J Oral Maxillofac Surg
54:1115-1118, 1996

Surgical Management of Patients on Warfarin Sodium

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Purpose: Management of anticoagulated patients has changed significantly over the past 10 years. The change occurred after the introduction of the international normalized ratio (INR) in 1983. This method of reporting prothrombin time for anticoagulated patients has resulted in a decrease in the level at which hematologists and cardiologists keep their patients anticoagulated. Currently, patients are anticoagulated less for the successful prevention of thromboemboli. Recent recommendations are to keep patients anticoagulated to an INR no greater than 3.5. It has been proposed that the extraction of teeth can be performed with INRs of 4 or less. Therefore, the current trend is to maintain patients on their anticoagulation regimens without altering their warfarin dosages.

Conclusion: With proper local measures, teeth can be extracted safely and the development of thromboemboli in high-risk patients can still be prevented. However, with procedures having a high risk of bleeding, warfarin dosage may need to be modified.

Oral anticoagulants are needed to prevent thrombosis and embolism. The most common drug used for this in North America is warfarin sodium (Coumadin, DuPont, Wilmington, DE). Warfarin competitively inhibits the enzyme vitamin K epoxide reductase, which is responsible for the reductive metabolism of vitamin K epoxide to the active hydroquinone form.[1] Active vitamin K is a cofactor for the enzymatic γ-carboxylation of several glutamate residues in factors II, VII, IX, and X and endogenous proteins C and S.[2] The inhibition of this posttranslational modification results in the production of factors that are biologically inactive. Warfarin will effect the factor with the shortest half-life first and the factor with the longest half-life last. The half-lives for factors VII, IX, X, and II are 6, 24, 40, and 60 hours, respectively.[3] Factor VII is affected first, and this increases the prothrombin time (PT). Factors IX, X, and II will be affected later and increase the partial thromboplastin time (PTT).

Since the early 1940s, the PT method developed by Quick has been the primary means of monitoring the level of oral anticoagulant control. Hematologists recommended that the level of anticoagulation be 1.5 to 3 times the control value to prevent thrombosis.[4]

The PT is performed by adding calcium and thromboplastin to citrated patient blood. Thromboplastins are phospholipid-protein extracts of tissues (brain, lung, or placenta) that are necessary to promote the activation of factor VII.[5] Laboratories in the 1940s prepared their own thromboplastins to conduct PT tests on blood samples. In the 1960s the Manchester Comparative Reagent (MCR), a very sensitive human thromboplastin, was commercially prepared and widely used throughout British laboratories.[4] Conversely, in North American laboratories, Simplastin (Organon Teknika, Durham, NC) (a less sensitive rabbit thromboplastin) became the reagent of choice.[4] In 1970s it was found that there were wide differences in the PTs when the two commercially available anticoagulants were used. A patient with a PT 2 to 2.5 times the control when rabbit thromboplastin (Simplastin) was used as the reagent would have a PT of 4.5 to 6 times the control if human thromboplastin (MCR) was used as the reagent (Table 1).[4] As a result, patients who were monitored

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0278-2391/96/5409-0014$3.00/0

Table 1. Comparison of Prothrombin Times Using Different Thromboplatins

Equivalent INR	Prothrombin Ratio Using Rabbit Brain Thromboplastin (ISI Value = 2.3)	Prothrombin Ratio Using Human Brain Thromboplastin (ISI Value = 1.3)
1.0	1.0 × control	1.0 × control
2.0	1.4 × control	1.7 × control
3.0	1.6 × control	2.3 × control
4.0	1.8 × control	2.9 × control
5.0	2.0 × control	3.4 × control

with sensitive thromboplastins in Europe were anticoagulated to a lesser extent than those in North America. Subsequently, it was found that the patients on lower levels of anticoagulation had no greater risk of thromboembolism and had fewer problems with atypical bleeding.[5]

By the late 1970s, there were many commercial thromboplastins available, with differing levels of sensitivity. In 1978, the World Health Organization (WHO) recommended that the PT be standardized. In 1983, the WHO published the recommendations for reporting the level of anticoagulation using an International Normalized Ratio (INR). The INR was developed to normalize the PT test based on the sensitivity of different thromboplastins and is calculated as shown below.

$$\text{INR} = \left(\frac{\text{PT}}{\text{mean normal PT}}\right)^{\text{ISI}}$$

INR, International normalized ratio, PT, prothrombin time; mean normal PT, PT time based on geometric mean of 20 fresh plasmas of healthy ambulant patients; ISI, International Sensitivity Index. As a result, an INR is essentially the same regardless of which thromboplastin a particular laboratory uses.

