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The Use of Topical Tranexamic Acid for the Prevention of Postextraction Bleeding in Patients on Oral Anticoagulants who are Undergoing Oral Surgery, Without Modification of Their Anticoagulant Regime

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A research report submitted in partial fulfillment of the requirements for the degree of Master of Dental Surgery in Hospital Dentistry of the University of Otago, Dunedin, New Zealand

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ABSTRACT

Optimal management of patients on warfarin who require oral surgery has been controversial. Historically the clinician has had to balance the risk of thromboembolism by reducing or stopping anticoagulant therapy, against the risk of triggering excessive postextraction bleeding if anticoagulation is maintained at therapeutic levels during surgery. Patients on anticoagulants have impaired fibrin formation that is more susceptible to normal fibrinolysis and is believed to be the major cause of postextraction bleeding. This report reviews normal haemostasis, oral anticoagulants, thromboembolism, the fibrinolytic system and oral fibrinolysis and the traditional methods of managing patients on oral anticoagulants. A technique, derived from that originally described by Sindet-Pedersen et al. (1989), was used where teeth were extracted from patients in whom therapeutic warfarin levels were maintained. The antifibrinolytic agent, tranexamic acid was used as a mouth rinse four times a day for seven days to reduce fibrinolysis and subsequent bleeding.

The aim of this study was to verify that this technique is a safe, simple, effective and acceptable method of patient management. The second objective was to identify potential risk factors that may increase the likelihood of bleeding.

One hundred consecutive warfarin patients with an International Normalised Ratio (INR) between 1.9 and 4.0 on the day of surgery and who required dental extractions were recruited to the study. Following removal of teeth, patients were instructed to use 5 millilitres of 10% tranexamic acid syrup as a mouthrinse 4 times a day for 7 days, to record bleeding that required pressure to control and their mouthrinse usage. The researcher collected demographic data, details of the state of anticoagulation, details of the surgery and details of bleeding that required additional management. Data entry and analysis were conducted using the statistical computer programme SPSS. Descriptive statistics were produced for the sample demographics, the haemostasis screen, the postextraction bleeding profile, the teeth removed and mouthrinse acceptance and utilisation. Identification of potential risks that might increase the likelihood of bleeding was carried out using the chi-square test and the independent-samples t test as appropriate. Multivariate analysis was then performed using logistic regression.
Of the 100 patients treated, 8 reported bleeding at home after day 1 that was controlled by pressure. A further 8 patients reported to the researcher’s dental surgery where bleeding was controlled by local measures. No patients required hospital admission for systemic management of bleeding.

Statistically significant risk factors for postextraction bleeding were: A pre-extraction INR equal to or greater than 3.0; periodontal pockets equal to or greater than 5 millimeters in depth; maxillary molar teeth and patients on long term aspirin therapy that was stopped seven days before the extraction.

Factors not statistically significant for an increased risk of bleeding included: The number of teeth removed; raising a mucoperiosteal flap; removing bone; pre-extraction activated partial thromboplastin time; pre-extraction bleeding time; time on anticoagulants and compliance with tranexamic acid mouthrinses.

The post-operative use of tranexamic acid mouthrinses in patients who have teeth removed at therapeutic warfarin levels is a safe, simple, effective and acceptable method of reducing postextraction bleeding.
ACKNOWLEDGEMENTS

First I wish to acknowledge my two supervisors for this report, Paul Ockelford and John Edwards. Both are very busy people, with many diverse responsibilities but freely gave their time, knowledge and ideas to help, guide and encourage me through this report. Thank you John and Paul for all you have done. It has been appreciated.

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Special mention should be made of David Hay whose determination and effort made the Master of Dental Surgery in Hospital Dentistry a reality. Thank you David for the opportunity to acquire further knowledge, develop new skills, pursue new interests and further develop my career.

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Thanks must go to the one hundred patients who consented to join this study. Without their help and co-operation this report would not have been possible.

Thanks to Murray Thomson, who provided a supportive lifeline from the Dental School and to Dean Papaconstantinou. Both gave valued help and guidance with data analysis.

Thanks to my friend, colleague and fellow student, Graeme Ting, whose support and encouragement helped me focus on the task ahead and made study a lot easier.

