical diagnoses were present in patients 1 and 2, stopping total anticoagulation therapy preoperatively and postoperatively for a defined period might have prevented the unintentional bleeding events. Future evidence-based studies might show that a subset of patients with specific medical diagnoses and medications should receive no anticoagulation therapy before dental extractions. Other risks would then arise and would warrant preoperative physician advice. In contrast, within the framework of routine oral surgery, more research might define a new protocol when treating patients taking warfarin and other medications, similar to that for American Society of Anesthesiologists classification III and IV.

Although the published data have supported the efficacy of warfarin in carefully monitored patients, replacement drugs for warfarin are being tested at Bayer AG and Bristol-Myers Squibb.<sup>11</sup> These drugs block factor Xa and might not require monitoring because of the fewer drug-food interactions and increased efficacy at low doses. Because the cost of enoxaparin to those without a Medicare Part D supplement or prescription insurance is substantial (more than \$400.00), many patients refuse this course of treatment before extractions. Given the national interest in reducing health care costs, newer replacement drugs might prove cost-effective.

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