The International Sensitivity Index (ISI) corrects for the sensitivity of the thromboplastin that a laboratory uses. The ISI is calculated by an orthogonal regression line that rates the activity of a thromboplastin relative to the international reference preparation, a human brain thromboplastin that has an ISI of 1.0.[6] The larger the ISI value, the less sensitive the thromboplastin. For example, a very sensitive human brain thromboplastin may have an ISI of 1.0, whereas a less sensitive rabbit brain thromboplastin may have an ISI value of 2.3. The ISI values currently being used in North America range from 1.8 to 2.8.[7] By correcting for the sensitivity of the thromboplastin using the ISI value, an INR in one laboratory is equivalent to the INR in another laboratory even if a different thromboplastin was used to test the blood sample. In 1985, the International Committee for Standardization in Hematology and the International Committee on Thrombosis and Haemostasis published their agreement with WHO recommendations based on international studies.[8]

In 1986, an Ad Hoc committee sponsored by the American College of Chest Physicians (AACP) and the National Heart, Lung, and Blood Institute formulated new guidelines for anticoagulation.[9] The committee reviewed the literature and clinical findings and determined that patients in North America could be effectively treated with lower doses of warfarin to prevent thrombosis and at the same time minimize the complications associated with anticoagulation. At this meeting, it was also recommended that the INR be used to monitor the level of anticoagulation. Since this first meeting, the guidelines for anticoagulation have been revised twice. The most recent guidelines were published in 1989 and are even lower than the 1986 recommendations (Table 2).[5]

Some investigators still recommend higher levels of anticoagulation.[10-12] In 1993, van der Meer et al[10] recommended a target INR of 4.0 for prosthetic heart valves, with an acceptable range of 3.2 to 5.3. This retrospective study analyzed 1,608 patients and concluded that the optimal intensity of anticoagulation ranged from 2.5 to 4.9. At this level, the incidence of complications from thromboemboli or bleeding was the lowest. He also suggested higher recommended target values for other uses of anticoagulants.[10] This was supported in the *New England Journal of Medicine* in 1995 by Cannegieter et al,[11] who recommended a target INR of 3.0 to 4.0 for prosthetic heart valves. An editorial by Fihn[12] suggested that the AACP standards continue to be followed until further research is com-

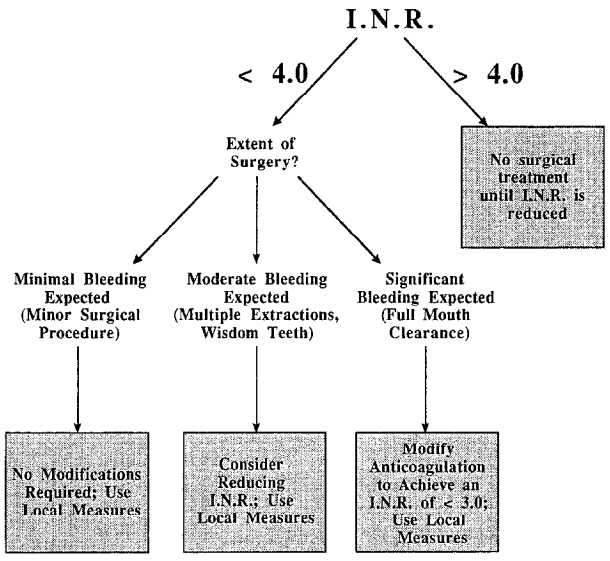

FIGURE 1. Managing Patients using the INR.

Table 2. Therapeutic Levels of Anticoagulation

Clinical State	INR	Therapeutic Range Using Rabbit Brain Thromboplastin (ISI value = 2.3)
Prophylaxis—venous thromboembolism (high-risk surgery)	2.0-3.0	1.35-1.6 × P.T.
Prophylaxis—venous thromboembolism (hip surgery)	2.0-3.0	1.35-1.6 × P.T.
Treatment of deep vein thrombosis or pulmonary embolism	2.0-3.0	1.35-1.6 × P.T.
To prevent systemic embolism in patients with atrial fibrillation, valvular heart disease, tissue heart valves, or acute myocardial infarction	2.0-3.0	1.35-1.6 × P.T.
Mechanical prosthetic heart valves, recurrent systemic embolism	2.5-3.5	1.5-1.7 × P.T.

Adapted from Hirsch et al 1992[5]

pleted. However, he recommended the use of the upper end of the recommended range.

Reasons for Using the INR

Reporting the ratio of the patient's PT to the mean laboratory PT does not normalize the results of the PT test. The only way to normalize the PT is to calibrate the different thromboplastins. It seems apparent that the only way to assess the meaning of the PT is either to know what thromboplastin was used by the laboratory, or by using the INR. The interlaboratory variation for the INR has been estimated to be 7% to 8%.[13] By using WHO calibration recommendations, it has been reported that the between-laboratory variation can be kept within 4%.[13] Thus, the reported value using the INR is essentially the same no matter which laboratory does the test.