Finally to my partner Eve. “Now we can sit on the grass in our top paddock amongst our cows, with a glass of wine and watch one of those amazing sunsets. Thank you for all your support and patience.”
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<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
</tr>
<tr>
<td>APTT</td>
<td>Activated Partial Thromboplastin Time</td>
</tr>
<tr>
<td>BT</td>
<td>Bleeding Time</td>
</tr>
<tr>
<td>Ca2+</td>
<td>Calcium ion</td>
</tr>
<tr>
<td>DDAVP</td>
<td>Desmopressin</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
</tr>
<tr>
<td>Gla</td>
<td>γ-carboxyglutamate</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
</tr>
<tr>
<td>ISI</td>
<td>International Sensitivity Index</td>
</tr>
<tr>
<td>LA</td>
<td>Local anaesthetic</td>
</tr>
<tr>
<td>mm</td>
<td>millilitre</td>
</tr>
<tr>
<td>ml</td>
<td>millimeter</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PF3</td>
<td>Platelet Factor 3</td>
</tr>
<tr>
<td>tPA</td>
<td>Tissue type plasminogen activator</td>
</tr>
<tr>
<td>Vitamin KH₂</td>
<td>Reduced form of Vitamin K</td>
</tr>
<tr>
<td>&gt;</td>
<td>Greater than</td>
</tr>
<tr>
<td>&lt;</td>
<td>Less than</td>
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</table>
CHAPTER 1  
INTRODUCTION

An increasing number of patients requiring oral surgery are on long-term anticoagulant therapy with coumarin derivatives. While a number of dental management protocols have been suggested, controversy remains. The clinician must balance the risk of thromboembolism by reducing or stopping anticoagulant therapy against the risk of triggering excessive postextraction bleeding if anticoagulation is maintained at therapeutic levels during surgery. In order to understand these risks and their management, normal haemostasis and the effect of oral anticoagulants, the role of fibrinolysis in oral bleeding and the risk of thromboembolism must be considered.

1.1 Normal haemostasis

Haemostasis is the arrest of bleeding from a broken blood vessel and involves vascular constriction, the formation of a platelet plug and blood coagulation. A cut or torn vessel immediately constricts as a result of both an inherent vascular responses to injury and sympathetically induced vasoconstriction. This vasoconstriction slows blood flow through the defect facilitating formation of the platelet plug.

Platelets normally do not adhere to the smooth endothelial surface of blood vessels but when this lining is disrupted because of vessel injury, platelets attach to the exposed collagen. Once platelets start aggregating at the site of the defect, they release adenosine diphosphate (ADP) which causes the surface of nearby circulating platelets to become sticky so that they adhere to the first layer of aggregated platelets. These newly aggregated platelets release more ADP which causes more platelets to adhere together. This process repeats itself so a plug of platelets is rapidly built up at the defect site in a positive feedback fashion. This aggregating process is reinforced by the formation of thromboxane A2 from a component of the platelet plasma membrane upon contact with collagen. Thromboxane A2 directly promotes platelet aggregation and further enhances it indirectly by triggering the release of more ADP from platelet granules. The platelet plug is limited to the site of vessel injury by the release of prostacyclin, a chemical that profoundly inhibits platelet aggregation, from normal endothelium. The aggregated platelet plug not only physically seals the break in the vessel but also performs 3 other important roles. First, the actin-myosin protein complex within the aggregated platelets contracts to compact and strengthen what was originally a fairly loose plug. Second, the chemicals released from the platelet plug include powerful vasoconstrictors...
(serotonin, epinephrine and thromboxane A2), that induce profound constriction of the affected vessel to reinforce the initial, self-induced vascular spasm. Third, the activated platelets release phospholipids that enhance blood coagulation.

Once the endothelium is damaged, and as a part of the dynamic process involved in the arrest of blood, the coagulation cascade is initiated (Figure 1.1). Clotting factors are present in the blood in an inactive form. Once the first factor in the sequence is activated, it in turn activates the next factor, in a series of sequential reactions resulting in the generation of thrombin which catalyses the final conversion of fibrinogen to fibrin. Inherent in the cascade process is amplification of each successive stage. This results in large amounts of fibrin being formed to make the normal “blood clot”.

There are 2 coagulation pathways referred to as the intrinsic and extrinsic pathways. The intrinsic pathway initiates clotting by contact with damaged vessels. All the elements of the intrinsic pathway are present in blood. This pathway is set off when Factor XII (Hageman factor) is activated by coming into contact with exposed collagen in an injured vessel. The exposed collagen also initiates platelet aggregation. Thus formation of the platelet plug and the chain reaction leading to clot formation are simultaneously set in motion when a vessel is damaged. Furthermore, these complementary haemostatic mechanisms reinforce each other. The platelets secrete platelet factor 3 (PF3) which is essential for the clotting cascade that in turn enhances further platelet aggregation.

