A retrospective review of clinical international normalized ratio results and their implications

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Warfarin is an oral anticoagulant commonly used to treat patients with conditions such as atrial fibrillation, deep venous thrombosis (DVT), stroke (cerebrovascular accident) and cardiac valve replacement. Warfarin affects the extrinsic clotting pathway by preventing the reduction of vitamin K into its active form. Its effectiveness in the patient is measured by means of a standardized prothrombin time (PT) test. PT and its derived ratios of prothrombin ratio (PR) and international normalized ratio (INR) all are measures of the extrinsic pathway of coagulation.1 The reference range for PT is about 11 to 16 seconds. The normal range for INR is 0.8 to 1.2. PT is measured by means of blood plasma, which is collected in a test tube containing citrate; the citrate acts as an anticoagulant and binds to the calcium in the sample. The blood is mixed and centrifuged to separate cells from the plasma. The separated plasma portion is infused with excess calcium, Dr. Kassab is an assistant professor, Department of Surgical Sciences, School of Dentistry, Marquette University, 1801 W. Wisconsin Ave., Milwaukee, Wis. 53201, e-mail “Moe.kassab@mu.edu”. Address reprint requests to Dr. Kassab.
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ABSTRACT

Background. Warfarin is a key element in therapy for atrial fibrillation, deep venous thrombosis (DVT), stroke (cerebrovascular accident) and cardiac valve replacement. Often, patients’ warfarin blood levels are not tightly controlled with regard to accepted therapeutic ranges, by virtue of the drug’s unpredictable nature.
Methods. The authors searched 16,017 active clinical charts for active patients of record from the three campuses of the School of Dentistry, Marquette University (MU), Milwaukee, for the years 2009 and 2010. Dental records of 315 patients contained entries including “INR,” the abbreviation for the term “international normalized ratio.” Only 247 of those records contained an indication of whether the patient’s INR values were within therapeutic range. The authors found that 1.96 percent of the total MU dental clinic patient population had a history of warfarin use.
Results. When the authors compared the INR values for patients with diagnoses of atrial fibrillation, DVT, stroke and cardiac valve replacement, they found that INR values for 107 of the 247 patients (43.3 percent) were not within therapeutic range for the respective diagnoses. For example, only 50 percent of the patients being treated for atrial fibrillation presented themselves for surgical dental treatment while their INR values were in tight control.
Conclusion. The INR values for a significant number of dental patients are not within the therapeutic range for their medical conditions. These patients need to seek follow-up care from their medical care providers.
Clinical Implications. Screening for INR in the dental office—especially before invasive dental treatment such as periodontal surgery, tooth extraction and dental implant placement—can help prevent postoperative complications. It also can aid the clinician in evaluating whether a patient’s INR is within therapeutic range and, subsequently, whether the patient’s physician needs to adjust the warfarin dosage.
Key Words. Extraction; periodontal surgery; warfarin; dental implant; international normalized ratio; prothrombin time; testing; point of care.
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Thus neutralizing the citrate; this enables the sample to clot again. Tissue factor III is added, and the time the sample takes to clot is measured. The PR is the PT divided by results from a control sample.

Because PT results may vary from laboratory to laboratory owing to equipment, different batches of tissue factor and reagents used to perform the tests, the INR was established by the World Health Organization, Geneva. Each manufacturer of tissue factor assigns an international sensitivity index (ISI) score to batches it produces by comparing the individual batch with an international standard established by a committee of the World Health Organization. The INR is the ratio of a patient’s PT to a normal control sample raised to the power of the ISI value for the analytical sample used. Each patient’s target therapeutic range of INR depends on the reason for treatment. Patients receiving warfarin for atrial fibrillation, DVT and stroke have a target INR of 2.0 to 3.0, whereas patients receiving warfarin after undergoing cardiac valve replacement surgery have a target range of 2.5 to 3.5. An INR below the therapeutic range increases the risk of a thrombotic event, and an INR above the therapeutic range increases the risk of a hemorrhagic event. Because it is based on PT, a patient’s INR can be elevated owing to other conditions that affect the extrinsic clotting pathway. These conditions include vitamin K deficiency, disseminated intravascular coagulation and liver failure. Conversely, patients whose clotting pathways are altered in other ways, such as those receiving aspirin (antiplatelet drugs) therapy and those with hemophilia (extrinsic pathway) or von Willebrand disease (platelet abnormality), will have unaffected PT results.

