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Dental Extractions in Patients Receiving Oral Anticoagulant Therapy

by

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ABSTRACT

Since 1983, the WHO has recommended the use of the INR for measuring the level of anticoagulation for patients receiving warfarin therapy. However, no scientifically-derived guidelines, using the INR, for the surgical management of this group of patients exists. In the ***first part of this study***, the protocols followed by oral surgeons, when treating patients receiving warfarin, and who require dental extractions were established by performing a mail survey. The results of the survey illustrated that although the majority of oral surgeons use the INR, most of them use the INR along with the PT and only one fifth of them use this measure alone. In the ***second part of this study***, dental extractions were performed on rabbits which were anticoagulated to various INR levels.The results of this study strongly suggest that dental extractions may be safely performed on subjects receiving oral anticoagulants using routine measures for local hemostasis.

RESUME

L'organisation mondiale de la santé suggére que le ratio international normalisé (RIN) soit utilisé comme guide d'anticoagulation pour les patient sous traitement avec warfarin. Malgré cela, il n'existe pas de guide obtenu de maniéres scientifiques, pour le traitements chirurgical de ces patients. Dans ***la premiére partie de cette étude***, les protocols suivis par des chirurgiens buccales traitant le patient anticoagulé a été déterminé par un sondage effectué par la poste. Ce qui a démontré que bien que la majorité des chirurgiens utilisent le RIN, la plupart d'entre eux l'utilisent en conjonction avec le PT, et que seulement un cinquiéme d'entre eux utilise uniquement le RIN. Dans ***la deuxiéme partie de cette étude***, des extractions ont été effectué sur des lapins a différent niveaux d'anticoagulation . Cette étude démontre que des extractions peuvent être effectuées en toute sécurité sur des patients a différent niveau d'anticoagulation en utilisant seulement que des agents hémostatiques.

INTRODUCTION

The surgical management of the patient receiving anticoagulant-therapy is an area of great interest to hematologists and surgeons alike. Current clinical guidelines for the surgical management of this group of patients is largely empirical. For many years, minor oral surgery, including dental extractions, has been for performed for these patients according to the existing, empirical guidelines. This treatment approach is no longer appropriate and new scientifically-based guidelines must be established.

A significant percentage of the population receives anticoagulation therapy in the prevention and treatment of thromboembolic disease states, such as deep vein thrombosis, pulmonary embolism, cerebrovascular disease, numerous cardiac disorders and the various prothrombotic states (i.e.: lupus, factor S and factor C deficiency). [1] Therefore, the likelihood of anticoagulant-treated patients requiring oral surgery is significant and increasing. The coumarin compounds are used world-wide to provide anticoagulation. In North America, warfarin (warfarin sodium and panwarfarin) is the most commonly used oral anticoagulant.[1,2]

Since 1983, the World Health Organization has recommended the use of the INR as a measure of the level of anticoagulation. [3] When using the PT (prothrombin time) ratio as a measure of anticoagulation, it is accepted (although not scientifically proven) that dental extractions can be performed safely on patients whose PT ratio is 1.5 to 2.0 times the normal value. [4] With the use of INR levels, a new set of guidelines must be defined. In general, hematologists and internists recommend that minor surgical procedures, including dental extractions may be performed on patients with an INR value of 1.5. In randomized trials of gynecologic and orthopedic surgical patients, this level of this level of anticoagulation was safe for performing surgery. [5] This would appear to be supported by the results of a study by Declerck, et al.[6,7] In this study, rabbit incisors were extracted at different INR values and it was determined that blood loss at INR levels between 1.4 to 1.8 , would be clinically acceptable. Previous clinical experience leads us to

believe that this INR level is low. For many years we have safely performed dental extractions on patients with PT ratios of 1.5 to 2.0. This implies that extractions have been performed with INR values much higher than 1.5 (Figure 1). [8]

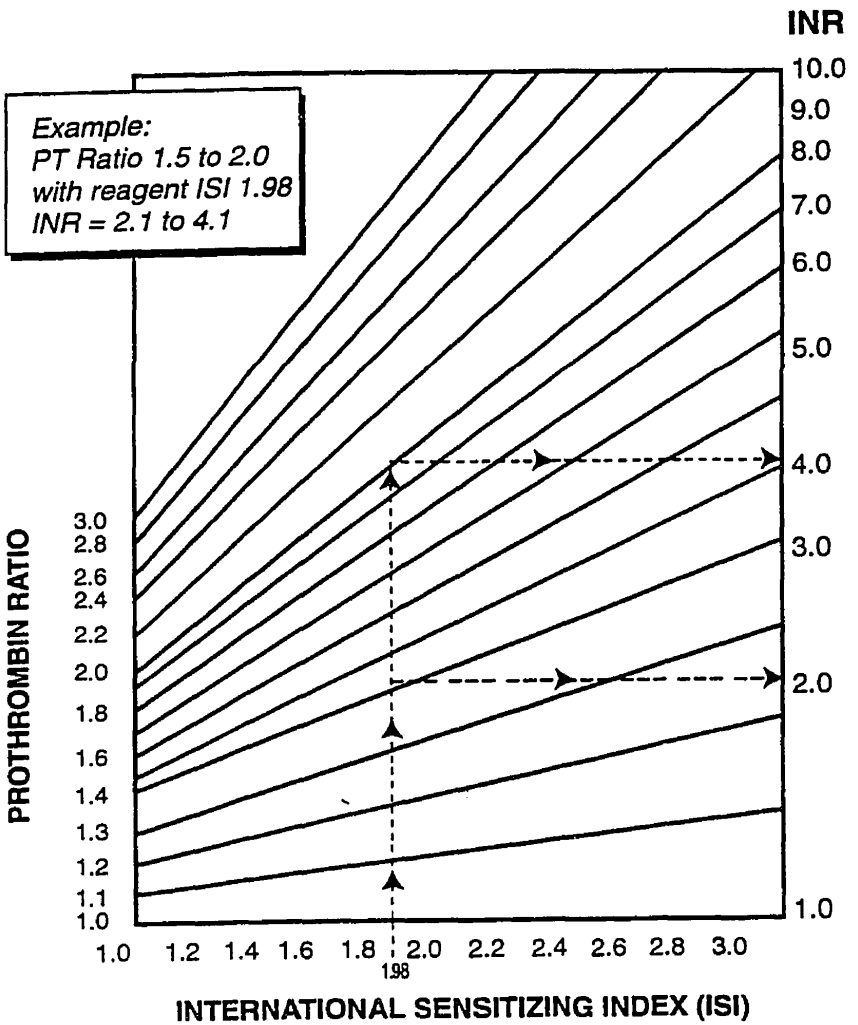


FIGURE 1. Relationship between the PT Ratio and the INR over a range of ISI.
[Adapted from Hirsh et al. 1992.]

Generally, two protocols are followed for the management of patients who are on anticoagulant therapy, and who require dental extractions. The patient either has their warfarin stopped prior to the surgical procedure or if the patient is considered to be at high risk of a thromboembolism, then the patient is hospitalized and heparin therapy is instituted during the perioperative period. There are three problems involved with these

procedures. First of all, stopping or decreasing a patient's coumadin places him/her at risk for a thromboembolic event.[9] Secondly, hospitalization is disruptive to a patient's life. Finally, hospitalization places a large financial burden on the health care system. Ideally, protocols that allow dental extractions to be performed on an outpatient basis, at all therapeutic INR levels, should be developed. This would increase patient convenience and reduce the cost to the health care system.

Initial studies with various local hemostatic agents appear to be promising. They indicate that patients on anticoagulant therapy can be safely treated without any alteration in their warfarin levels. In 1989, Sindet-Pedersen, et al [10] performed a study of 39 patients whose level of anticoagulation would be comparable to an INR range of 2.5 to 4.8. Teeth were extracted with no significant postoperative bleeding when tranexamic acid mouthwash was used as the local hemostatic agent. These findings were supported in 1993 in a study by Borea, et al. [11] A biological adhesive, Beriplast™, was used by Martinowitz, et al [12] to successfully provide local hemostasis at dental extraction sites in 40 patients with INR levels from 2.5 to 4.29. These reports support the belief that it is possible to perform outpatient surgical procedures, such as dental extractions, in this patient population without altering the level of anticoagulation. However, in these studies, more *elaborate* methods of local hemostasis were used. These agents are expensive and may in fact not be necessary.

When using the PT ratio, it is generally recommended that, for anticoagulated patients, dental extractions may be performed at a PT ratio of 1.5 to 2.0. [4] For many years this guideline has been followed by surgeons. The PT value varies among institutions, depending on the sensitivity of the thromboplastin used. Therefore, this guideline is not consistent between different institutions. However, it is interesting to estimate the INR that would be comparable to the recommended PT ratio. Beirne and Koehler,[13] illustrate that if rabbit thromboplastin is used (which was the predominant thromboplastin at the time that the PT ratio guidelines were established), a PT ratio of 1.5 to 2.0 would be comparable to an INR of 2.6 to 5.0. In the past, at the Montreal General Hospital, the

protocol for performing dental extractions for patients on warfarin therapy included maintaining the PT ratio between 1.5 to 2.0. The ISI at that time, at this institution, was estimated to be 1.98. This would therefore imply that we had been safely performing dental extractions at INR ranges of 2.1 to 4.1 (Figure 1). In fact, it appears that in the past, we were safely performing dental extractions at all therapeutic INR ranges, using only *routine* measures of local hemostasis. Now that a reliable, consistent and universal measure for the level of anticoagulation, exists, well controlled studies are required to determine the INR levels at which dental extractions can be safely performed.

The ***first part of this study*** will determine the protocols which are presently followed, by surgeons, when patients receiving anticoagulant treatment, require minor oral surgery. To achieve this, a mail survey was conducted of the directors, of the Oral and Maxillofacial Surgery Training Programs in North America.

In the ***second part of this study***, the highest INR level at which dental extractions can be safely performed on an animal model receiving warfarin treatment, using *routine* local hemostatic measures, will be established. It is expected that this study will provide some scientifically based guidelines for the surgical management of patients on warfarin.

Having determined the INR levels at which routine measures are not sufficient, the aim of a future project would be to compare the effectiveness of more *elaborate* local hemostatic agents at the higher INR levels. Finally, future clinical trials will confirm if local hemostatic agents (routine and/or elaborate) are effective at all therapeutic INR levels. Therefore, the need to either decrease a patient's level of anticoagulation or to hospitalize them for heparin therapy will no longer be necessary. We expect to find that this is a safe and cost efficient treatment protocol for this population of patients.

LITERATURE REVIEW

Intravascular thrombosis and embolism are common clinical manifestations of numerous diseases. The arrest of bleeding after injury to a blood vessel involves the precise interactions between three components; the blood vessel wall, the platelets and the plasma coagulation proteins. This interaction results in normal hemostasis. If this process is exaggerated, thrombosis occurs. [14] "Thrombosis is coagulation occurring in the wrong place or at the wrong time". [2]

Normal Hemostasis

The process of hemostasis is divided into primary and secondary hemostasis. These two events are intimately intertwined. The process of hemostasis commences when trauma, surgery or disease disrupts the vascular endothelial lining and blood is exposed to the subendothelial connective tissue. *Primary hemostasis* refers to the formation of the platelet plug at the site of injury. *Secondary hemostasis* is the process whereby the plasma coagulation proteins (coagulation cascade) result in fibrin formation. The fibrin strands strengthen the primary hemostatic plug to form the definitive plug. [2,14]

Primary hemostasis starts immediately after injury with vasoconstriction and thrombus formation. Platelets adhere to the collagen fibrils on the endothelium (Figure 2).

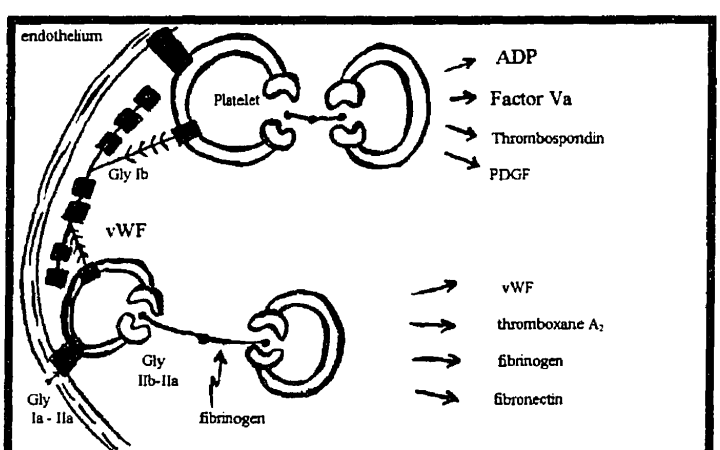


FIGURE 2. Schematic presentation of the major factors of primary hemostasis. The molecular basis of platelet adhesion and aggregation is shown. [Adapted from Harrison's Principles of Internal Medicine, 12th Edition., 1991.]

At the cellular level, platelet adherence occurs via a specific collagen receptor made up of glycoproteins Ia and IIa. This bond is then stabilized by the von Willebrand factor (vWF), an adhesive glycoprotein that assures that the platelets remain attached to the vessel wall. The von Willebrand factor forms a link between the platelet receptor site on the glycoprotein and the subendothelial collagen fibrils. The adherent platelet will then release constituents and mediators, such as ADP, Thromboxane A_2, vWF, Factor Va, and Thrombospondin.[2,14] The primary hemostatic plug is complete in three to seven minutes. Clinical assessment of primary hemostasis is performed with the bleeding time, which is a sensitive test for platelet function. [14]

As the primary plug is formed, blood coagulation proteins which normally circulate as inactive zymogens are activated to initiate *secondary hemostasis* (Figure 3). The coagulation cascade is a series of reactions which produces the serine protein, thrombin, which will convert plasma fibrinogen into fibrin.[2,14] In each step an inactive protein precursor is converted into an active protease. Each step is regulated by plasma and cellular cofactors as well as calcium. In the *intrinsic or contact phase*, three plasma proteins, Hageman factor (XII), high-molecular-weight kininogen (HMWK), and prekallikrein (PK) form a complex on the subendothelial collagen.[2]

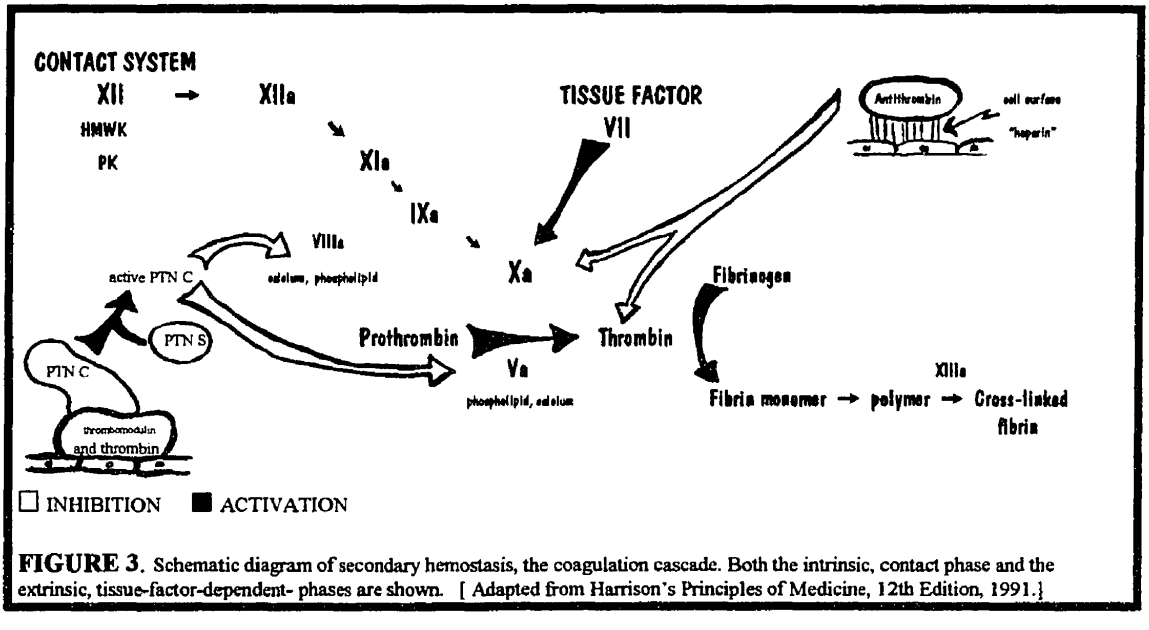
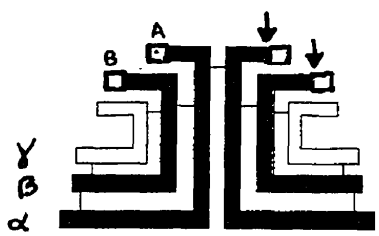


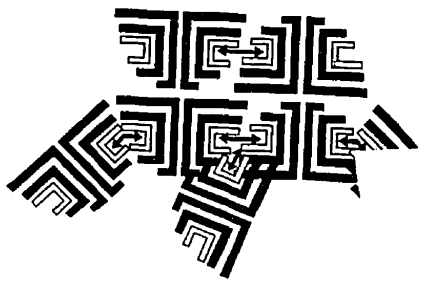
FIGURE 3. Schematic diagram of secondary hemostasis, the coagulation cascade. Both the intrinsic, contact phase and the extrinsic, tissue-factor-dependent- phases are shown. [Adapted from Harrison's Principles of Medicine, 12th Edition, 1991.]