Acceptable INR for Oral Surgery

The American Medical Association and the American Dental Association previously recommended that the PT be between 1.5 and 2.5 times the normal PT before a surgical procedure be attempted. Currently the literature is unsettled on what appropriate INR level is acceptable to perform extractions. In 1992, Weibert[14] a pharmacist, published recommendations that the warfarin be withheld for 5 days or longer with any high-risk procedures (ie, multiple extractions). For simple extractions, he recommended that the INR be adjusted to achieve a level between 2.0 and 3.0.[14] In 1994, Lippert and Gutschik[15] published recommendations that the INR be no greater than 4.0, and preferably less than of 3.0, before patients undergo procedures with a high risk for bleeding. They also recommended that a fibrinolytic inhibitor mouth rinse (eg, 5% transexamic acid) be used in conjunction with other local measures to decrease bleeding.[15] Both Weiber[14] and Lippert and Gutschik[15] agree that the use of a fibrinolytic inhibitor for 7 days, four times a day, will significantly decrease postoperative bleeding and avoid prolonged interruption of anticoagulation. This approach is more favorable, because patients with a mechanical valve prosthesis would be exposed to a high risk for thromboembolism if the INR were significantly reduced.

An alternate approach for patients at high risk for thromboembolism is to discontinue warfarin and introduce heparin to achieve a PTT of 1.5 to 2.0 times the control midway between injection times.[14] The heparin should be discontinued for a minimum of 6 hours before surgery and resumed 12 to 24 hours after surgery and continued until the INR returns to an optimal range.[14] This method requires hospitalization and is often a very expensive process.

In patients in whom the risk of thromboembolism is less of a problem, it has been suggested by some that the warfarin should be discontinued a minimum 48 hours before the surgical visit and reinstituted the day of surgery.[14] The INR should always be checked the morning of surgery.

With recent decreases in the levels of anticoagulation used to prevent thromboembolism, it is recommended that the INR not be altered before surgery unless it is greater than 4 (Fig 1). It is interesting to calculate the predicted INR values using the old American Dental Association recommendations for tooth extraction. Assuming that a rabbit thromboplastin was used to develop these guidelines because this was the predominant thromboplastin in North America at the time, a PT of 1.5 to 2.0 times the control is equivalent to an INR of 2.6 to 5.0. Thus, recommending that oral surgery procedures can be performed with an INR of 4 or less does not seem inappropriate. However, an INR above 5.0 has been shown to have unacceptable risks for bleeding, and no surgical procedures should be attempted.[13]

When large amounts of blood loss is expected, the INR should be less than 3.0. For third molar extraction, it is conceivable to proceed with surgery as long as the INR is less than 4, provided that local measures to control bleeding are used. The local measures include such things as microfibrillar collagen (Avitene Alcon, Ft Worth, TX), packed collagen (CollaPlugs, CollaCote; Colla-Tec, Inc, Plainsboro, NJ), Gelfoam (Upjohn, Kalamazoo, MI) impregnated with activated

thrombin, Surgicel (Johnson & Johnson, Skillman, NJ) and sutures. In the future, managing a patient on warfarin may be modified by the use of fibrin glues. These products have shown promise in recent well-controlled studies by simulating the last stages of the coagulation cascade despite the lowered endogenous level of coagulation factors.[16]

Limitations of the INR

Even though the INR was established to normalize laboratory results, there are still some limitations to its use. The INR is not suited for assessing the hemostatic function of patients with liver disease because other bleeding problems may also be present, and all of the coagulation factors may not be affected equally.[17] The error between laboratory machines also has been an issue that seems to be of some importance. It has been shown that there is error between machines, and that this error is relatively small and may not be clinically significant.[18] To maintain internal quality assurance and limit the systematic error of automated instruments, it is suggested that instrument calibration be done by using 20 lyophylized plasma samples that are centrally certified.[18]

It has been reported that the coefficient of variation of the INR is equal to the coefficient of the prothrombin ratio multiplied by the ISI value. Therefore, less sensitive thromboplastins (having higher ISI values) will have larger coefficients of variation. Research has shown an estimated total error of 11 to 13.5% for INR values using a thromboplastin with an ISI value of 1.0. The error can be greater for less sensitive thromboplastins, and can be as high as 20%.[6]

Summary

Clinical research supports the use of the INR over the PT. The INR allows clinicians to establish the level of anticoagulation regardless of the laboratory that conducts the test. Many authors agree that the failure to use the INR constitutes substandard medical care.[5] Without the INR, it is impossible to compare the safety and efficacy of research on bleeding in relation to levels of oral anticoagulation.

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