Traditionally, patients underwent monthly blood testing by a physician to confirm that their INR values were within their target range. However, study findings have shown that more frequent testing results in tighter control of a patient’s INR values. The additional testing most often is achieved by means of home testing devices or point-of-care (POC) testing devices. The results of numerous studies have shown that POC testing devices, when used correctly, are able to give reliable INR results in 1 to 2 minutes.

Many medical practitioners modify or stop a patient’s anticoagulation therapy before he or she undergoes dental treatment. However, myriad studies indicate that patients can maintain therapeutic levels of warfarin through routine dental procedures without incurring increased risk of experiencing major bleeding complications. Beirne noted that “stopping warfarin with or without bridging for dentoalveolar surgery is not supported by clinical evidence when the INR is within or below the therapeutic range.” To minimize the patient’s potential risk of experiencing thromboembolism or hemorrhage, it is important that his or her INR is within therapeutic range on the day of treatment. For patients receiving anticoagulation therapy because they have a diagnosis of atrial fibrillation, DVT or stroke, there is no need to delay therapy if the INR is higher than 1.0 point above the therapeutic range for these three conditions (2.0-3.0). However, for those who receive anticoagulation therapy after undergoing cardiac valve replacement, increasing the acceptable level of INR beyond 4.0 may result in an exponential increase in the risk of a postoperative bleeding event. INR is an expression of a normalization value of PT expressed in seconds. Proceeding with invasive dentoalveolar treatment in a patient whose reported INR values are above 4.0 can lead to a significant increase in postoperative bleeding, even when the clinician undertakes local hemostatic measures. In a 2003 report, Jeske and Suchko found that dental treatment can be performed safely in patients whose INR is 4.0 or lower, regardless of their medical condition or why the warfarin has been prescribed.

Brennan and colleagues suggested “that dentists should not rely on a patient’s previous INR test result as a reliable predictor of his or her current INR and that a new INR be obtained 24 to 48 hours before the patient undergoes an invasive dental procedure.”

A review of the literature indicates several aspects of warfarin therapy that the dental practitioner should keep in mind, such as the importance of maintaining patients’ INR values in a narrow therapeutic window. The high prevalence of patients outside this window in a hospital setting and inconsistencies found between teaching practices in U.S. dental schools along with consistencies of medical evidence indicates a cause for concern for the dental professional. An analysis of the day-of-surgery INR values for dental patients receiving oral anticoagulants is

indicated to determine whether POC testing should become customary care in a non–hospital-based dental practice.

**METHODS**

The institutional review board of Marquette University (MU), Milwaukee, approved our protocol for a retrospective review of clinical INR results at the MU School of Dentistry and their implications, along with a waiver of consent for the study and an authorization to use protected health information, in July 2010 (HR-2035). Our review was simplified by the fact that MU School of Dentistry began using axiUm (Exan Group, Coquitlam, British Columbia, Canada) to document medical records and provide electronic forms of progress notes in 2007. The software program allows for a search of key terms in the progress notes section of the electronic dental record.

We searched 16,017 clinical charts for active patients of record from the three campuses in the MU School of Dentistry—comprising patients at the main clinic and those from the north and south community dental clinics in Milwaukee—for the years 2009 and 2010. Dental records of 315 patients contained entries including the term “INR.” Only 247 patient records had an indication of whether or not the patient’s INR values were within therapeutic range. Of the 247 patients whose records contained INR notations in the progress notes, 206 patients had one, 36 patients had two and five patients had three of the following conditions: atrial fibrillation, DVT, stroke or cardiac valve replacement. Sixty-eight records contained an INR entry without a provisional diagnosis. We manually inspected these records to retrieve information from the health history that would aid in determining the reason for the patient’s receiving warfarin therapy. The manual inspection did not yield information about a provisional diagnosis; therefore, we excluded these records from consideration. We identified 247 records that met all of the parameters we had established.