Once HMWK binds to factor XII, it converts factor XII to an active protease (XIIa). This then converts both PK and factor XI into their active forms, kallikrein and factor XIa respectively. Kallikrein (K) will then accelerate the conversion of XII to XIIa and cleave the HMWK to form bradykinin. Factor IX will activate factor VII in the extrinsic system as well as cleave plasminogen into plasmin during fibrinolysis. [14]

Another pathway that can initiate the coagulation cascade is the conversion of VII to an active protease and is known as the *extrinsic or tissue-factor-dependent pathway*. A complex is formed between factor VII, calcium and tissue factor. The tissue factor is a lipoprotein present on cellular membranes and is exposed during cellular injury. [2,14] Factors II (prothrombin), VII, IX, and X require calcium and vitamin K for biological activity. These proteins are made in the liver where a vitamin K dependent carboxylase catalyzes a unique posttranslational modification which adds a second carboxly group to specific glutamic acid residues. [2] Pairs of these di-gamma-carboxyglutamic acid (GLA) residues bind calcium, which anchors the proteins to the phospholipid surfaces and confers activity. As will be shown later, inhibition of the posttranslational modification by vitamin K antagonists, such as warfarin, is the basis of the most common form of therapeutic anticoagulation. [2,14]

In the common pathway, the proteases formed in both the intrinsic or extrinsic pathways will activate factor X. From the intrinsic pathway, a calcium and lipid-dependent complex is formed between factors VIII, IX, and X. In this complex, factor IX is converted to IXa by factor XIa. Then factor IX a and VIII convert factor X to an active form. Alternatively, factor VIIa (from the extrinsic pathway) activates factors IX and X. Finally, factor V, calcium and phospholipid convert prothrombin to thrombin. This conversion can occur on numerous phospholipid surfaces but is accelerated a thousand fold on the activated platelet surface. [14] The principle role of the thrombin is to convert fibrinogen into fibrin but thrombin will also activate factors V, VIII, XIII, and stimulate platelet aggregation. [2,14] Once the fibrinogen is activated, by releasing the fibrinopeptides, A and B, from its alpha and beta chains, it is known as the fibrin monomer (Figure 4). This fibrin monomer





Fibrinopeptides A and B are cleaved off and fibrinogen is activated.

Covalent cross linking occurs between the γ – chains to form an insoluable clot.

FIGURE 4 The fibrinogen molecule and its polypeptide chain.
[Adapted from Oral and Maxillofacial Surgery Knowledge Update, Vol 1, Part II, page 53, 1995.]

is polymerized into an insoluable gel by cross-linking individual chains by factor XIIIa (a plasma transglutaminase). Measurement of secondary hemostasis is made with the whole blood clotting time, which averages 8 to 10 minutes. [14]

The third stage of coagulation is clot retraction. In this process the loose meshwork, made up of platelets, fibrin strands, and red blood cells, is made into a firm clot by the contraction of a smooth protein, thrombosthenin, within each platelet. In vitro this process takes one hour to be complete. [14]

The final step of coagulation is fibrinolysis. Clot lysis and vessel repair start immediately after the definitive hemostatic plug is formed. [2,14] The three main activators in the fibrinolytic system are Hageman factor fragments, urokinase and tissue plasminogen activator (t-PA). The principle factor t-PA diffuses from the endothelial cells and converts plasminogen into plasmin. The plasmin then degrades the fibrin polymer into small fragments which are taken up by a monocyte/macrophage scavenger system. Antifibrinolytics will inhibit the plasminogen activators and augment hemostasis (Figure 5).

The plasma coagulation system is tightly regulated and the hemostatic plug does not grow beyond the site of injury. Blood fluidity is maintained by the flow of the blood which reduces the concentration of the reactants, the absorption of the coagulation factors to surfaces and the presence of inhibitors in the plasma.[14] Antithrombin, protein C and protein S are important inhibitors that help maintain the fluidity of the blood.[2,14]

Antithrombin forms complexes with all the protease coagulation factors except factor VII. The rate of complex formation is accelerated by heparin and heparin-like molecules on the surface on endothelial cells. This is how heparin acts as a potent anticoagulant. Protein C and its cofactor protein S will inactivate both factors V and VIII to slow down their coagulation reactions.[2,14]

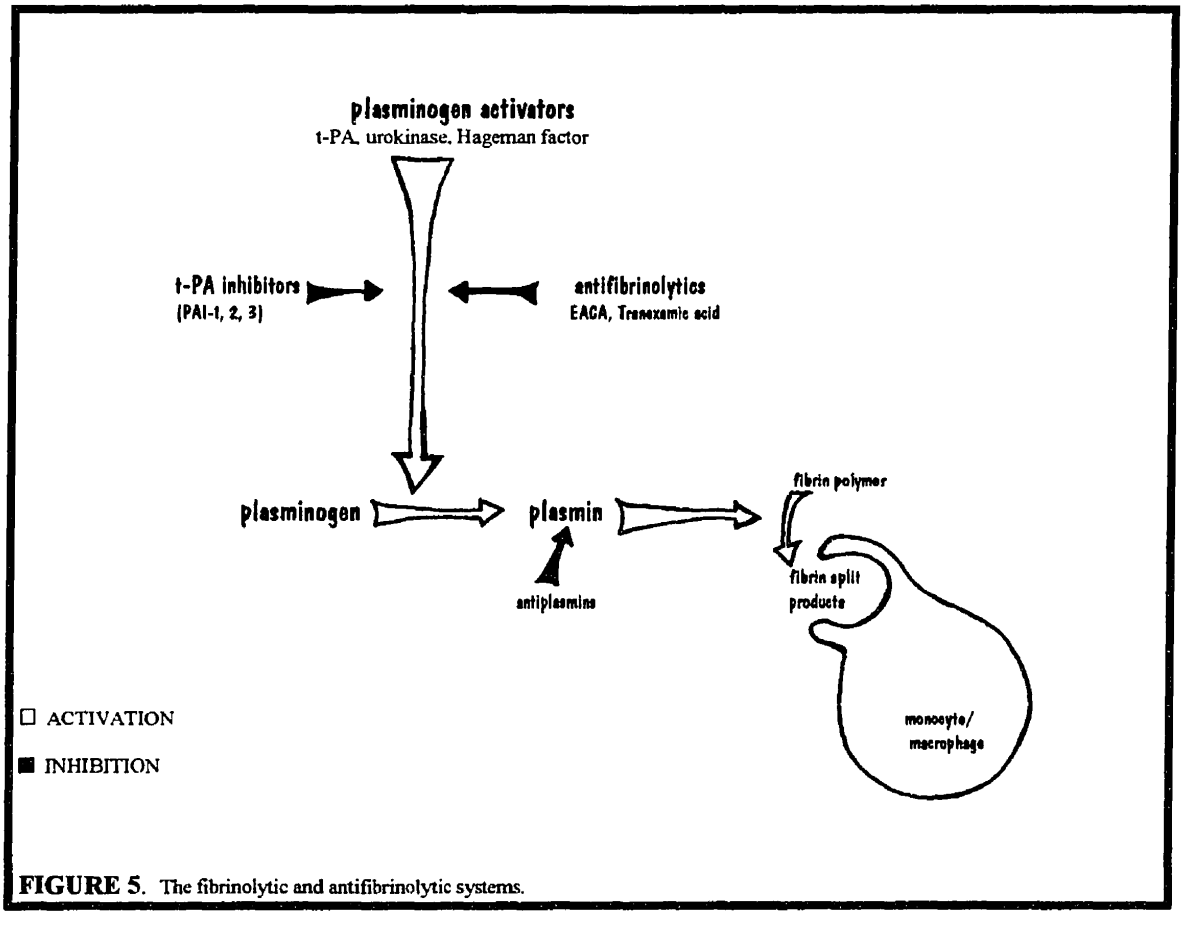


FIGURE 5. The fibrinolytic and antifibrinolytic systems.

Abnormal Hemostasis - Thromboembolism:

Antithrombotic therapy is used in the prevention and treatment of venous thromboembolism such as deep vein thrombosis and pulmonary embolism. It is also used in the prevention of systemic embolism in diseases such as atrial fibrillation, heart valve disease, prosthetic valves, cardiomyopathies, and prothrombotic conditions. Antithrombotic therapy is also used in the prevention of arterial thromboemboli in conditions such as, myocardial infarct, angina, coronary artery bypass grafts, peripheral arterial disease and cerebral vascular disease. Some of these conditions are discussed further below.

Risk Groups

Unregulated activation of the hemostatic system may cause thrombosis or embolism. These two events can cause irreversible tissue damage, by either the reduction or obstruction of blood flow. There are certain patient groups that are identified to be at particular risk of thrombosis and embolism.

- **Venous Thromboembolism**

Thrombus formation is common at the valves of the leg veins. Usually, vascular stasis, vessel wall disease or hypercoagulable conditions lead to this event. The danger in deep vein thrombosis is that the clot may either fragment or dislodge and form emboli which then occlude the pulmonary vessels (pulmonary embolism), or other vessels.

Venous thromboembolism is a major cause of death and morbidity in hospitalized patients. In the hospital setting, it is estimated that pulmonary embolism causes death in more than 100,000 patients per year in the United States. [15] A study in Worcester, Massachusetts, found an annual incidence of verified pulmonary embolism of 23/100,000 and a fatality rate of 12%.[15,16] When this data is extrapolated, it is estimated that 260,000 cases of clinically recognized pulmonary embolism occur each year in hospitalized patients in the United States.[16] The actual number is probably much higher since these studies were carried out in nonacute treatment centers, did not include rehabilitation and nursing

homes, where in fact the incidence would be much higher. In addition, the autopsy rate in the United States is low. This disease is usually silent and pulmonary embolism is not suspected in 70 to 80% of the cases diagnosed at autopsy. It has been concluded based on these observations that fatal pulmonary embolism is the most common preventable cause of death.[15]

The rationale for prophylactic treatment in the prevention of venous thromboembolism is based on the clinically silent nature of this disease.[15] Both deep vein thrombosis (DVT) and pulmonary embolism have very few specific symptoms.

Certain patient groups have been identified to be at an increased risk of developing a venous thromboembolism. These patients are " *thrombosis-prone*" but have no detectable hemostatic disorder. Clinical risk factors include advanced age (age 40 and increases with further aging); prolonged immobility or paralysis; prior venous thromboembolism; cancer (especially adenocarcinoma of the lung, breast and viscera)[17]; major surgery (especially surgery to the abdomen, pelvis and lower extremity, including hip and knee replacement)[15]; neurosurgery[17]; acute spinal cord injury[17]; obesity; varicose veins; congestive heart failure; myocardial infarction; stroke; fractures of the leg, pelvis or hip; high dose estrogen use[15]; and pregnancy. [2,18] If multiple risk factors are present, the risks are cummulative. [15]

Another group of patients who are at increased risk of venous thromboembolism are patients with "*hypercoagulable states*". These patients have an acquired or inherited defect in their hemostatic mechanism. Hemostatic abnormalities include activated protein C resistance; antithrombin III deficiency; protein C deficiency; protein S deficiency; dysfibrinogenemia; disorders of plasminogen and plasminogen activation; antiphospholipid antibodies and lupus anticoagulant; heparin induced thrombocytopenia; myeloproliferative disorders including polycythemia vera; and hyperviscosity disorders.[15,16]

❑ Systemic Embolism

Thrombi may form in areas of turbulent blood flow, such as in the wall of a ventricle or the heart valves. These clots may fragment and circulate as systemic emboli which lodge at a distant site.

Systemic embolism is a major complication of *valvular heart disease*. The incidence of systemic embolism is high in rheumatic mitral valve disease. A patient with rheumatic heart disease has a one in five chance of having a systemic embolism during the course of the disease. If the patient also has atrial fibrillation, the risk of embolism increases seven times. The risk of systemic embolism also increases with age and with lowered cardiac indices. If a patient suffers an embolism, emboli will recur in 30 to 65% of cases. Interestingly, valvuloplasty does not decrease the risk of embolism. Long term anticoagulant therapy is indicated in this population of patients. It is not recommended to give anticoagulant therapy for isolated aortic valve disease, mitral valve prolapse, patent foramen ovale, atrial septal anuerysm, or infective endocarditis unless the patient has a history of embolism or atrial fibrillation. Anticoagulant therapy is recommended for nonbacterial thrombotic endocarditis.[19] Long-term anticoagulant therapy is strongly recommended for *mechanical prosthetic valves* but only short term therapy (3 months) is recommended for *bioprosthetic valves.*[20]

Atrial Fibrillation (AF) is a common arrhythmia that is an independent risk factor for stroke. [2,14,21] Over 2 million people in the United States suffer from AF. The prevalence and incidence increase after the age of 40 and rises rapidly after the age of 65 (Figure 6).[21]

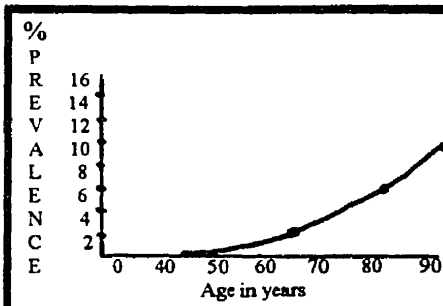


FIGURE 6. Prevalence of atrial fibrillation at various ages. [Adapted from Laupacis et al, 1995.]

Aside from increasing age, conditions associated with AF are rheumatic valvular disease, congestive heart failure and hypertensive cardiovascular disease.

The stroke rate of patients with atrial fibrillation is six times the stroke risk of people without atrial fibrillation. In patients who have atrial fibrillation with mitral stenosis the relative risk is 15 times greater. The average risk of stroke in a patient with atrial fibrillation and one other risk factor for stroke, is 5% or greater.[21]

Antithrombotic Therapy

There are four main types of therapy used in the treatment or prevention of thrombosis. These are antiplatelet agents, thrombolytic agents, heparin and vitamin K antagonists. Each of these therapies act by interfering at specific sites of the hemostatic system.

Antiplatelet Agents

Antiplatelet agents, such as aspirin, are predominantly used for prophylaxis against arterial thrombosis since platelets are more important in initiating arterial rather than venous thrombi.[2,14] Aspirin blocks the conversion of arachidonic acid to prostaglandin H_2 by inhibiting the first enzyme in this pathway, prostaglandin H_2 synthase. Normally, prostaglandin H_2 would be processed by the platelets into thromboxane A_2 and by the vascular wall endothelium into prostacyclin.[22] Thromboxane A_2 stimulates platelet aggregation and vasoconstriction; interestingly, prostacyclin does the reverse. Aspirin at all doses will suppress thromboxane A_2 production by more than 80%.[23] It is thought that this is the major mechanism for the antithrombotic effect of aspirin. Aspirin has also been reported to have other effects on hemostasis. These include the inhibition of platelet function, enhancement of fibrinolysis and the suppression of plasma coagulation. Aspirin is recommended in patients with stable and unstable angina, acute myocardial infarction, transient cerebral ischemia, thrombotic stroke and peripheral arterial disease. Aspirin is also used with warfarin in patients with prosthetic valves, who develop emboli while on warfarin therapy and for patients with atrial fibrillation who cannot take warfarin .[23]

Fibrinolytic Agents - Thrombolytic Therapy

Fibrinolytic agents, such as tissue plasminogen activator (t-PA) and the fibrinolytic enzymes, streptokinase and urokinase act to directly activate plasmin. These agents bring about the dissolution of thrombi by activating a plasma proenzyme, plasminogen, into an active agent, plasmin. When plasmin comes close to a hemostatic plug or thrombus, it degrades fibrin into soluble peptides (Figure 5). [17] The fibrinolytic drugs are used to lyse freshly formed arterial and venous thrombi.[2,14,17]

Streptokinase is a purified protein, derived from group C, β – hemolytic streptococci. Presently, streptokinase is used for venous thrombolysis, pulmonary embolism and deep venous thrombosis, and occluded arteriovenous cannulas or fistulas. *Urokinase* is a protein derived from human fetal kidney cells grown in culture. It is used for the treatment of pulmonary embolism and acute coronary thrombosis. Tissue plasminogen activator (tPA), is a protein that is produced by a genetic recombinant process. In vivo, the principle source of this protein is the vascular endothelium. [17] As a therapeutic agent, it is used in the treatment of acute coronary thrombosis.

Anticoagulant Therapy: Heparin

There are three classes of anticoagulant therapies: heparin, low-molecular-weight heparin and warfarin. *Heparin,* a glycosaminoglycan, has an immediate onset. It acts by preventing the generation of thrombin and antagonizing thrombin's action.[22] Its anticoagulant effect comes from a unique pentasaccharide sequence with a high affinity to bind antithrombin III. This causes a conformational change in the antithrombin III which allows it to inactivate factor Xa (Figure 3). At very high doses, heparin, will accelerate the inactivation of thrombin, through a second cofactor, heparin cofactor II.[22]

Heparin is heterogeneous in molecular weight, activity and properties. The molecular weight of heparin ranges from 5,000 to 30,000. The activity is heterogeneous for three reasons. First, only one third of the heparin molecules administered carry the unique pentasaccharide required. Secondly, the chain length which influences its anticoagulant

properties varies. Finally, the clearance of heparin is influenced by its molecular size, the higher molecular weight heparins are cleared faster. [22] Heparin is not absorbed orally and therefore must be administered either parentally or subcutaneously. The anticoagulant effects of heparin are monitored by the APTT, activated partial thromboplastin time. This test is sensitive to the inhibitory effects of heparin on thrombin, factor IXa and factor Xa. The recommended therapeutic range for APTT for the treatment of thrombosis is based on a study by Chiu et al, [24] in which thrombus extension was prevented in rabbits when the heparin dose prolonged the APTT ratio to 1.5 to 2.5.

Low- molecular-weight heparin (LMWH) is prepared by the chemical or enzymatic depolymerization of standard heparin. These heparins have a more predictable anticoagulant response, a longer plasma half life and good bioavailability when administered subcutaneously.[22,25] Like standard heparin, LMWH has a heterogeneous molecular weight that ranges from 1,000 to 10,000.[24] The depolymerization results in the LMWH having a changed anticoagulant profile with progressive loss in its ability to cause thrombin inhibition. LMWH also has a reduced protein binding capacity and better pharmacokinetic properties. Finally, LMWH has a reduced interaction with platelets which may account for the decrease in microvascular bleeding seen in animal models treated with LMWH as compared to standard heparin.[22] LMWH, like standard heparin produces its anticoagulant effect by binding to antithrombin III via a pentasaccharide sequence. Although only 25 to 50 % of the LMWH has the critical chain length of 18 saccharides required to inactivate the antithrombin III, all the fragments can inactivate Xa.[22] The low-molecular weight heparins are administered by subcutaneous injection in weight adjusted doses that do not require laboratory monitoring making administration and maintenance extremely simple.[22,25] This anticoagulant therapy is becoming a promising alternative to conventional treatment.

Oral Anticoagulant - Warfarin

Warfarin, (coumadin, panwarfarin), is the most common oral anticoagulant in North America.[1,2,26] It has a predictable onset, duration and good bioavailability.[5] It is an

effective drug for the treatment and prophylaxis of thromboembolism.

Warfarin is a derivative of the 4 - hydroxcoumarin molecule. It is the 4-hydroxycoumarin residue with the nonpolar carbon at the 3 position that renders the molecule active. Numerous anticoagulants have been synthesized as derivatives of the 4 - hydroxycoumarin parent molecule.[26] Figure 7 shows the structural formulas of some of the oral anticoagulants.

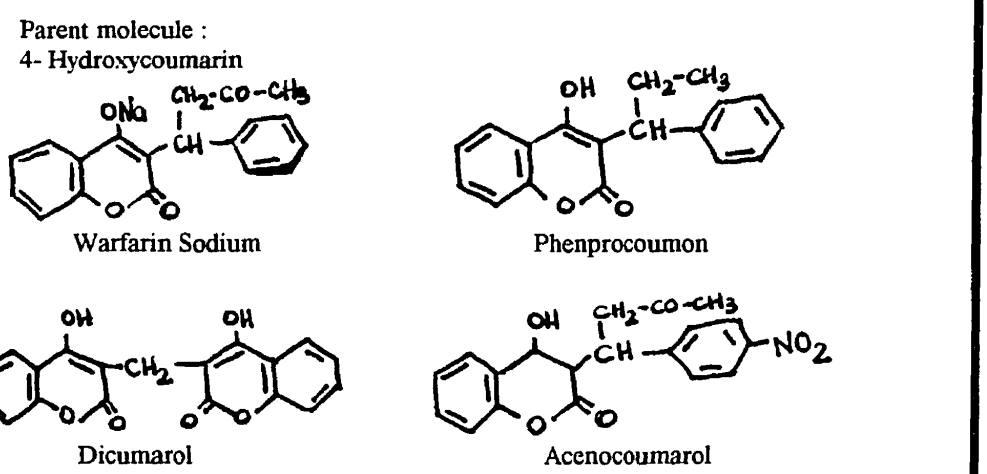


FIGURE 7. Structural formulas of some of the oral anticoagulants.
[Adapted from Goodman and Gilman's The pharmacological Basis of Therapeutics. 8th Edition. 1990.]

Oral anticoagulants inhibit two enzymes, vitamin K quinine reductase and vitamin K epoxide reductase. These enzymes are responsible for the conversion of the inactive vitamin K epoxide into active vitamin K hydroquinine.[5,13,27] The active vitamin K is the cofactor in the posttranslational carboxylation of glutamate residues to gamma carboxyglutamates on the N-terminal regions of vitamin K dependent proteins. The proteins which depend on vitamin K are prothrombin (factor II), factor VII, factor IX, factor X, protein C and protein S. These proteins are synthesized in the liver and in the presence of calcium these proteins will undergo conformational change which allows them to complex with their cofactors on phospholipid surfaces and become biologically active.[26] Warfarin by inhibiting vitamin K epoxide reductase and vitamin K quinine reductase,

renders the coagulation factors II, VII, IX and X as well as the anticoagulant proteins C and S inactive.[5,26,27] There is increasing evidence that the most important anticoagulant effect of warfarin is in the reduction of factors II and X.[27] The mechanism of inhibition of the reductase enzymes by the coumarin drugs is unknown. [26] Figure 8 demonstrates how warfarin blocks the generation of reduced vitamin K.

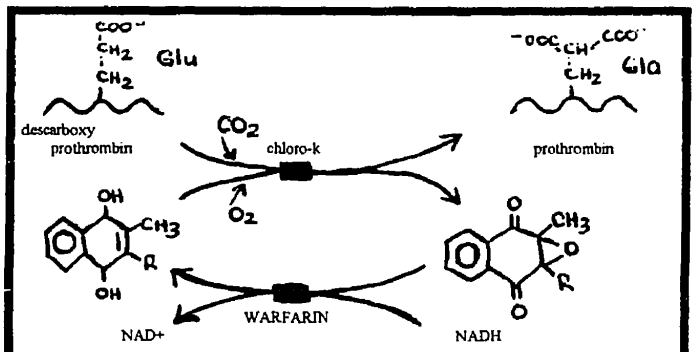


FIGURE 8. The Vitamin K Cycle.
[Adapted from Goodman and Gildman's The Pharmacological Basis of Therapeutics. 8th Ed. 1990.]

The effects of warfarin can be overcome by low doses of vitamin K_1 because it can be reduced through a warfarin resistant vitamin K reductase system. It is for this reason that patients are unresponsive to warfarin, for up to one week, after vitamin K_1 administration.[5]

Figure 9 shows the oral anticoagulants, some of which are generally not available in North America but are often prescribed in Europe. [26,27]

GENERIC NAME	TRADE
Warfarin Sodium	Coumadin
	Panwarfarin
Warfarin Potassium	Athrombin-K
Phenprocoumon	Marcumar
	Liquamar
Adenocoumarcol	Nicoumalone
	Sinthrone
Ethyl bicoumacetate	Tromexan
Bishydroxycoumarin	Dicumarol

FIGURE 9. Generic and trade names of the oral anticoagulants.

Warfarin is administered orally and is rapidly absorbed by the gastrointestinal tract. It is administered as a racemic mixture of two active optical isomers, R(+) and S(-), and the mixture has a half life of 36 to 42 hours.[27] The S-form of warfarin has a shorter half life but is five times more potent than the R isomer.[5,27] The two isomers are metabolized differently.

The dose response of warfarin can vary widely among healthy and sick patients; therefore the dosage must be monitored closely.[5] The dose response to warfarin is influenced by numerous factors such as its absorption, metabolic clearance and differences in hemostatic response. As well, drugs and diet can influence the pharmacokinetics of warfarin. Drugs will influence the response of warfarin by reducing its absorption by the intestine or by altering its metabolic clearance (Figure 10). Cholestyramine impairs the absorption of warfarin and the anticoagulant effect is decreased.[5,27] The anticoagulant effect is potentiated by drugs that decrease the potent S-isomer's clearance, such as phenylbutazone, sulfinpyrazone, metranidazole and trimethoprim-sulfamethoxazole. Cimetidine and omeprazole affect the clearance of the less potent R-isomer and therefore produce a small potentiation of warfarin.[5] The anticoagulant effect of warfarin is inhibited by barbituates, rifampicin, and carbamazepine which increase its clearance by inducing the activity of mixed oxidases. Chronic alcohol abuse will induce hepatic enzymes to increase the clearance of warfarin thereby decreasing its anticoagulant effect.[5,27] In contrast, large intermittent doses of alcohol will cause enzyme inhibition and potentiate the effect of warfarin.[27]

Fluctuations in vitamin K can occur and will influence the anticoagulant effect of warfarin. Patients who are on diets rich in green vegetables or on intravenous nutritional supplements rich in vitamin K will have a reduced anticoagulant effect with warfarin. The effects of warfarin are potentiated in sick patients who have a poor vitamin K intake, are on antibiotics, intravenous fluids without vitamin K supplementation, have a malabsorption state, or diarrhea.[5,27] Hypermetabolic states such as fever or hyperthyroidism will increase the effect of warfarin by faster degradation of the

coagulation factors.[5] The third generation cephalosporins will potentiate warfarin's effect by inhibiting the cyclic interconversion of vitamin K. It appears stress and some infections can have a direct effect on P_{450} and effect warfarin's metabolism.[27]

Drugs that potentiate the effect of warfarin	Drugs that decrease the effect of warfarin
Phenybutazone	Carbamazepine
Sufinpyrazone	Barbituates
Metranidazole	Rifampicin
Cephalosporin	Chronic ETOH ingestion

FIGURE 10. Summary of some drug interactions with warfarin.

Drugs such as aspirin and other nonsteroidal antiinflammatories, as well as high doses of penicillin, can increase warfarin-associated bleeding by impairing platelet function.[27] Aspirin in high doses (3g/day) can have a direct effect on the synthesis of the vitamin K dependent proteins. Other drugs such as erythromycin and anabolic steroids will potentiate the warfarin effect through unknown mechanisms.[5] Sulfonamides and other broad spectrum antibiotics can eliminate intestinal bacterial flora and cause vitamin K deficiency in patients, thereby potentiating the warfarin effect.[27]

There are significant inherited differences in enzyme activity which may cause dose response variations of warfarin. This is marked in the autosomal dominant syndrome of warfarin resistance. In this syndrome the vitamin K converting enzyme has a decreased affinity for warfarin.[5,27] As well, there are inherited polymorphisms of the P_{450} enzymes which have been implicated in the adverse drug reactions seen with warfarin. In addition, there may even be different mechanisms inherited for warfarin metabolism.[27]

Finally, technical factors also contribute to the variability of the dose response seen with warfarin. These include inaccuracies in laboratory testing and reporting, patient compliance and patient-physician communication.[5]

❑ Hemorrhage Complications with Warfarin

The major complication of warfarin therapy is bleeding. The factors that are associated with oral anticoagulant-induced bleeding are the level of anticoagulation, patient characteristics, the use of other drugs that interfere with hemostasis, and the length of time that anticoagulant therapy has been used. [28]

The highest rates of bleeding complications occur with patients who have cerebral vascular disease. The risk of a bleeding complication is much higher with high-intensity anticoagulant therapy as compared to low intensity therapy (INR= 2.0 to 3.0). The median rate of bleeding for patients receiving anticoagulant therapy for venous thrombosis is 0.9%. For patients receiving oral anticoagulant therapy for prosthetic heart valves, the median rate of bleeding was 2.4%/year and fatal bleeding 0.7%/yr. [28] The benefit of anticoagulation for patients at risk of thromboembolism is much higher than the risk of bleeding.

❑ Methods of Monitoring the Effect of Warfarin

The effect of warfarin is monitored by measuring the patient's *prothrombin time,* (PT). This test is performed by adding calcium and commercially produced thromboplastin to a patient's platelet poor plasma. "Thromboplastin" refers to the phospholipid extract of tissues. [1] Hematologists recommend a PT of 1.5 to 3 times the control value to prevent thrombosis. [13]

Quick, in 1935 developed the prothrombin time using tissue thromboplastin extracted from rabbit brain. [29] Initially, laboratories made their own thromboplastin to conduct the PT test. [13] Traditionally, PT values were reported as the *PT ratio,* the patient's PT was divided by a laboratory normal value. This normal value is the mean of the Pts of a number of healthy patients. [1] In the 1960s, the Manchester Comparative Reagent (MCR), was used in British laboratories. The MCR is a very sensitive human thromboplastin. Simultaneously, in North America, Simplastin (Organon Teknika, Durham, NC), a less

sensitive thromboplastin, became the reagent of choice. A patient with a PT 2.0 to 2.5 times the control with the Simplastin reagent would have a PT of 4.5 to 6 times the control if the MCR reagent was used (Figure 11). [13]

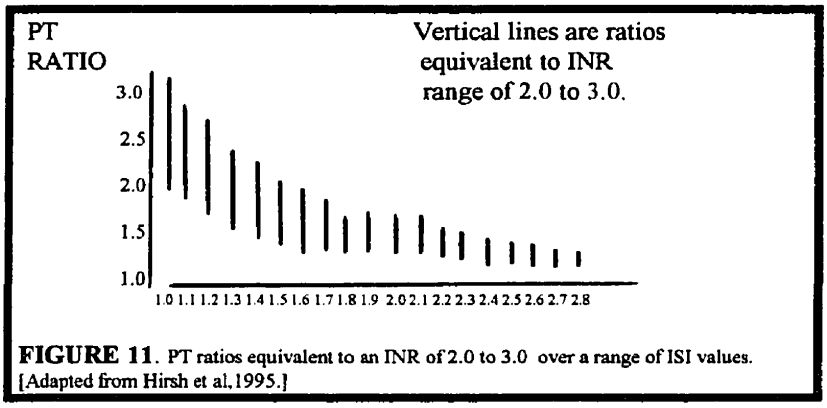


FIGURE 11. PT ratios equivalent to an INR of 2.0 to 3.0 over a range of ISI values. [Adapted from Hirsh et al, 1995.]

Today there are numerous commercially available thromboplastin reagents processed from human, rabbit, bovine, or monkey brain, lung, and placenta. [30] The PT values obtained from one plasma sample can be widely divergent depending on the thromboplastin reagent used (Figure 1).[1] This leads to difficulties in interpretation, communication, and control of a patient's level of anticoagulation. [1,31]

To standardize the PT value, a calibrating system known as the *International Normalizing Ratio, INR,* was introduced in 1982. [1,8] In this system each commercially available thromboplastin is assigned an ISI, International Sensitizing Index. The ISI compares each thromboplastin's sensitivity to the international standard preparation which is a human brain thromboplastin with an ISI of 1.00. [13] The closer the ISI is to 1.00, the more sensitive the reagent will be . [1,8] The INR is obtained by dividing the patient's PT by the normal PT and raising it to the power of the ISI:

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

The INR eliminates the variability that occurs when different sources of thromboplastin reagent are used. If the World Health Organization's (WHO) calibration recommendations are followed, the inter-laboratory variation can be maintained at 4%. [13,32,33]

Since 1983, WHO [3] has recommended the use of the INR as the method of reporting a patient's anticoagulation level. This approach was endorsed by the International Committee for Thrombosis and Hematology in 1985, which recommended that scientific papers should express PT results in the INR form. [8,34] Some authors feel that failure to use the INR constitutes substandard medical care. [8,13]

The INR system is being adopted by an increasing number of North American hospitals. With the increasing use of the INR, a number of problems have been identified. First of all, the INR is criticized as not being accurate when warfarin therapy is first instituted. The PT is responsive to the reduction of factors II, VII, and X; but these factors have varying plasma clearance rates which are 60 , 6, and 40 hours respectively. Their contribution to prolonging the PT will vary when warfarin is first instituted. This is most marked in the first four days. However, when using the unadjusted PT , the variation seen is even greater. Therefore, the INR is a superior method for monitoring the level of anticoagulation even soon after starting warfarin therapy. [31]

Another problem is INR inaccuracy at high ISI values. This problem can be solved by using more sensitive thromboplastins (ISI close to 1.00). Other problems include the use of automated clot detectors and the lack of reliability of the manufacturer's ISI. However, manufacturers should be providing reliable ISIs. Laboratories should be trying to use the more sensitive thromboplastins and to calibrate their clot detectors with each new batch of thromboplastin. Finally, the laboratory must calculate the normal PT by using plasma from at least 20 healthy individuals. [31]

An alternative to the INR is the factor II antigen assay. Studies are required to determine if this test is as effective as the INR. However, its use may be limited by its expense and

complexity. Despite the INR's faults, it is a much better measure than the unadjusted PT.[31] At the present time, the literature strongly supports the use of the INR as the method of reporting levels of anticoagulation in patients receiving warfarin therapy. Figure 12 shows some therapeutic INR levels for some disease states.[1]

Prevention of DVT	**INR = 2.0 - 3.0**
Treatment of DVT or PE	**INR = 2.0 - 3.0**
Atrial Fibrillation	**INR = 2.0 - 3.0**
Porcine cardiac valve	**INR = 2.0 - 3.0**
Mechanical cardiac valve	**INR = 2.5 - 3.5**

FIGURE 12. Example of therapeutic INR levels for some disease states.