The POC device used at the MU School of Dentistry is the INRatio PT Monitoring System Professional Kit (model +M30400100043Z) (Alere, San Diego). The INRatio involves the use of disposable test strips with a recombinant thromboplastin reagent as the reactive component. The meter detects clot endpoints by measuring the electrical impedance of a capillary blood sample. Each test strip incorporates two control channels that test high and low for each sample. Control results outside the accepted range result in an error message and no reported INR value. All testing was accomplished with capillary blood and performed under the manufacturer’s published protocol by faculty members and students of the MU School of Dentistry. (Students learned to use the POC device and conducted the testing under the direct supervision of members of the dental school’s faculty in the Department of Surgical Sciences.) By using the POC device, we performed INR testing in patients receiving anticoagulation therapy immediately before they underwent any invasive dental treatment.

Of particular significance to this method of testing is the fact that a “hanging” drop of blood must enter the test chamber of the coded and calibrated strip for the test to be valid (Figures 1 and 2).

**RESULTS**

We found that 1.96 percent of the total MU dental clinic patient population had a history of warfarin use. Records indicating a working
diagnosis for the warfarin therapy (n = 247) represented 1.53 percent of the population visiting all MU dental facilities for patient care on the three Milwaukee campuses. This percentage, which is significantly higher than the national average, can be attributed to the relatively aged and medically compromised population that constitutes the MU School of Dentistry patient base.

When comparing patients with diagnoses of atrial fibrillation, DVT, stroke or cardiac valve replacement in terms of therapeutic range, we found that 107 of the 247 patients had INR values that were not within the therapeutic range for their diagnosis (Table 1). Patients included in this analysis had a diagnosis of at least one of the following: atrial fibrillation, DVT, stroke or cardiac valve replacement. We evaluated patients with each diagnosis individually for therapeutic range. We found that the INRs of 34.6 percent of patients with atrial fibrillation, of 55.1 percent of patients with DVT, of 14.0 percent of patients with stroke and of 12.1 percent of patients with cardiac valve replacement were not within therapeutic range.

Table 1 lists the individual P value, calculated according to the Fisher exact test, for each diagnosis. Because the sample size was relatively small, we used a Fisher exact test to determine significance. The range of INR values for any diagnosis, as reported in Table 2, was 0.2 to 7.0. Table 2 also reports individual ranges for each of the four diagnoses; for example, the range of recorded INR results for atrial fibrillation ranged from 1.0 to 6.6. Notwithstanding the fact that any condition that requires anticoagulation therapy has the potential for a life-threatening outcome when that therapy is modified, the condition involving anticoagulation for cardiac valve replacement that could result in a thromboembolic event is the INR's being below the therapeutic range. In this study, the values ranged from 1.1 to 3.8, which indicates that many of these patients were not in a state of therapeutic anticoagulation.

**DISCUSSION**

If one goal of dental education is to protect public welfare, and if dental educators and all of dentistry really are at the “crossroads” with medicine, then a concerted effort among all health care providers to use all of the current technology to assess all of our patients’ health care needs is critical. This goal includes education of students regarding the use and clinical application of POC devices to assess warfarin therapy. In MU’s rural outreach programs, this becomes more important because patients in those areas often have difficulty accessing primary care physicians. This training is a primary goal of public health policies that appear on the Association of State and Territorial Dental Directors’ (ASTDD’s) Web site. Certainly, we can emphasize assessment of patients who are receiving warfarin therapy in addition to developing policies regarding the first three items on a list of public health issues that the ASTDD identified as facing dentistry in 2006: methamphetamine use and “meth mouth,” tooth grills (removable cosmetic dental appliances and jewelry) and human papillomavirus.