Hemostasis Following Dental Extractions

In all surgical wound healing, the specific events that occur are individualized to specific characteristics such as the patient's age, the anaesthesia used, and the specific surgical procedure that is performed. As such, the unique anatomy of the surgical wound resulting from dental extractions and the environment of the oral cavity, may pose a significant challenge to the hemostatic mechanism.[35,36]

The Dental Socket

A *simple* dental extraction involves syndesmotomy, the disruption of the periodontal attachment from the tooth. The alveolar bone is expanded through luxation of the tooth and this allows the tooth to be removed (Figure 13a). In a *surgical extraction*, a mucoperiosteal flap is raised and bone is removed to facilitate the extraction (Figure 13b). Once the tooth is removed, either by performing a simple or surgical extraction, a dental socket remains (Figure 13c). Although primary soft tissue closure may be possible, no primary closure can be obtained in the bony component.[36] Primary wound closure aids in hemostasis by applying pressure along the wound margins.[35] The dental socket has firm walls with a disrupted apical artery and numerous open marrow cavities. It is difficult for

the vascular channels that line this inflexible socket to retract. [4,35] The role of fibrin in occluding the vascular channels, in this case when vessel retraction may not occur, may be especially important. [37]

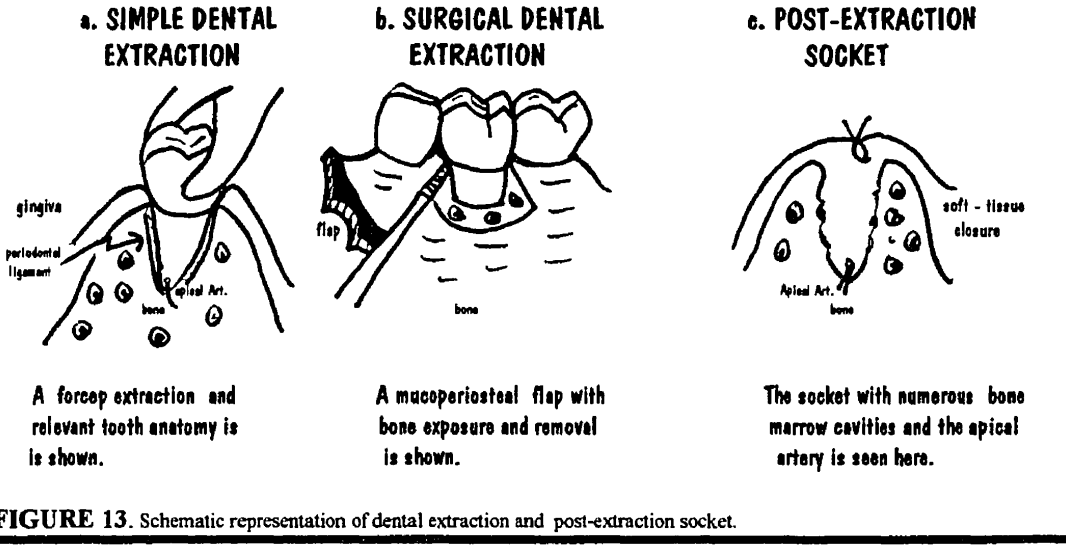


FIGURE 13. Schematic representation of dental extraction and post-extraction socket.

As the tooth is removed, blood from the periodontal ligament, bone and apical vessel fills the empty socket. Both processes of inflammation and coagulation start immediately after initiating the surgical procedure. The early products of these two processes are not maintained due to continued manipulation and irrigation of the tissues. Once the procedure is complete, the wound begins its reparative process. The three phases involved in the healing of the socket are the coagulative, the inflammatory and the osteogenic phase. [4]

In the initial step, *the coagulative phase*, a large coagulum fills the socket. This clot is composed of fibrin, red blood cells and platelets. Fibrin formation is an important step for hemostasis in this phase. The surface of the clot is exposed to the oral cavity and covered by bacteria and debris. The center of the clot has no oxygen supply whereas the part of the clot adjacent to the bone has a higher oxygen tension. This forms an oxygen gradient which attracts fibroblasts into the area. The other chemotactic factors that attract the fibroblasts are PDGF (platelet-derived growth factor), fibronectin, lymphocytes and

thrombin. The fibronectin allows fibroblasts to grow into the clot. Endothelial cells also respond to PDGF and migrate to this area and they attach by the laminin, secreted by the fibroblasts, to the new collagen matrix. The clot begins to organize. This coagulative phase lasts 1 to 3 days and at the end of this phase, the endothelial cells along with the fibroblasts are ready to replace the clot with granulation tissue. [4]

In the *proliferative phase,* the fibrin clot is dissolved, a connective tissue matrix replaces it, a new blood supply forms, and osteoblasts and osteoclasts prepare for bone formation. Granulation tissue will replace the entire fibrin clot but granulation tissue cannot grow if the clot is not simultaneously dissolved by fibrinolysis. As will be shown later, excessive fibrinolysis has been implicated in impaired healing such as alveolar osteitis and idiopathic bleeding. Fibrinolysis has been shown to start on the third post-extraction day with maximal activity on day 4 to 6. By the seventh post-extraction day, the clot should be completely replaced by granulation tissue. [4] At the end of this phase, the socket is filled with a dense connective tissue matrix with large numbers of fibroblasts and new vessels.

The final phase is the *osteogenic phase.* This phase starts when the osteoblasts, which are lining the bony socket, begin to lay down bone. This process starts on about the fifth post-extraction day and continues for approximately 3 months. At the end of this phase, bone will have been remodelled and mature trabecular bone will fill the socket. [4]

The Environment of the Oral Cavity

There are several factors, unique in the oral cavity, which may interfere with blood clot formation. First of all, patients may rinse their mouth frequently or too aggressively and may dislodge the clot. The actions of straw sucking, finger exploration or smoking may also dislodge the clot.[7]

The second factor is that it is common treatment to extract teeth in the presence of infection. Local infection can increase local vascularity and enhance vessel fragility. The inflammatory reaction associated with the infection will also release plasminogen from the

endothelial cells. This will increase local fibrinolysis and accelerate degradation of the blood clot. Also, there are fibrinolytic activators of bacterial origin, including streptokinase and staphylokinase. [38]

Finally, the oral cavity has tissue plasminogen activator (t-PA) in the epithelial cells of the mucosa. [35,39,40,41] Delayed bleeding and dry socket, after dental extractions have been attributed to increased fibrinolysis. Fibrinolysis has been found to be 20 to 25 times greater in extraction sites diagnosed with dry socket.[41] In an animal and clinical study by Pham, [42] it was found that extraction sites treated with epsilon aminocaproic acid (EACA), an antifibrinolytic agent, decreased the incidence of dry socket, increased the degree of healing and decreased the post-operative pain. Enhanced fibrinolysis may not effect patients with an intact system for hemostasis but for patients with a compromised hemostatic system, such as those on warfarin, early clot dissolution may play a central role in post-operative bleeding. [35,39] As will be shown later, the incidence of postoperative bleeding in hemostatically compromised patients is greatly reduced with the use of local antifibrinolytic agents. [10,35,39]

Surgical Management of Patients on Warfarin

The patient on warfarin therapy has reduced factors II, VII, IX and X. As was previously shown, these factors are important in the formation of fibrin which fortifies the hemostatic plug. The problem of performing surgery in this population group is in arresting bleeding from the surgical wound. This is a significant problem since stopping or decreasing a patient's anticoagulant therapy, places them at risk of thromboembolism. [9] A study which followed patients who were on oral anticoagulant therapy for prosthetic heart valves and had their therapy stopped for surgery, showed a 10% incidence of thromboembolic complications. [43]

For patients on warfarin therapy who require surgical procedures, two protocols are presently advocated. Either the patient has his/her warfarin stopped and heparin therapy

instituted in the perioperative period or the warfarin dose is decreased to obtain an INR of 1.5. In randomized trials of gynecologic and orthopedic surgical patients, this intensity of anticoagulation was determined to be safe for performing surgery. [5]

Risks in Performing Dental Extractions for Patients on Warfarin Therapy

The dentist treating a patient on anticoagulant therapy is faced with a dilemma. If warfarin therapy is stopped, the patient is placed at risk of a thromboembolism. The extraction of teeth is considered a challenge to the hemostatic mechanism as both soft and hard tissues are severed often without primary closure. [36] The specific anatomy of the wound formed by dental extractions, the environment of the oral cavity, compounded with a defective coagulation system when warfarin therapy is maintained, creates a significant risk of severe or prolonged bleeding. To the surgeon, the risk of bleeding is of major concern and this problem may present in three ways and at different stages of treatment.

The first potential problem is that when local anaesthesia is achieved using a nerve block injection, a hematoma may form. Studies indicate that there is an 11% incidence of the vascular bundle being penetrated during an inferior alveolar nerve block.[44] If a small hemorrhage occurs, an intramuscular hematoma may occur within the medial pterygoid muscle and may result in trismus. [45] Although an exceedingly rare problem, frank hemorrhage in this region can be life-threatening by causing airway compromise.[36,46] An article by Owens et al, [47] which is often quoted, is a case report of a retropharygeal hematoma. In this report, the authors state that there have been 19 cases of retropharygeal hematoma reported in the literature, of which 2 were associated with anticoagulation. They report a case of a 61 year old male with a violent tussive episode who was receiving oral anticoagulants and was suspected to have had a platelet abnormality. Lepore [48] reported an unusual case of upper airway obstruction secondary to a spontaneous, nontraumatic sublingual hematoma in a 58 year old male receiving warfarin therapy.

Mulligen and Weitzel, [49] claim that evolving complications caused by a nicked vessel bleeding into the tissues, during an inferior alveolar nerve block in an anticoagulated patient, may be difficult to detect and manage, and may be life threatening. These authors report that this is an unrecognized potential problem in the patient receiving anticoagulants, as evidenced by the fact that there are reports of ecchymosis, hematomas and facial swelling documented as postoperative complications. On the other hand, Carr and Mason, [50] report that there is no increase in complications reported with the use of regional blocks or local infiltration of local anesthetics in anticoagulated patients undergoing oral surgery. Bailey and Fordyce, [36] performed dental extractions on 25 patients without altering their anticoagulant dose. These authors state that they used local infiltration and regional nerve block for the delivery of anesthesia. Likewise, Waldrep and McKelvey, [51] performed oral surgery on 20 anticoagulated patients after administering local anesthesia either through infiltration or nerve blocks. In both of these articles, there were no reported complications with the delivery of local anesthesia.

The second potential problem for any surgical patient, is uncontrolled bleeding that can occur intraoperatively, may persist postoperatively, or may recur after bleeding has been arrested. In addition, with warfarin therapy, the secondary hemostatic mechanism is compromised and the hemostatic plug formed in primary hemostasis may not be stabilized into a definitive plug. Studies have shown that, in anticoagulated patients in whom dental extractions have been performed, if delayed bleeding occurs, it generally does so from day 1 to day 5 postoperatively. [6,36]

Finally, patients who experience a significant blood loss are subject to a range of symptoms depending on the amount of blood loss and the patient's cardiovascular status. These symptoms range from mild to severe hypovolemia leading to hypotension, tachycardia, heart failure, myocardial infarction and shock [46] (Figure 14). A serious consideration is that the patient who is receiving oral anticoagulants may not be able to tolerate even a relatively small blood loss due to the nature of their underlying disease (i.e.: AF, previous myocardial infarct, cardiomyopathy).

% circulating blood volume		symptoms	
Mild shock	< 20 %	blood loss	pale -cool skin , thirsty
Moderate shock	20 - 40 %	blood loss	oliguria. restlessness, postural pressure drop
Severe shock	> 40 %	blood loss	oliguria, hypotension EKG changes, agitation

FIGURE 14. Definition of varying degrees of shock.

Protocols for Performing Dental Extractions on Patients Receiving Warfarin Therapy

Three management strategies exist for performing dental extractions for patients on oral anticoagulants. The patient either has their *warfarin stopped* prior to the surgical procedure or if the patient is at high risk of thromboembolism, then the patient is hospitalized and *heparin therapy* is instituted in the perioperative period. A third protocol for managing this patient population is to use *local hemostatic agents* and perform the dental extractions without any alteration in the level of anticoagulation.

❑ Method 1: Withdrawal of Warfarin

A commonly used protocol for performing dental extractions for patients who are on oral anticoagulants is to *stop the warfarin* prior to proceeding with the procedure and thereby greatly reducing the risk of hemorrhage. There are three problems associated with this protocol. First of all, the PT should be monitored closely, which may imply frequent hospital or clinic visits for the patient, both prior to the dental extractions and then postoperatively to reestablish the desired therapeutic level of anticoagulation.

Secondly, warfarin has a long half-life of approximately 42 hours, due to its slow rate of biotransformation and high amount of plasma-protein binding.[5,46] It takes a minimum of 2 days for the level of anticoagulation to decrease once warfarin therapy is withdrawn. Therefore, it has been recommended that there be a delay of 2 to 6 days prior to proceeding with the surgery. Reinstitution of anticoagulant therapy after a withdrawal period has also been considered to pose a significant bleeding risk. This has caused some authors to recommend a delay of 4 to 10 days prior to reinstitution of the warfarin

therapy.[49] Most surgeons would reinstitute warfarin therapy within a 24 hour postoperative period since warfarin has a delayed onset. Therefore, the patient may remain without anticoagulant therapy for a period of 3 to 12 days.

Short term withdrawal of a patient's anticoagulant therapy places them at a 10% risk of thromboembolism. In a study by Tinker and Tarhan,[43] in 1978, the records of 159 patients with previously placed mechanical cardiac valves were reviewed. These patients underwent 180 subsequent non-cardiac operations with short-term discontinuation of their oral anticoagulants. The oral anticoagulants were withheld for 1 to 3 days preoperatively and 1 to 7 days postoperatively. The overall incidence of documented thromboembolic complications was found to be 10%. Although a 10% risk of thromboembolism is considered to be low, by the authors, the consequences of a thromboembolism are serious to the patient, for their quality of life and are costly to the health care system.

Considerable controversy exists about the "rebound phenomenon". It has been postulated that there is a higher incidence of thrombosis and pulmonary embolism, due to an increased coagulative ability of the blood, when patients who are on long term anticoagulants have their medication withdrawn. [9,49] Other authors feel that a rebound state of hypercoagulability does not exist. In a controlled prospective study of 19 patients receiving oral anticoagulants, Harenberg et al [9] demonstrated that fibrinopeptide A (Figure 4), increased significantly in the 9 patients in whom phenprocoumon was withdrawn. Elevated fibrinopeptide A plasma levels have been previously described in patients with thrombosis, pulmonary embolism and myocardial infarction. [9] Whether the rebound phenomenon occurs or not, these patients have a underlying thrombotic tendency which may be life-threatening when oral anticoagulants are withdrawn. Abrupt discontinuation of anticoagulants in patients with prosthetic heart valves has led to fatal consequences.[52]

Finally, when we stop a patient's warfarin we do not know to what level to decrease the level of anticoagulation. For anticoagulated patients, it has been recommended that dental

extractions be performed at a PT ratio of 1.5 to 2.0. [4] However, as discussed earlier, the PT value varies among institutions, depending on the thromboplastin used. Therefore this guideline is not consistent between different institutions. In fact, depending on the sensitivity of the thromboplastin used to derive the PT, a PT ratio of 1.5 to 2.0 is comparable to an INR value of 3.0 to 8.0 (Figure 1).

As mentioned above it is recommended that minor surgical procedures including dental extractions, may be performed on patients with an INR value of 1.5. In randomized trials of gynecologic and orthopedic surgical patients, this level of anticoagulation was safe for performing the surgery. [5]

The only well controlled study attempting to establish the highest INR level at which teeth can be safely extracted is by Declerck, et al. [6] In this study, 5 experimental groups with eight rabbits in each group, were anticoagulated with warfarin to various levels, (INR between 1.3 and 1.4, INR between 1.4 and 1.6, INR between 1.6 and 1.8, INR between 1.8 and 2.0 and INR between 2.0 and 3.0), the control group consisted of rabbits which did not receive warfarin treatment. Blood loss was measured following the removal of the four incisors in warfarinized and control rabbits. The immediate blood loss was evaluated using tooth socket bleeding times and by using a hemoglobin determination technique. The long-term blood loss was determined using sodium chromate 51, red-blood-cell labeling, disappearance curves. The authors state that according to their results, at therapeutic anticoagulation activity, blood loss was significantly greater in the anticoagulated than in non-anticoagulated rabbits. At INR level of 1.3 and 1.4, the amount of blood loss was within the normal range, at INR levels of 1.6 to 1.8 the blood loss was clinically acceptable, and at INR levels greater than 1.8 the blood loss was deemed to be unacceptable.[6]

Although the results of Declerck et al [6] are consistent with the recommendation of hematologists and internists, that is that dental extractions be performed at INR levels below 1.5, previous clinical experience leads us to believe this value is low. For many

years dental extractions have been safely performed on patients with PT ratios of 1.5 to 2.0. This implies that dental extractions have been performed with INR values much higher than 1.5 (Figure 1). [8]

Another problem with this study is that the anticoagulation levels were not measured using the INR. In the Ph.D thesis by Declerck, [7] and in the article, based on the thesis, by Declerck et al, [6] it is stated that the level of anticoagulation was measured using the Thrombotest [TM] (Nyegard). The Thrombotest percentages (TT) were derived from a calibration curve that was designed for rabbit venous blood.

In the article by Declerck et al, [6] the authors report the levels of anticoagulation as INR values. It is difficult to understand how the INR value was obtained from the percent coagulation activity. The only way to determine an INR value is to obtain a PT, divide it by the normal PT and raise this to the ISI of the thromboplastin used, as in the equation:

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

Since the authors do not explain how the INR was derived but have reported obtaining the percent coagulation activity, one must assume that they extrapolated to report the INR from the percent coagulation activity they had obtained. This is at best a gross estimate and therefore, the INR values reported cannot be considered accurate. Figure 15 indicates the different levels of anticoagulation as reported in the thesis and in the article.

ANIMAL GROUP	% COAGULATION as reported in thesis [7]	INR as reported in article [6]
B1- control	control	control
B2	10 - 15 %	2.0 - 3.0
B3	15 - 20 %	1.8 - 2.0
B4	20 - 25 %	1.6 - 1.8
B5	25 - 30 %	1.4 - 1.6
B6	25 -35 %	1.3 - 1.4
	Thrombotest [TM], therapeutic level = 7 - 13 %	INR, therapeutic level = 1.5 - 3.5.

FIGURE 15. Experimental groups and anticoagulation levels, as reported in the thesis by Declerck [7] and in the article by Declerck et al. [6]

In this study, the authors reported that an INR level between 1.6 and 1.8 is the safe level at which dental extarctions can be performed on anticoagulated subjects. This low INR value may be due to the conversion of the thrombotest percentage to the INR, mentioned above.

❑ Method 2: Hospitalization and Heparin Therapy

The second protocol followed for patients, on oral anticoagulants, who are at high risk of having a thromboembolism if warfarin therapy is withdrawn, is to hospitalize the patient and institute *heparin therapy* during the perioperative period.[50,52,53] An example of this protocol is seen in Figure 16.

Admit patient to hospital and discontinue warfarin therapy.
Start heparin therapy:
5000 U bolus and 1200 U per hour → APTT in 6 hours.
Adjust to obtain APTT of 60 to 85.

APTT	bolus	hold (min)	rate	repeat APTT
< 50	5000U	0	+200	6hr
50-59	0	0	+100	6hr
60-85	0	0	0	daily
86-95	0	30	-100	daily
96-110	0	30	-100	6hr
>110	0	60	-200	6hr

Hold 6 hours prior dental extractions.
Reinstitute heparin 6 to 12 hours post-operative.
Reinstitute warfarin and once therapeutic discontinue heparin and discharge patient.
FIGURE 16. Schedule for heparin therapy in the perioperative period.

Heparin has an immediate onset and a short half life, 1.5 to 4 hours.[46,52] For these reasons the degree of anticoagulation is easily adjusted. Since heparin is administered intravenously, the patient must be hospitalized during this period and the APTT followed closely. This procedure provides the least risk of thromboembolic event since the patient remains without anticoagulant therapy for only 12 to 24 hours. [46,49,52] However, hospitalization is disruptive to the patient's life and is costly to the health care system.

❑ Method 3: Unaltered Warfarin and Local Hemostatic Agents

Finally, the third protocol that is presently being promoted is the use of *local hemostatic agents* and maintaining the patient's level of anticoagulation unaltered. If using local hemostatic agents proves to be effective, this would allow dental extractions to be performed on an outpatient basis, at all therapeutic INR levels. This would increase patient convenience as well as reduce the cost to the health care system. Initial studies with various elaborate local hemostatic agents appear promising.

Tranexamic acid, a local antifibrinolytic, is a known local hemostatic agent. Local fibrinolysis may be a factor in bleeding after dental extractions. Activators of fibrinolysis have been identified in the epithelial cells of the oral mucosa. [39,40,41] It is possible that the enhanced antifibrinolytic activity of the oral cavity may contribute to the development of post-extraction bleeding in patients with a defective coagulation system.

In 1986, Sindet-Pedersen and Stenbjerg [54] demonstrated that bleeding complications and transfusion requirements, after oral surgery, in patients with hemophilia, were significantly reduced when local tranexamic acid mouthwash was used. These findings were supported in a study by Sindet-Pedersen et al [55] in gingival bleeding in patients with hemophilia.

In 1989, Sindet-Pedersen et al [10] carried out a placebo controlled, double-blind, randomized study of the local hemostatic effect of tranexamic acid mouthwash after dental extractions were performed in 39 anticoagulated patients. Dental extractions were performed with no alteration in the level of anticoagulation. Anticoagulation levels were measured by two different methods. At one hospital, the prothrombin-proconvertin assay (PP) was performed and found to be between 10 to 20%. At the other hospital the Thrombotest™ (TT) was used yielding results between 5 to 12%. The authors state that these levels of anticoagulation correspond to a PT ratio of 1.4 to 2.0 or an INR of 2.5 to 4.8 in the United States. [10] After the teeth were extracted, the wound was irrigated with 10ml of 4.8% aqueous solution of tranexamic acid in 19 patients and with a placebo solution in 20 patients. The patients continued using the assigned mouthwash 4 times a

day for 7 days. Eight patients in the placebo group had a total of 10 postoperative bleeding episodes requiring treatment whereas, only 1 patient in the tranexamic acid group experienced postoperative bleeding. Analysis of the plasma of 10 patients, for tranexamic acid, showed only 1 patient to have a detectable level of tranexamic acid of 2.5ug per milliliter. The therapeutic plasma level of tranexamic acid is 10 to 15ug per milliliter. Therefore, presumably little systemic suppression of fibrinolysis occurs. [10] This is important since this group of patients have an underlying thrombotic tendency, which would be enhanced by systemic antifibrinolysis.

It is unfortunate that in this study, the investigators did not use the INR to determine the degree of anticoagulation for the involved patients. The authors state "with the the thromboplastin reagents usually employed in the United States", [10] that the level of anticoagulation would correspond to a PT ratio of 1.4 to 2.0 and an INR of 2.5 to 4.8, but this is only a rough estimate. Interestingly, the authors estimate that the PT ratio would be 1.4 to 2.0, this is the ratio which has been recommended for dental extractions to be performed, using only *routine* measures of hemostasis. [4,13] The failure to standardize the reporting of the level of anticoagulation, by using the INR, makes accurate comparisons of the intensity of anticoagulation of the patients in this study, impossible. Furthermore, as Hirsh [8] points out " the term 'typical North American thromboplastin' used in earlier publications is no longer valid." In order to determine an accurate INR, the PT value and the ISI are required.

Ramstrom et al [56] in 1993, supported the results of the previous study in a group of 93 patients (44 in the tranexamic acid mouthwash group and 45 in the control group). In the placebo group,10 patients developed a postoperative bleed requiring treatment and none of the patients in the tranexamic group had bleeding. This study confirmed the reduction in postoperative bleeding in patients who undergo dental extractions with unchanged oral anticoagulant-therapy when treated with 4.8% tranexamic acid solution as a mouthwash.

In the Ramstrom study, the level of anticoagulation was measured using the prothrombin-proconvertin (PP) and the prothrombin-complex (PC) assay methods. Since the ISI was known for the thromboplastin used in the PC method, the INR was calculated and found to be between 2.1 to 4.0. To correlate the levels of anticoagulation between the three different clinics, a factor X assay was performed. The authors conclude that these patients had a similar level of anticoagulation, at all three clinics.[56] In this study, the authors, albeit indirectly, attempted to determine a comparable INR for their population group.

Since 1983, the WHO [3] has recommended that the INR be used to measure the level of anticoagulation. The INR serves to eliminate the variability between institutions and allows accurate comparisons of the intensity of anticoagulation, when comparing different treatments. However, investigators must determine the INR. It is confusing and it leads to inaccuracies, when each investigator utilizes a different assay to determine the level of anticoagulation and then tries to relate it to the INR. As Hirsh [8] states, "... failure to standardize reporting of the PT ratio by the use of the INR constitutes substandard medical care and makes accurate comparisons of the anticoagulant intensity used in studies evaluating efficacy and safety of oral anticoagulant therapy impossible to achieve."

Borea et al [11] in 1993, in a double blind study, used the INR to measure the level of anticoagulation. Two groups of anticoagulated patients underwent dental extractions and were treated with either 5% tranexamic acid or a placebo solution, both used as a mouthwash. In the 15 patients treated with tranexamic acid the INR was 3.0 to 4.5 and only one patient returned with a postoperative bleed. In the 15 patients treated with a placebo solution, the INR was 1.5 to 2.5 and two patients returned with a bleeding complication. The authors conclude that anticoagulant treatment does not have to be withdrawn prior to oral surgery provided that tranexamic acid mouthwash treatment is used. [11]

Caminiti and Katsikeris[57] in 1994, presented a case series of 28 patients who underwent dental extractions. Twenty-one of these patients were on oral anticoagulants with an INR

between 1.5 to 3.04. The seven other patients suffered from ASA-induced platelet abnormalities, myeloproliferative disorders or liver cirrhosis. After the dental extractions were performed, the sockets were packed with "Glynn's Glue".[57] This is a combination of sulcralfate, gelfoam, topical thrombin and calcium chloride. If immediate hemostasis was not obtained, tranexamic acid was prescribed. Of the 28 patients only 4 had a post-operative bleed, two of which required transfusion.

Although the Caminiti report presents an interesting series of cases, unfortunately the patients had a variety of defects in their hemostatic mechanism and there were no controls. Although they describe a range of INR of 1.5 to 3.04 in the anticoagulated patients, we do not know how many were at the higher INR levels versus the lower.

Another local hemostatic agent is fibrin sealant. This agent mimics the final stages of coagulation and is a two component agent manufactured for example as Beriplast™ or Tissel™. The two components come in a two chamber device (Figure 17) and consist of concentrated thrombin, calcium chloride, fibrinogen and factor XIII, these are fractionated from pooled human plasma. Bovine aprotinin is also a component (Figure 18).

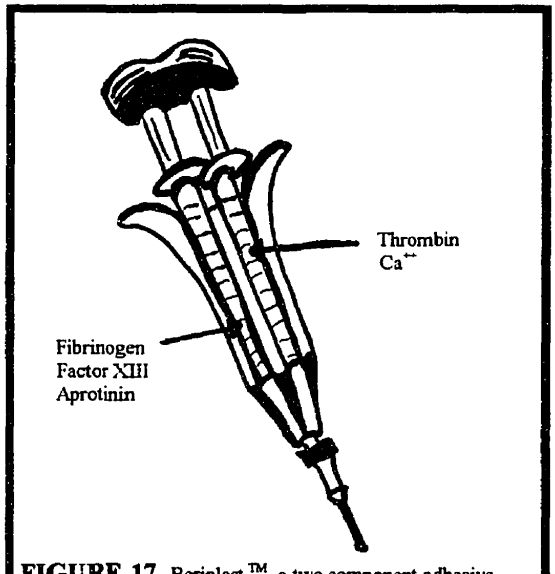


FIGURE 17. Beriplast ™, a two component adhesive.

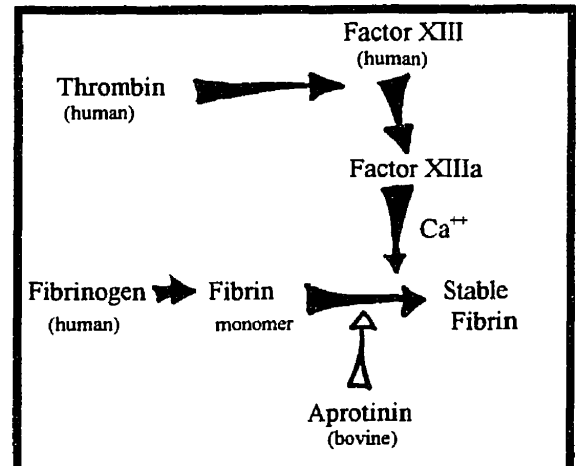


FIGURE 18. Fibrin formation in the Beriplast ™ system.

In 1990, Martinowitz et al[12] performed 63 dental extractions in 40 patients receiving oral anticoagulant therapy with an INR of 2.5 to 4.29. Anaesthesia was provided either by infiltration or intraligamental injection. After the socket was dried with thrombin soaked gauze for 3 minutes, local hemostasis was achieved with Beriplast ™ and a collagen fleece (Figure 19). Only one patient had a mild postoperative bleed which was controlled with local pressure. There was no control group in this study. The authors felt that it was unethical to study a control group since known complications occur in anticoagulated patients undergoing dental extractions. Although this product is from human sources, apparently there is virtually no risk of viral infection due to the pasteurization processes of all the components. [12,58] A problem with both the Martinowitz [12] and the Caminiti [57] studies, is that more than one agent is used. Therefore, we do not know which component of the product used is providing the hemostasis.

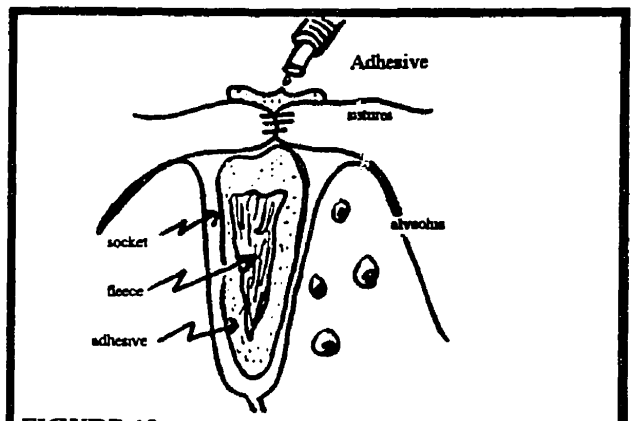


FIGURE 19. Biological adhesive applied along the walls of the socket, collagen fleece inserted, sutures applied, and covered with adhesive. [Adapted from Martinowitz et al, 1990.]

The reports discussed above certainly support the belief that dental extractions may be performed for patients receiving oral anticoagulants without altering the level of anticoagulation. However, in these studies, *elaborate* agents of local hemostasis were used. These agents are not only expensive (Beriplast ™ $100 per socket / tranexamic acid $150 per 200cc) but some of these agents are not readily available in North America. In fact, these *elaborate* local hemostatic agents may not be necessary.

When using the PT ratio, it is recommended that, for anticoagulated patients, dental extractions may be performed at a PT ratio of 1.5 to 2.0. [4,13] For many years this guideline has been followed by surgeons. In the past, at the Montreal General Hospital, we safely performed dental extractions, for patients on warfarin, with PT ratios between 1.5 to 2.0. The estimated ISI at that time, at our institution was 1.98. This would therefore imply that we were safely performing dental extractions within the INR range of 2.4 to 4.3 (Figure 1), using only *routine* measures of local hemostasis, such as, Gelfoam™, Surgicel™, sutures and local pressure.

As early as 1961, Behrman and Wright [59] reported a case series of 20 patients with a PT between 17.6 to 37.3 seconds and a control value between 14.5 to 16.6 (PT ratio 1.2 to 2.25) These patients underwent dental extractions with no alteration in their level of anticoagulation. They reported that none of these patients experienced postoperative hemorrhage and only one patient had periodic episodes of slight oozing from a raw area that could not be sutured. They recommend four steps to ensure local clotting in this patient population: constant pressure during the procedure, absorbable gelatin, multiple sutures placed under tension and heavy biting postoperatively. They claimed that in the smaller vessels encountered during oral surgery, agglutination may be adequate and clotting may not be necessary for hemostasis.[59]

In 1968, Waldrep and McKelvey [51] reported on 20 patients, maintained on oral anticoagulant therapy, in whom oral surgery was performed, including dental extractions and an open reduction of a mandibular fracture. These patients had a PT ratio of 2 or greater and a prothrombin activity of 30% or less. Sutures were the only local hemostatic agent used. Only three patients returned with postoperative oozing. One of these patients responded to gelfoam/thrombin and two were over-anticoagulated and were treated with gelfoam/thrombin and their level of anticoagulation was decreased to a therapeutic level. These authors felt "... the risk of hemorrhage seems to have been overemphasized. In most patients, episodes of postsurgical bleeding seem to be satisfactory controlled locally." [51]

In 1983, Bailey and Fordyce [36] reported on a controlled clinical trial which compared the post-extraction complication rate for 25 anticoagulated (PT ratio 1.2 to 4.3, mean of 2.4) and 25 control patients. From the results of their study, it appears that there was no difference between the two groups in the time required for immediate post-extraction bleeding to stop. The anticoagulated group had a significant tendency to rebleed 1 to 5 days postoperatively. However, the late bleeding episodes were easily controlled with local measures (pressure pack, oxidised cellulose, and resuturing). Only 3 patients required resuturing. The authors conclude that it appears clinically unnecessary to stop anticoagulant therapy, provided the level of anticoagulation lies in the therapeutic range and sutures are used as the local hemostatic agent.

The three articles discussed above report the level of anticoagulation in the form of the PT ratio (they were published prior to the implementation of the INR). However, the information provided in these publications suggests that *routine* measures of local hemostasis, may be sufficient to obtain acceptable hemostasis, after dental extractions in patients receiving oral anticoagulant therapy.

Prior to continuing studies with the more *elaborate* techniques of hemostasis, it is important to obtain some baseline values. With the development and implementation of the INR, a reliable, consistent and universal measure of anticoagulation exists. Using the INR, in well-controlled studies, the highest INR at which teeth can be extracted, achieving acceptable hemostasis with *routine* measures, must be determined. Once the highest INR at which teeth can be extracted using *routine* local hemostatic measures has been determined, then more *elaborate* agents should be studied at the higher INR levels, where *routine* measures did not suffice.

Before embarking on laboratory and clinical studies, the protocols which are presently followed, by other institutions, when treating patients receiving anticoagulant treatment needed to be established. The aim of the ***first part of this study*** is to determine whether the INR is used to monitor a patient's level of anticoagulation and to determine which

protocols are followed, by surgeons, when anticoagulated patients require dental extractions. To achieve this a mail survey, of the directors of the Oral and Maxillofacial Surgery Training Programs in North America, was performed.

The aim of the ***second part of this study*** is to determine the highest INR level at which dental extractions can be safely performed on subjects receiving warfarin treatment, using *routine* local hemostatic measures. To achieve this, an animal study was performed. Local hemostasis, following dental extractions was evaluated in rabbits which were anticoagulated to various INR levels. It is expected that this study will provide some scientifically based guidelines for the surgical management of patients on warfarin.

MATERIALS and METHODS

Study - Part 1

Mail Survey

A survey of practices followed in North America when patients, on oral anticoagulant therapy, require dental extractions.