We need to address the significance of the results in Table 1, along with the challenge that those results reflect. Our null hypothesis was that all patients receiving warfarin therapy who reported to the MU School of Dentistry or to one of its community dental centers for invasive dental care had INRs that were controlled and within the targeted therapeutic range for patients with atrial fibrillation, DVT, stroke or cardiac valve replacement. The P values for patients with atrial fibrillation and DVT indicate a significant probability that the INRs of the patients seen were not within therapeutic range. In our review, we found that the INRs of
12.1 percent of patients with valve replacement and of 14.0 percent of patients with stroke were not within therapeutic range. POC testing and teaching the value of testing to dental students are extremely important, because patients are not always aware of the results of their blood tests. The reported INR values are in themselves a cause for alarm. Patients with INR values higher or lower than the suggested therapeutic range (again, the range varies according to diagnosis; see Table 2) were informed of their INR number, then were referred to their physicians for management of their anticoagulation therapy and to bring the INR values within therapeutic range. As much as a patient with a higher INR value might experience significant postsurgical complications, including bleeding, patients with lower INR values, who might seem to have a better level of coagulation, such as that needed to undergo dental surgery, run the risk of developing thromboembolism. Referral to a physician and proper treatment can ensure that the patient’s INR is in therapeutic range before the initiation of invasive dental procedures.

It is important for practitioners to be aware of their patients’ medical history and any anticoagulation therapy they might be receiving. If properly trained, dental practitioners can use a POC tester to confirm an appropriate INR value before beginning invasive dental procedures. It seems prudent for dental practitioners to adopt preoperative POC testing for invasive dental procedures to provide safer treatment for their patients. This also provides an avenue for collaboration with other health care professionals to yield more comprehensive care for patients.

In evaluating INR testing for patients treated in our institution, we found that the purchase of the INR testing machine provided a threelfold benefit. First, it addressed anticoagulation therapy as a case selection criterion in evaluating the timing of invasive dentoalveolar procedures, as well as the concomitant need to provide appropriate hemostatic measures. Second, it introduced the concept of POC testing and monitoring to our students. Third, the device provided a service to patients who did not have day-of-surgery INR test results available at the time of their surgical appointment, thereby alleviating the problem of canceling surgery and rescheduling, as well as the inherent costs of such activity.

The cost of such equipment is a factor in providing INR monitoring. In a large institution such as MU, the cost-benefit ratio is weighted heavily by the instructional value. That is not a factor in a private practitioner’s decision-making process. Fortunately, as of March 2008, the Center for Medicare and Medicaid Services expanded the Part B coverage for home PT/INR monitoring beyond that for people who have artificial heart valves. This reduction in out-of-pocket costs resulted in 3 million additional patients’ potentially conducting self-testing. Many private insurance companies have begun to follow through with coverage. The private practitioner may include INR testing in the preoperative protocol by instructing patients to bring their monitors to the dental office at the time of surgery. Available machines for home and office use include the feature of stored memory, thus providing access to prior results.

**CONCLUSION**

INR testing should be incorporated into any dental practice in which invasive procedures are performed. POC devices provide valuable information comparable with that derived from laboratory-based testing. Either method should be incorporated into practice when a patient is exposed to the risk of bleeding or a thromboembolic event.

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### TABLE 2

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>INR† VALUE</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD†</td>
<td>Range</td>
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<tr>
<td>Any Diagnosis</td>
<td>2.37 ± 0.9</td>
<td>0.2-7.0</td>
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<tr>
<td>Atrial Fibrillation</td>
<td>2.46 ± 0.8</td>
<td>1.0-6.6</td>
</tr>
<tr>
<td>Deep Venous Thrombosis</td>
<td>2.35 ± 1.0</td>
<td>0.2-7.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.34 ± 0.9</td>
<td>1.0-6.6</td>
</tr>
<tr>
<td>Cardiac Valve Replace</td>
<td>2.52 ± 0.8</td>
<td>1.1-3.8</td>
</tr>
</tbody>
</table>

* Patients drawn from among active patients of record at three clinics of the School of Dentistry, Marquette University, Milwaukee.
† INR: International normalized ratio.
‡ SD: Standard deviation.