One hundred and thirteen survey questionnaires were mailed to the program directors of the Canadian and American Oral and Maxillofacial Surgery Training Programs. The survey consisted of six questions (Figure 20). The first question addressed the method, which a surgeon would use, to monitor a patient's level of anticoagulation; that is prothrombin time (PT), prothrombin time ratio (PTR) or the international normalized ratio (INR). The second question established the highest level of anticoagulation which surgeons perceived as safe to perform dental extractions, that is, without altering a patient's warfarin level. This value will be referred to as the *safe limit* from here forward. The third question pertained to the protocol followed when a patient's level of anticoagulation was above the level perceived as safe. Question number four addressed whether surgeons used different protocols for treating this patient population depending on the type and number of extractions required. Questions five and six considered the management protocols followed for patients considered to be at high risk of thromboembolism. These questions addressed the patient who required extractions with a level of anticoagulation that was above that which the surgeon perceived to be safe to proceed with dental extractions.

1. When you are treating a patient who is anticoagulated with warfarin, what measure do you use to monitor his/her level of anticoagulation?
   - ☐ P.T. (Prothrombin Time)
   - ☐ P.T. Ratio (Prothrombin Time/Control Ratio)
   - ☐ I.N.R. (International Normalization Ratio)
2. If an anticoagulated patient requires a surgical extraction (mucosal incision/bone removal), at what P.T. ratio or I.N.R. would you consider it safe to perform the extraction without any medical intervention, (i.e. without alterating the warfarin dosage) and without the use of local or systemic pharmaceutical agents?
   - ☐ I would perform the extraction and use only local measures (i.e. sutures, gelfoam, etc.) at a P.T. ratio of _____ or an I.N.R. of _____.
3. If a patient presented for a surgical extraction and had a P.T. ratio or I.N.R. above the level at which you consider it safe to perform surgery, how would you manage the patient? (You may pick more than one.)
   - ☐ I would use local hemostatic agents. Please name agent and dose if applicable: _____.
   - ☐ I would use systemic agents. Please name agent(s) and dose: _____.
   - ☐ If not contraindicated (see #5), I would request that the patient's level of anticoagulation be lowered. Please state to what P.T. Ratio or I.N.R.: _____.
   - ☐ Please state if you use another protocol: _____.
4. Would you use a different management approach for an anticoagulated patient requiring a simple extraction versus surgical extraction(s):
   - ☐ No. The same protocol would be followed regardless of the type of extractions or the number of extractions.
   - ☐ Yes. If yes, please state the indications for your different protocols and please state your management procedures(s). _____.
5. If an anticoagulated patient presented with a P.T. ratio or an I.N.R. level that you consider unsafe to perform extractions and it is contraindicated (high risk of a thromboembolic event) to decrease the patient's level of anticoagulation, what would you do? (You may pick more than one.)
   - ☐ I would use local hemostatic agents. Please indicate which ones: _____.
   - ☐ I would use systemic agents. Please state agents(s): _____.
   - ☐ I would admit the patient to hospital, heparinize the patient and stop his/her warfarin. Please state your specific protocol: _____.
   - ☐ Other. Please specify: _____.
6. For the anticoagulated patient, where it is contraindicated to decrease the level of anticoagulation, would you use a different management approach for a patient requiring a simple extraction versus surgical extraction(s)?
   - ☐ No. The same protocol would be performed regardless of the type of extractions or the number of extractions.
   - ☐ Yes. Please state the indications for your different protocols and please state your management procedure(s): _____.
7. Please discuss any treatment modalities or protocols not previously mentioned. Please feel free to add any comments. _____

FIGURE 20. Mail Survey.

Study - Part 2

Animal Experiment

Local hemostasis in anticoagulant- treated subjects.

❑ Animal Model

This study was carried out on forty rabbits.[6,7,60,61] The rabbits used were New Zealand White, male adults (16 to 20 weeks old) with a body weight of 2.5 to 3.0 kg, (Charles River, Canada). Each rabbit was caged separately and received dry pellet food and water at libitum, preoperatively and postoperatively.

❑ Anticoagulation and Adjusted INR Levels.

Initially, animals were anticoagulated following the protocol of Haugen,[61] using warfarin sodium in a dose of 1.0mg/kg per day (crystalline 1 mg tablets, DuPont Pharma,U.S.A.). A modification of the protocol was required in some animals and consisted of 1.0mg/kg on day 1, 0.5mg/kg on day 2 and 0.1-0.25mg/kg on following days depending on the INR. The tablets were fed to the rabbits to achieve various degrees of anticoagulation (Figure 21).

Control:	Experimental:			
Group 1	Group 2	Group 3	Group 4	Group 5
INR = 0.8 - 1.4	**INR = 1.5 - 2.0**	**INR =2.1 - 2.6**	**INR = 2.7 - 3.5**	**INR = 3.6 -4.0**
8 rabbits	8 rabbits	8 rabbits	8 rabbits	8 rabbits

FIGURE 21. Different anticoagulation groups.

The level of anticoagulation was measured with an automated clot detector (ACL, Automated Coagulation Laboratory, Coulter, Canada)using venous blood. The 1.8ml of blood was collected from the marginal ear vein using pediatric citrate vacutainers (Becton-Dickinson, U.S.A.). The anticoagulation levels obtained from the hematology laboratory were reported as a PT value and an INR level. The INR was calculated by an automatic

clot detector using the rabbit's PT, a laboratory control PT of 10.0 and the ISI of 1.60, as in the equation :

$$INR_{lab} = \left(\frac{\text{rabbit PT}}{\text{laboratory normal PT=10.0}} \right)^{1.6}$$

Blood samples were obtained from 20 New Zealand White, male rabbits who had not received warfarin. The PT values obtained were averaged to determine a *control rabbit PT*, which was 7.9. The INR levels were then recalculated using the rabbits' PT , the rabbit control PT of 7.9 and the ISI of 1.60 :

$$INR_{adjusted} = \left(\frac{\text{rabbit PT}}{\text{rabbit normal PT = 7.9}} \right)^{1.6}$$

❑ Surgical Procedure

The rabbits received preoperatively, a cocktail of ketamine 1gm, xylazine 400mg, and acepromazine 100mg, in .1ml intravenous increments, and titrated to effect. Local anaesthesia was obtained with .5ml of lidocaine hydrochloride 2% with 1: 100,000 epinephrine (Xylocaine,™ Astra Pharma Canada.) using the infiltration technique and an intraligamental injection.

The left lower incisor was extracted. This gave a well-defined extraction site which did not interfere with normal food intake on the days following the extraction. The extraction was carried out using a 76S dental forcep. Two 15 x 2 mm strips of absorbable gelatin sponge (Gelfoam,™ Upjohn Canada) were placed in the socket and the wound was sutured with a nonresorbable 4-0 silk suture in a figure of eight fashion. With a moist gauze, firm pressure was applied for 5 minutes postoperatively. If bleeding persisted, local pressure was applied for another 15 minutes.

❑ **Evaluation of local hemostasis**

Three complementary methods were used to assess local hemostasis following the extractions.

1. Clinical Assessment

Postoperatively the surgeon, assessed the sockets for bleeding at the following intervals: 5 minutes, at 20 minutes, 40 minutes, every 2 hours for 6 hours postoperatively and twice a day for 6 days. The postoperative bleeding was graded according to the scale in figure 22, modified from Dolman. [62]

Grade	Definition
1	no oozing
2	minimal oozing
3	frank bleeding

FIGURE 22. Scale used to grade bleeding.

2. Evaluators - blinded to the treatment group.

The extraction sites were video taped at the following time intervals: 5 minutes, 20 minutes, 2 hours, 4 hours and day 6 postoperatively. Later, two surgeons who were blinded to the level of anticoagulation, viewed the video and graded the postoperative bleeding according to the scale stated above. This protocol for the assessment of postoperative bleeding is modified from a method described by Dolman. [62]

3. Red-blood-cells labelling with Sodium Chromate, 51.

The long-term blood loss was assessed by comparing the remaining labelled red blood cells, radioactivity, on day 0 and day 6.

Immediately prior to the surgery, a 5 ml blood sample was taken from the animal and mixed with 1 ml of ACD (acid-citrate-dextrose) solution. The red blood cells were radioactively labelled with sodium chromate 51, (Frosstimage®, Frosst, Merckfrosst,

Canada), as follows. Sodium chromate 51 (1.5 uCi/kg) was added to the blood sample and incubated at 39°C for 10 minutes. The reaction was stopped with 50 mg ascorbic acid (vitamin C) and the blood was reinjected into the animal. Thirty minutes later, a 3ml reference blood sample was taken in a sodium heparin pediatric vacutainer (Becton-Dickinson, USA). This technique is method C as described by the ICSH panel on diagnostic applications of radio-isotopes in hematology.[63]

Immediately after the radiolabelling procedure, the tooth was extracted. Blood sampling was repeated on day 6. The radioactivity of the preoperative and postoperative blood samples was determined on an automatic gamma-counter (LKB Wallac, Clinigamma). The radioactive count obtained preoperatively was used to represent 100% (reference sample) and the radioactive count of the samples taken postoperatively were expressed in percentages of the reference sample.[6,7] The change in radioactive counts was used as an indicator of the red blood cell loss.

RESULTS

Study - Part 1

Mail Survey

A total of 113 surveys were mailed, 73 (64%) of which were returned.

The INR was the most popular method of measuring a patient's level of anticoagulation. Seventy-three per cent of surgeons use the INR, either as the sole method (20.5%) of measuring a patient's level of anticoagulation or in combination with the PT or PT ratio. Twenty-seven per cent of respondents report using the PT as the only measure of their patient's level of anticoagulation. Figure 23 indicates the distribution of respondents in each category.

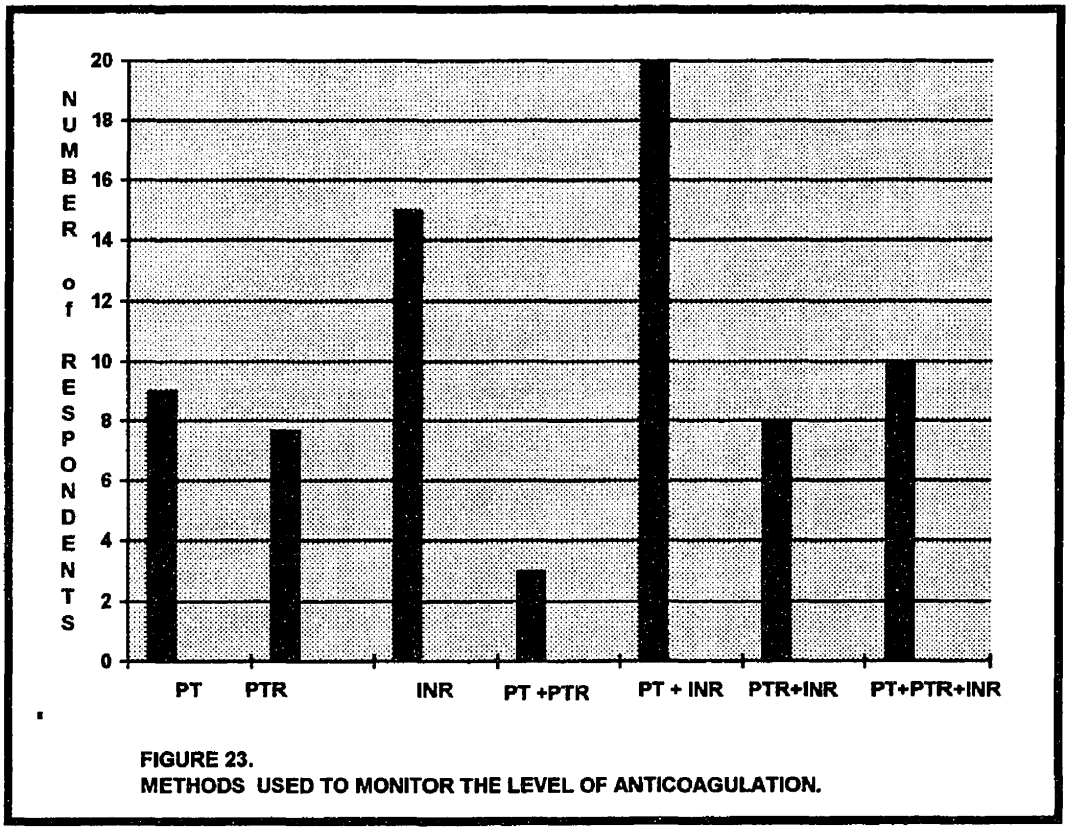


FIGURE 23.
METHODS USED TO MONITOR THE LEVEL OF ANTICOAGULATION.

The intensity of anticoagulation at which surgeons felt it was safe to perform dental extractions, using either the PT, the PT ratio or the INR value, are shown in figures 24a, 24b, and 24c, respectively. The majority of surgeons indicate a PT ratio of 1.5 to be the highest degree of anticoagulation at which they would perform dental extractions. A few surgeons indicate a PT of 2.0 as their perceived *safe limit*. No one indicated a PT ratio above 2.0 as their *safe limit*. Among the surgeons who use the INR, the majority (52.4%) would perform extractions within the INR range of 1.6 to 2.0. Three respondents stated that they would proceed with extractions within the INR range of 2.1 to 2.6. Three other respondents would proceed in the INR range of 2.6 to 3.0. One respondent gave an INR of 3.5 as the *safe limit*, while two respondents stated that they would extract teeth up to an INR of 4.0 (Figure 24c).

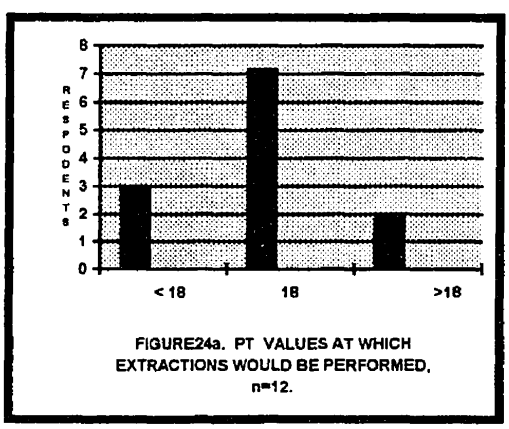


FIGURE24a. PT VALUES AT WHICH EXTRACTIONS WOULD BE PERFORMED, n=12.

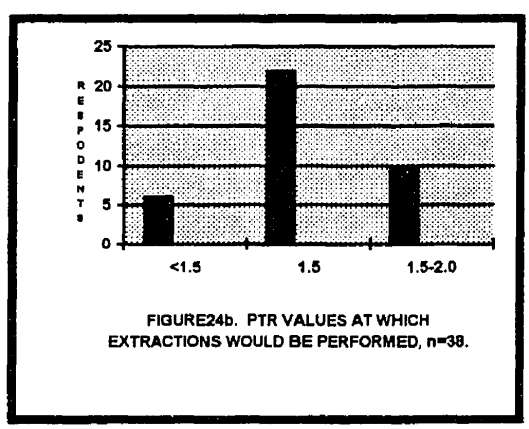


FIGURE24b. PTR VALUES AT WHICH EXTRACTIONS WOULD BE PERFORMED, n=38.

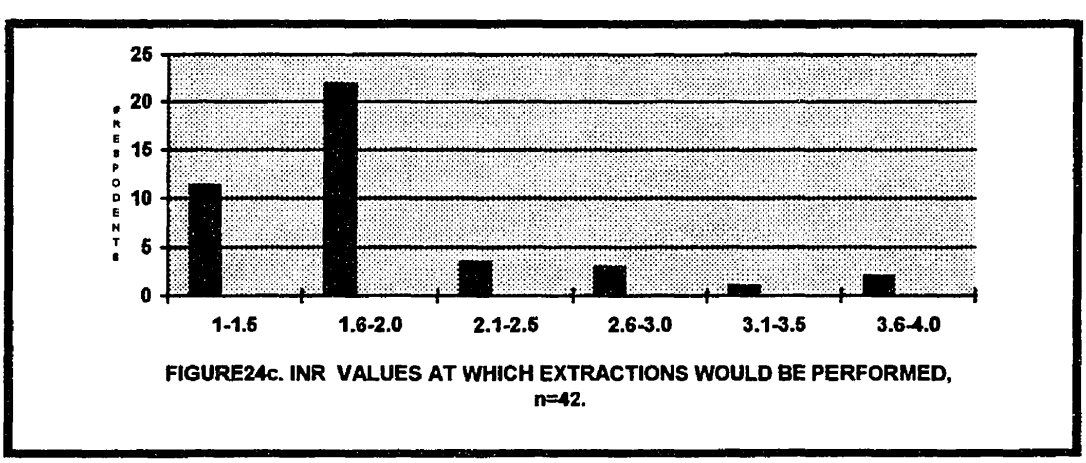


FIGURE24c. INR VALUES AT WHICH EXTRACTIONS WOULD BE PERFORMED, n=42.

With regard to the management protocols for patients who require dental extractions and whose level of anticoagulation is above the *safe limit*, 96% of the surgeons would decrease the level of anticoagulation, to their perceived *safe limit*, if the patient is not considered to be at a high risk of developing a thromboembolism. Figure 25 shows the number of respondents who use each of the various treatment protocols. The same treatment protocols were used by 76% of respondents for patients requiring multiple extractions while 24% of the respondents would alter the treatment procedure with these cases.

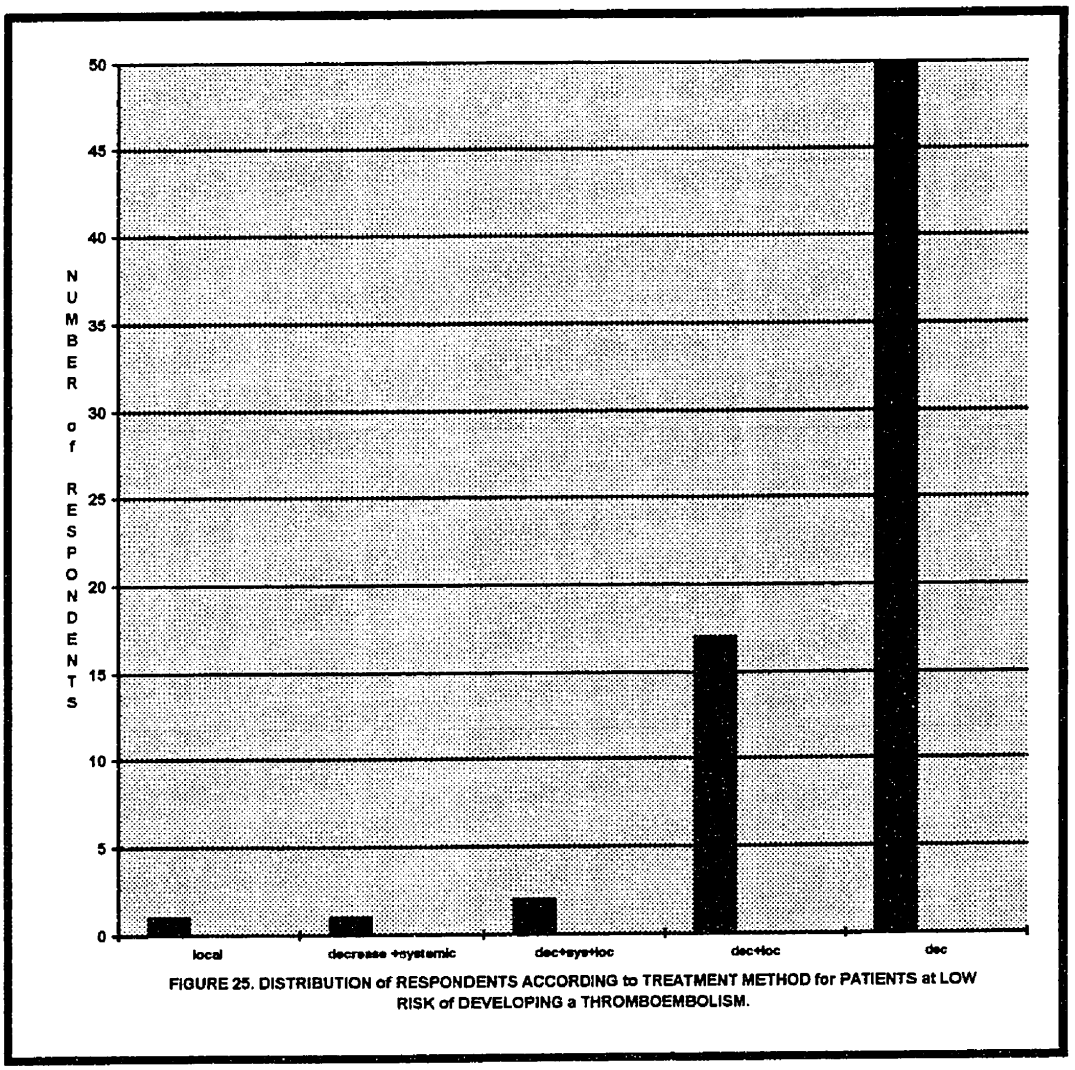


FIGURE 25. DISTRIBUTION of RESPONDENTS ACCORDING to TREATMENT METHOD for PATIENTS at LOW RISK of DEVELOPING a THROMBOEMBOLISM.

For patients who are considered to be at a high risk of having a thromboembolic event if the level of anticoagulation is decreased, the majority , 91.6%, of surgeons would admit the patient for heparin therapy in the perioperative period. Figure 26 indicates the number of replies for each treatment option. Only 6 respondents claim they would not admit the patient for heparin therapy. Of these, four respondents stated they would use local measures such as sulcralfate/CaCl/thrombin/tranexamic acid or Surgicel™. One respondent stated he would use local and systemic tranexamic acid. When asked whether the method of management would be altered for the high risk patient depending on the type or quantity of extractions to be performed, 72.2% of surgeons claim the protocol of management would not change whereas 27.8% stated that it would.

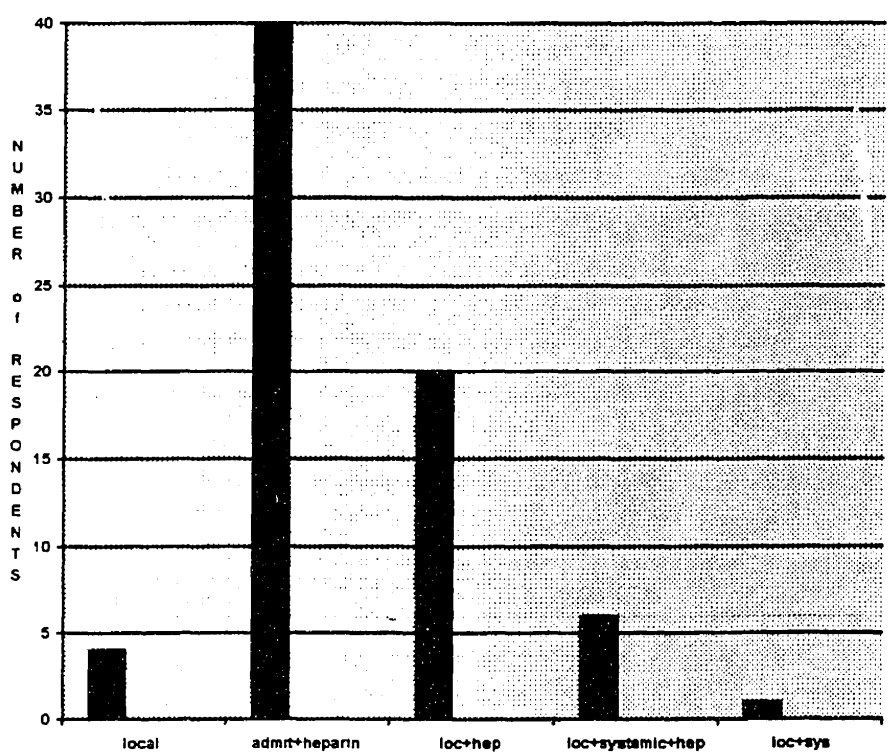


FIGURE 26. DISTRIBUTION of RESPONDENTS ACCORDING to TREATMENT METHOD for PATIENTS at a HIGH RISK for THROMBOEMBOLISM.

Study- Part 2

Animal Experiment

Unexpected findings with Warfarin Therapy, in the New Zealand White Rabbit

❑ Warfarin Dosage

The dose of warfarin, recommended by Haugen[61] and Declerck et al,[6,7] was followed in this study to anticoagulate the rabbits. Two observations were made about the warfarin dose required to anticoagulate the rabbits, in this study. First, of the thirty-two rabbits which were anticoagulated, 27 rabbits responded to the recommended or a slightly higher dose regimen. Five rabbits (16%) required much higher doses ranging from 6 times to 46 times the recommended dose (Figure 27). Second, in some animals, the effect of warfarin was unexpected. If a rabbit was over-anticoagulated and the warfarin was withheld overnight, the level of anticoagulation would drop drastically. Figure 28 indicates some examples of unexpected INR values.

RABBIT	GROUP and INR LEVEL	WARFARIN DOSE	INCREASE in the RECOMMENDED DOSE
12	Group 3: INR = 2.1 to 2.6	50 mg per day	16 times
17	Group 2: INR = 1.5 to 2.0	30 to 38 mg per day	10 times
20	Group 5: INR = 3.6 to 4.0	130 to 140 mg per day	46 times
28	Group 5: INR = 3.6 to 4.0	75 to 80 mg per day	26 times
31	Group 2: INR = 1.5 to 2.0	18 to 20 mg per day	6 times

FIGURE 27. Rabbits requiring an increase in the recommended warfarin dose.

	INITIAL INR	WARFARIN WITHHELD OVERNIGHT	INR AFTER 12hrs
Rabbit 19	4.2	⇒	0.8
Rabbit 20	6.2	⇒	0.6
Rabbit 28	9.0	⇒	0.7
Rabbit 37D*	7.4	⇒	1.3
Rabbit 37D*	6.2	⇒	0.8

FIGURE 28. Some examples of the change in INR when warfarin was withheld overnight.
* D= rabbit died prior to having dental extractions.

❑ Maintenance of the level of anticoagulation

Once the desired level of anticoagulation was achieved in a rabbit, regardless of the amount of warfarin required, it was difficult to maintain that level of anticoagulation. Figure 29 shows the INR level for each rabbit on the day of surgery (Day 0) and on the day the animal was sacrificed (Day 6).

	Rabbit #	Day 0		Day 6		Rabbit #	Day 0		Day 6
Group 1 INR = 0.7 - 1.4									
Group 2	11	1.9	⇒	0.8	**Group 4**	3	3.3	⇒	6.5
INR= 1.5 - 2.0	13	1.9	⇒	1.8	INR = 2.7 - 3.5	7	2.7	⇒	1.0
	17	1.6	⇒	unknown		8	2.8	⇒	2.1
	23	1.6	⇒	unknown		14	3.3	⇒	>20
	24	1.7	⇒	1.0		16	2.8	⇒	0.9
	27	1.7	⇒	1.7		18	3.5	⇒	1.1
	31	1.6	⇒	0.8		26	3.3	⇒	2.0
	38	2.0	⇒	0.8		33	3.4	⇒	2.4
Group 3	9	2.2	⇒	4.0	**Group 5**	15	3.8	⇒	>20
INR = 2.1 - 2.6	10	2.3	⇒	1.0	INR = 3.6 - 4.0	19	3.7	⇒	>20
	12	2.3	⇒	0.9		20	4.1	⇒	12.0
	21	2.2	⇒	0.9		28	3.6	⇒	0.7
	22	2.3	⇒	0.9		29	3.8	⇒	6.6*
	25	2.6	⇒	1.9		32	3.8	⇒	4.9
	30	2.4	⇒	2.0		36	3.6	⇒	3.2
	34	2.2	⇒	2.0					

FIGURE 29. Level of anticoagulation on Day 0 and Day 6 for each group. * rabbit died on day 2.

❑ Preoperative Complications

Five rabbits died prior to having extractions performed, during the anticoagulation period. Figure 30 describes the events preceding their death and the autopsy results. The death of the final rabbit and time constraints, caused group 5 to have 7 rabbits.

	Events prior to death	autopsy results
Rabbit 14 D	INR=2.0 died during induction of G.A.	small fibrotic lungs
Rabbit 37D	INR=4.4 sudden onset, hemiparalysis	- hematoma at spinal cord - hematoma in thorax
Rabbit 43D	INR=6.2	general internal hemorrhage
Rabbit 44D	INR=9.8	retroperitoneum hemorrhage
Rabbit 19D	INR=1.9	accidental cervical spine fracture

FIGURE 30. Events leading to the death of five animals, prior to entering into the study. D = rabbit died prior to having dental extractions.

❑ Adjusted INR levels

The anticoagulation levels were reported as a PT value, an INR (INR_{lab}) and an INR adjusted for rabbits (INR_{adj}), as described in the materials and methods. As figure 31 indicates, the adjusted, *rabbit INRs* are higher than the *laboratory INRs.*

	PT	INR_{lab}	$INR_{adjusted}$		PT	INR_{lab}	$INR_{adjusted}$
	7.8	0.7	1.0		21.2	3.3	4.9
GROUP 1	7.9	0.7	1.0	GROUP 4	21.0	3.3	4.8
INR = 0.7 - 1.4	9.6	0.9	1.4	INR = 2.7 - 3.5	18.8	2.8	4.0
	9.1	0.9	1.3		18.5	2.7	3.9
	8.6	0.8	1.2		21.5	3.4	5.1
	7.9	0.7	1.0		20.9	3.3	4.7
	7.9	0.7	1.0		21.8	3.5	5.0
	7.9	0.7	1.0		19.2	2.8	4.1
	15.0	1.9	2.8		21.2	3.6	5.2
GROUP 2	13.6	1.6	2.4	GROUP 5	23.3	3.8	5.6
INR = 1.5 - 2.0	13.9	1.7	2.5	INR = 3.6 - 4.0	22.9	3.8	5.5
	13.2	1.6	2.3		22.1	3.6	5.2
	15.1	1.9	2.8		23.1	3.8	5.6
	13.5	1.6	2.4		25.2	4.1	6.4
	14.0	1.7	2.5		22.5	3.7	5.3
	15.5	2.0	2.9				
	16.5	2.2	3.3				
GROUP 3	16.7	2.3	3.3				
INR = 2.1 - 2.6	17.0	2.3	3.4				
	16.7	2.3	3.3				
	16.2	2.2	3.2				
	17.2	2.4	3.5				
	18.1	2.6	3.8				

FIGURE 31. The laboratory PT, the laboratory INR and the adjusted INR levels are shown .

Assessment of local hemostasis

❑ Surgeon's Assessment of Local Hemostasis

Figure 32 displays the results of the surgeon's assessment of local hemostasis. For each INR group, the number of rabbits who were observed to have no ooze, a slight ooze or a frank bleed, are shown at each time interval.

		POSTOPERATIVE TIME										
	GRADE	5min	20min	2hr	4hr	6hr	day 1	day 2	day 3	day 4	day 5	day 6
GROUP 1 INR=0.7-1.4	no ooze	5	7	8	8	8	8	8	8	8	8	8
	slight ooze	3	1	-	-	-	-	-	-	-	-	-
	frank bleed	-	-	-	-	-	-	-	-	-	-	-
GROUP 2 INR=1.5-2.0	no ooze	7	7	8	8	8	8	8	7	7	7	7
	slight ooze	1	1	-	-	-	-	-	1	-	-	-
	frank bleed	-	-	-	-	-	-	-	-	1*	-	-
GROUP 3 INR=2.1-2.6	no ooze	4	8	8	8	8	8	8	8	8	8	7
	slight ooze	4	-	-	-	-	-	-	-	-	-	1
	frank bleed	-	-	-	-	-	-	-	-	-	-	-
GROUP 4 INR=2.7-3.5	no ooze	4	7	7	8	8	8	8	8	8	8	8
	slight ooze	4	1	1	-	-	-	-	-	-	-	-
	frank bleed	-	-	-	-	-	-	-	-	-	-	-
GROUP 5 INR=3.6-4.0	no ooze	2	2	4	6	6	6	6	6	6	5	4
	slight ooze	5	5	2	-	1	1	-	-	-	1	2
	frank bleed	-	-	1	1	-	-	1**	-	-	-	-

FIGURE 32. Surgeon's assessment of local hemostasis. * rabbit died - INR unknown

** rabbit died - INR=6.6.

Statistical Analysis (Data Figure 32)

An assessment of the data indicated that there was no difference between groups 1 to 4. These groups (1 to 4) were then compared as one group (1-4) to group 5.

A Fisher's exact test was used to compare, the hemostasis obtained by 2 hours, between group (1-4) and group 5.

	[1]	[2]	
[1]	1	31	
[2]	3	4	p-value = 0.014

There was a *statistically significant difference*, in the local hemostasis observed by 2 hours, when comparing group (1-4) to group 5.

A Fisher's exact test was used to compare the number of episodes of recurrance of bleeding observed in group (1-4) as compared to group 5.

	[1]	[2]	
[1]	2	30	
[2]	4	3	p-value = 0.055

There was a *statistically significant difference* in the number of episodes recurrance of bleeding when comparing group (1-4) to group 5.

❑ Surgeons' Assessment of Local Hemostasis -- Video

The extraction sites were video taped at defined time intervals. Two surgeons, who were blinded to the treatment groups, assessed the local hemostasis and graded it according to the scale: no ooze, slight ooze or frank bleed. Figure 33 displays the results from the two surgeons' assessments.

		POSTOPERATIVE TIME									
		SURGEON No. 1					SURGEON No. 2				
	GRADE	5min	20min	2hr	4hr	day 6	5min	20min	2hr	4hr	day 6
GROUP 1 INR=0.7-1.4	no ooze	5	7	4	4	8	5	4	5	5	8
	slight ooze	3	1	-	-	-	2	1	-	-	-
	frank bleed	-	-	-	-	-	-	-	-	-	-
GROUP 2 INR=1.5-2.0	no ooze	7	7	8	8	7	7	7	8	8	7
	slight ooze	1	1	-	-	-	1	1	-	-	-
	frank bleed	-	-	-	-	-	-	-	-	-	-
GROUP 3 INR=2.1-2.6	no ooze	5	6	8	8	6	4	7	8	8	7
	slight ooze	3	2	-	-	1	4	1	-	-	1
	frank bleed	-	-	-	-	-	-	-	-	-	-
GROUP 4 INR=2.7-3.5	no ooze	4	5	8	8	8	3	7	8	7	8
	slight ooze	4	2	-	-	-	5	1	-	-	-
	frank bleed	-	-	-	-	-	-	-	-	-	-
GROUP 5 INR=3.6-4.0	no ooze	1	1	5	6	4	2	3	5	6	4
	slight ooze	5	6	1	-	2	4	4	1	-	2
	frank bleed	1	-	1	1	-	1	-	1	1	-

FIGURE 33. Two surgeons' assessment of local hemostasis.

Statistical Analysis (Data Figure 33)

Surgeon #1

A Fisher's exact test was used to compare the local hemostasis observed by surgeon # 1, when comparing group (1-4) to group 5:

	[1]	[2]	
[1]	0	25	
[2]	2	5	p-value = 0.0423

Surgeon # 2

A Fisher's exact test was used to compare the local hemostasis observed by surgeon # 2, when comparing group (1-4) to group 5:

	[1]	[2]	
[1]	0	26	
[2]	2	5	p-value = 0.0398

There was a *statistically significant difference* in local hemostasis observed by both surgeons, who were blinded to the treatment groups, when comparing group 5 to group (1-4).

❑ Radioactive labelling, Sodium Chromate 51.

Figure 34 indicates the radioactive counts obtained on day 0 and on day 6. The count on day 6 is expressed as a percentage of the day 0 count which serves as the reference sample.[6,7] The percentage indicates the relative amount of radioactively, labelled red-blood cells, remaining in the animal, on day 6.

	DAY 0	DAY 6	PERCENT REMAINING
GROUP 1 INR = 0.7 - 1.4	unknown	808.5	unknown
	1538.9	1174.7	76.3
	938.6	529.0	56.4
	2038.4	1214.2	59.6
	2059.5	1433.2	69.7
	1138.2	805.0	70.7
	2167.6	940.1	43.4
	1155.3	791.0	68.5
GROUP 2 INR = 1.5 - 2.0	910.1	614.4	67.5
	1046.6	79.3	7.6
	1329.8	946.1	71.1
	1219.7	800.6	65.6
	710	336.9	47.5
	1427.8	919.1	64.4
	1425.8	1020.5	71.6
	959.1	676.0	70.5
GROUP 3 INR = 2.1 - 2.6	1159.2	300.3	25.9
	1325.3	991.6	74.8
	1573.8	1127.7	71.7
	1227.7	1074.2	87.5
	1355.2	245.3	18.0
	1274.7	900.1	70.6
	963.6	725.0	75.2
	1215.7	647.5	53.3

	DAY 0	DAY 6	PERCENT REMAINIMG
GROUP 4 INR = 2.7 - 3.5	1046.2	738.0	70.5
	1599.3	1065.1	66.6
	1514.3	1013.1	66.9
	1387.3	1370.0	98.8
	905.6	418.5	46.2
	1166.7	280.4	24.0
	1304.8	753.5	57.7
	1169.2	690.5	59.1
GROUP 5 INR = 3.6 - 4.0	1042.2	76.9	7.4
	1595.4	1341.3	84.0
	1257.2	unknown	unknown
	1346.2	847.2	62.9
	1363.2	1134.1	83.2
	1506.8	988.6	65.6
	2919.3	832.6	28.5

FIGURE 34. **Radioactive counts on day 0, day 6 and as a percent of remaining activity on day 6.**

Statistical Analysis (Data Figure 34)

The radioactivity remaining on day 6 and the percent radioactivity was compared by a Welch Modified, Two Sample t- Test, to determine if a significant change in radioactivity had occurred.

The *radioactivity* remaining on day 6, was compared between group 1 (control) to group (2-5). At a 95 % confidence interval (CI), (-65.0 to 458.7), there was no statistically significant difference, p- value = 0.1282.

The *radioactivity* remaining on day 6, was compared between group (1-4) to group 5. At a 95 % CI (-528.3 to 377.5), there was no statistically significant difference between these groups, p-value = 0.6989.

The *percent radioactivity* remaining on day 6 was compared between group 1 and group (2-5). At a 95% CI (-7.8 to 17.2), there was no statistically significant difference between these groups, p-value = 0.4423.

The *percent radioactivity* remaining on day 6 was compared between group (1-4) to group 5. At a 95 % CI (-27.0 to 37.6), there was no statistically significant difference between these groups, p-value = 0.7012.

There was *no statistically significant change* in the radioactivity.

DISCUSSION

Study - Part 1

Mail Survey

This survey highlights a number of issues on the management by Oral and Maxillofacial Surgeons, of patients on oral anticoagulants. The majority of surveyed surgeons use the INR but only one fifth of them rely on this method alone. Since only oral surgeons from large academic centers, were surveyed, the results cannot be extrapolated to those practicing in non-academic institutions. It is possible that the high rate of use of the INR in our survey merely mirrors the more widespread use of this method in academic institutions. Only 21% of surgeons use the INR alone and 27% of the respondents report using the PT, as the sole measure of the level of anticoagulation for their patients. This may be an indication that surgeons still do not completely understand the INR value. The fact that the majority of respondents (52.5%) use the INR along with the PT value, may reflect the lack of scientifically-based guidelines for the INR, as well as, the fact that the PT is a more familiar value. Another reflection of the lack of experimental data on this issue, is the broad range of anticoagulation levels cited as safe for performing dental extractions.

Beirne and Koehler [13] state that minor oral surgical procedures may be performed with a PT ratio ≤ 2.5. For many years, this empirically-derived guideline has been followed by many surgeons. In fact, the same plasma sample will have widely divergent PT ratios depending on the sensitivity of the thromboplastin used to derive the PT. Therefore, by following these guidelines, surgeons have been extracting teeth in a wide range of anticoagulation levels. It is interesting to estimate the INR value that would be equivalent to the recommended PT ratio. As previously shown, Beirne and Koehler [13] have illustrated that if a rabbit thromboplastin is used (which was the predominant thromboplastin at the time that the PT ratio guidelines were established), a PT of 1.5 to 2.0 would be equivalent to an INR of 2.6 to 5.0. At the

Montreal General Hospital, dental extractions were performed at a PT ratio of 1.5 to 2.0, which when roughly calculated, implies an INR of 2.1 to 4.1 (Figure 1). From the examples stated above, it appears that in the past, oral surgeons were safely performing dental extractions at all the therapeutic INR ranges.

Although recommending oral surgery procedures at higher INR levels does not seem inappropriate based on the implications of the above arguments, it would be far superior to obtain scientific data to support these observations. For many years, dental extractions have been performed for patients on anticoagulant therapy according to the existing empirical guidelines. It is no longer appropriate to monitor the level of anticoagulation using the unadjusted PT ratio. Many authors feel that not using the INR constitutes substandard medical care.[8,31] Furthermore, it is no longer appropriate to follow empirical guidelines based on the PT ratio for surgical procedures. With the development and implementation of the INR value, a reliable and consistent measure of the level of anticoagulation now exists.

Using the INR, as a meausre of the level of anticoagulation, an animal study was performed. The goal of this animal study was to define the highest INR level, at which dental extractions can be safely performed, using *routine* measures of local hemostasis, in subjects receiving warfarin. The results of this animal study will now be discussed.

Study - Part 2

Animal Experiment

The animal study performed, illustrates a number of issues concerning the anticoagulation of New Zealand White rabbits. As well, this study highlights a number of issues concerning local hemostasis, following dental extractions, using only *routine* measures, in rabbits receiving oral anticoagulant-therapy.

Surprisingly, the response to the warfarin was unpredictable. This finding was contrary to the results of Haugen [61] and Declerck et al [6,7] in three ways. First, although the majority of the rabbits responded to the dose recommended by Haugen [61] and Declerck et al, [6,7] 16 per cent of the anticoagulated rabbits, required a much higher dose regimen. This may be comparable to humans. Approximately 10% of patients on anticoagulant therapy will require a relatively high dose of warfarin to achieve a therapeutic level of anticoagulation. [64] However, some rabbits required astonishingly high doses of warfarin (80 to 130 mg per day) to achieve the desired level of anticoagulation (Figure 27). The dose response of warfarin is influenced by numerous factors such as absorption, metabolic clearance and differences in the hemostatic response. As well, medications and diet will influence the pharmacokinetics of warfarin. [5,46] The rabbits in this study, received the same diet and the same medications. Therefore, the variations in dose response to warfarin, observed amongst the rabbits, is most probably due to individual variation in absorption or metabolic clearance.

Second, the metabolism of warfarin appears to be extremely fast in the rabbit as compared to the human. In humans, warfarin has a long half life of 36 to 42 hours, due to its slow rate of biotransformation and high amount of plasma-protein binding. It takes at least 2 days to see a decrease in the level of anticoagulation when warfarin therapy is withdrawn. [5,46] After warfarin treatment is stopped, it takes

about 4 days for the INR to reach 1.5 in almost all patients. [65] In this study, when rabbits were over-anticoagulated and the warfarin treatment was withdrawn, the level of anticoagulation would drop to an INR of 0.7 to 1.3 within a 12 hour period (Figure 28).

Finally, once a rabbit was in the desired level of anticoagulation, regardless of the amount of warfarin required, it was difficult to maintain that level of anticoagulation (Figure 29). These three responses to warfarin were not anticipated. Haugen found "that a reliable controlled anticoagulant treatment of rabbits is practicable." [61] In this study, the anticoagulant treatment, was not predictable. The recommended dose of warfarin was not always sufficient, the level of anticoagulation achieved was not stable and the metabolism of warfarin appeared to be accelerated. An unexpected response to warfarin has also been observed in pigs. It is thought that warfarin has a much shorter half life in the pig as compared to the human. [66] Assay studies (thrombin levels, prothrombin levels and warfarin levels), at various time intervals after warfarin administration would be able to confirm this suspicion.

If an unpredictable level of anticoagulation had been anticipated, daily PT and INR levels would have been performed. As well, once an desired level of anticoagulation was established, an attempt would have been made to maintain the level of anticoagulation, with the required dose of warfarin, for a longer period of time, preoperatively. This would have established if an INR level could be maintained *reliably* for a prolonged period.

Since the level of anticoagulation was not maintained during the postoperative period, the degree of hemostasis observed can only be related to the level of anticoagulation on the day that a PT and INR were performed. The rabbits had the dental extraction performed a hour after determining the PT and INR. Therefore, for the few hours following the dental extraction, the INR was known. The results of this study strongly suggest that local hemostasis, using *routine* local measures, is

achievable to an INR of 3.5. There was a statistically significant difference in hemostasis, as graded by three different surgeons, when comparing group (1-4) with group 5. However, two factors which may be important are that primary closure was obtained at all the extraction sites and only one tooth was removed. Multiple extractions and the inability to obtain primary closure, may provide a larger challenge to the hemostatic mechanism in subjects taking oral anticoagulants.

Local hemostasis was observed, by 20 minutes, in all rabbits in the INR range of 0.7 to 3.5, except for one rabbit within the INR range of 2.7 to 3.5, which was observed to have a slight ooze up to 2 hours postoperatively. In the INR range between 3.6 to 4.1, six rabbits had evidence of bleeding after the 20 minute postoperative period. Two of these six rabbits, had a frank bleed, one up to 2 hours postoperatively and one up to 4 hours postoperatively. Figure 32 summarizes these findings. Statistically, a difference in the hemostasis observed over two hours exists when comparing group (1-4) to group 5.

A problem in patients receiving oral anticoagulant therapy can be the recurrance of bleeding. [6,36] If bleeding recurs, it generally does so from day 1 to day 5. [6,36] This was seen in the present study. One rabbit in group 2 (INR = 1.5 to 2.0) had recuurance of bleeding from the extraction site on the second postoperative day. The bleeding was controlled with local pressure. However, this rabbit was found dead on the third postoperative day with evidence that further bleeding had occurred. Unfortunately, the INR was not known at the time that the animal died. One rabbit in group 5 (INR = 3.5 to 4.0) had a slight ooze on the first postoperative day and a frank bleed on the second postoperative day. This rabbit had an INR of 6.6 and died on the second postoperative day from exsanguination. Two other rabbits from group 5 (INR = 3.5 to 4.0) had recurrance of bleeding from the extraction site on the fifth and sixth postoperative days. As the results of figure 32 indicate, there were only two episodes (two rabbits) of recurrance of bleeding from the extraction site in groups 1 to 4 (INR < 3.6). However, there were six episodes (4 rabbits), of

recurrant bleeding from the extraction sites in group 5 (INR =3.6 to 4.1). Statistically, there was a significant difference in the number of episodes of recuurance of bleeding when group (1-4) was compared with group 5.

There was an obvious difference in hemostasis observed and in the episodes of recurrance of bleeding seen in group 5 (INR = 3.6 to 4.0). Up to an INR of 3.5, (group 1-4), hemostasis was obtained using only *routine* measures. Also, the number of episodes of rebleeding in group 1-4 were minimal (Figures 32 and 33).

Interestingly, group 5 had a *laboratory INR* in the range of 3.6 to 4.0. However, the rabbit *adjusted INR* was in the range of 5.2 to 6.4 (Figure 31). In this group with an extremely high level of anticoagulation, a lack of hemostasis would be expected. In fact, all other experimental groups , groups 2 to 4, had rabbit *adjusted INR* levels in the range of 2.3 to 5.0 (Figure 31), and good hemostasis was obtained. Group 2 (INR_{lab} = 1.5 to 2.0) and group 3 (INR_{lab} = 2.1 to 2.6), had rabbit *adjusted INR* levels which would be comparable to the clinical situation. That is, group 2 and group 3, had rabbit *adjusted INR* levels (INR_{adj} = 2.3 to 3.8), which represent the recommended therapeutic level of anticoagulation. In these two groups acceptable hemostasis was obtained using only *routine* measures.

During the postoperative period, some rabbits appeared to be very pale and withdrawn , in spite of the fact that there was no bleeding from the extraction wounds. Verification of the INR revealed that these animals were over-anticoaguilated and autopsy examination revealed evidence of internal hemorrhage. When internal hemorrhage was seen, it occurred in the thorax and the retroperitoneum. The clot at the extraction wound was apparently stable enough to prevent recurrance of bleeding, despite the fact that these animals were over-anticoagulated.

In an attempt to assess the total blood loss during the study period, sodium chromate 51, radioactive labelling of the red blood cells was used. The radioactivity of the preoperative and postoperative blood samples was determined. The preoperative count was used to represent 100% (reference sample) and the radioactive count of the postoperative sample was expressed as a percentage of the reference sample. This technique was modified from the protocol of Declerck et al. [6,7] There was no statistically significant change in the radioactivity. This measure of the total blood loss during the study period may not have been sensitive enough to detect changes which may have occurred.

An alternative method, which would be more accurate, would be to measure the preoperative and postoperative red cell volume (RCV) using the following equation:

$$\mathbf{RCV} = \frac{\text{radioactivity of standard x dilution of the standard x volume injected}}{\text{radioactivity of post-injection sample}} \times \mathbf{HCT}$$

An even more accurate RCV can be obtained by determining an accurate PV (plasma volume). In most cases, red cell volume (RCV) and plasma volume (PV) can be estimated reproducibly using, respectively, labelled red cells or labelled proteins, therefore, a dual tracer technique would be recommended. Sodium chromate 51, would be used to to radiolabel the red blood cells and ^{131}I or ^{125}I, would be a suitable protein label for the PV determination. [67] Each variable can be estimated by this procedure and the total blood volume obtained by summation. The red cell volume (RCV) is calculated as follows: [67]

$$\mathbf{RCV} = \frac{D\ V\ H_v\ [S_i - S_s(I - H_i)]}{[B - P(I-H_v)}$$

I = total injected radioactivity (c/min)
D = dilution of diluted standard solution
V = volume of labelled red cell suspension injected (ml)
Hv = PCV of sample corrected for trapped plasma
Si = counting rate of injectate standard (c/min per ml)
Ss = counting rate of standard supernatant (c/min per ml)
Hi = PCV of labelled red-cell suspension corrected for trapped fluid
B = counting rate of blood sample (c/min per ml)
P = counting rate of plasma sample (c/min per ml)

In spite of the accuracy of the techniques described above, the evaluation of local hemostasis, using the change in red cell volume, may be inappropriate. In this study, some rabbits had evidence of internal hemorrhage with no bleeding from the extraction wound. Therefore, in cases where internal hemorrhage had occurred, a change in the red cell volume would be detected, with no bleeding having occurred from the surgical wound. Therefore, the most accurate assessment of local hemostasis would be the evaluation by evaluators, who are blinded to the level of anticoagulation of the subject.

SUMMARY and SUGGESTIONS

The results of the ***mail survey*** indicate that oral surgeons may still not understand the significance of the INR value. It is no longer appropriate to use the unadjusted PT to monitor a patient's level of anticoagulation. It is also no longer appropriate to follow empirical guidelines based on the PT ratio prior to performing surgical procedures. A greater understanding of the INR value is required among dentists and oral surgeons. In addition, scientifically-based guidelines, using the INR value, need to be established for surgical procedures.

The results of this animal study indicate that further ***animal studies*** are required. First, the half life of warfarin needs to be determined in the New Zealand White Rabbit. This could be accomplished by performing assay studies. Second, it must be determined if predictable long-term anticoagulation (3 to 6 months), can be obtained in this animal model. Finally, animal studies should establish if multiple and/or surgical extractions provide a greater challenge to the hemostatic mechanism.

The results of this study strongly suggest that local hemostasis can be achieved, using only *routine* measures, after performing dental extractions, in subjects receiving oral anticoagulants. ***Clinical trials*** are required to confirm these findings. Single extractions with primary closure (Gelfoam™ and sutures) could be performed in patients receiving warfarin while maintaining their level of anticoagulation at an INR < 3.5. If in the clinial trials, local hemostasis is not maintained using only *routine* measures, more *elaborate* measures of local hemostasis such as, tranexamic acid and Beriplast,™ could be used. [10,11,12]

The results of the previously suggested animal studies will determine if local hemostasis can be achieved using *routine* measures when multiple and/or surgical dental extractions are performed. Future clinical trials will determine whether or not

the local hemostatic agents are effective at all therapeutic INR levels and for single, multiple, or surgical extractions.

If local hemostatic agents are effective for all types of dental extractions and at all therapeutic INR levels, the need to either decrease a pateint's level of anticoagulation or to hospitalize them for heparin therapy will no longer be necessary. We expect to find that local hemostatic agents will be a safe and cost efficient treatment protocol for this population of patients.

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IMAGE EVALUATION TEST TARGET (QA-3)

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