The extrinsic pathway requires contact with tissue external to the blood, which initiates clotting of the blood that has escaped into the tissues. When tissue is traumatised, it releases a protein complex known as tissue thromboplastin that directly activates factor X, thereby bypassing all preceding steps of the intrinsic pathway.

The Prothrombin Ratio is used as a diagnostic test of abnormalities in the “extrinsic” (Factor VII) and common (Factors V, X, prothrombin and fibrinogen) pathways. Activated Partial Thromboplastin Time (APTT) is a useful and sensitive test to screen for deficiencies and abnormalities of the “intrinsic” coagulation pathway. Although bleeding time maybe an unreliable predictor of surgical bleeding (De Rossi and Glick, 1996), it may be used as a screen for prolonged bleeding times due to thrombocytopenia and acquired abnormalities of platelet function.
Figure 1.1  The clotting pathways

Damaged Vessel surface

Inactive Factor XII → Active factor XII (Hageman factor)

Inactive Factor XI → Active factor XI

Ca2+ (factor IV)

Inactive Factor IX → Active factor IX

Ca2+ Factor VIII PF3

Ca2+ Factor VII PF3

Intrinsic pathway

Extrinsic pathway

Tissue Damage → Tissue Thromboplastin

Prothrombin (factor II) → Thrombin

Thrombin Activates

Factors affected by warfarin *

Fibrinogen → Fibrin (Loose meshwork)

Fibrin (stabilised meshwork)

Entrapment of red cells

Clot
1.2 Thrombembolism

A thrombus is an abnormal intravascular clot attached to a vessel wall. Free-floating clots are called emboli. Several factors, acting independently or simultaneously can cause thromboembolism. These include: Roughened vessel surfaces with arteriosclerosis; imbalances in the clotting-anticlotting systems; slow moving blood, probably because small quantities of fibrin are formed and allowed to accumulate in the stagnant blood; the release of tissue thromboplastin into the blood from large amounts of traumatised tissue.

In a recent review, Kearon and Hirsh (1997) quantified the risk of thromboembolism in various situations. After an acute episode of venous thromboembolism, the risk of recurrence declines rapidly over the following 3 months. In the absence of anticoagulation the risk of recurrence of venous thromboembolism in the 3 months after proximal deep vein thrombosis is approximately 50%. One month of warfarin therapy reduces this risk to about 10% and 3 months of warfarin therapy reduces this risk to about 5%. On this basis, it is estimated that stopping anticoagulation in the first month after an acute thromboembolic event is associated with a very high risk of recurrent venous thromboembolism (40% in a 1-month interval). In the second or third month after an acute event, the risk of thromboembolism becomes intermediate (10% in a 2 month interval) if anticoagulants are stopped. A patient on long term anticoagulation, for multiple episodes of venous thromboembolism, hereditary hypercoagulable states, or active cancer has an estimated risk of thromboembolism of 15% per year if warfarin is discontinued. It is estimated that anticoagulation reduces the risk of recurrent venous thromboembolism by about 80%. A patient with non-valvular atrial fibrillation, not on antithrombotic therapy has an average risk of systemic embolism of 4.5% per year. In this situation, anticoagulation reduces the risk of embolism by 66%. It is estimated that the risk of major thromboembolism in patients with mechanical heart valves is 8 % per year. Anticoagulation reduces this risk by 75%. Warfarin is therefore highly effective at preventing recurrent thromboembolic events in patients receiving this medication for venous and arterial disease.
1.3 Oral anticoagulants

Warfarin (a 4-hydroxycoumarin compound) is the most common oral anticoagulant in use in New Zealand (Richardson, 1996). This is because of its predictable onset, duration of action and its excellent bioavailability.

Oral anticoagulants (Hirsh, 1991) induce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2, 3 epoxide (vitamin K epoxide). Vitamin K is an essential cofactor for the post-translational carboxylation of glutamate residues on the N-terminal regions of vitamin K-dependent proteins to γ-carboxyglutamates (Gla). This carboxylation reaction is catalysed by a vitamin K-dependent carboxylase and requires the reduced form of vitamin K (vitamin KH\(_2\) ), molecular oxygen and carbon dioxide. During this reaction, Gla residues are formed and vitamin KH\(_2\) is oxidised to vitamin K epoxide. Vitamin K epoxide is cycled back to vitamin K by vitamin K epoxide reductase, and the vitamin K is the reduced to vitamin KH\(_2\) by vitamin K reductase. By inhibiting vitamin K epoxide reductase and possibly vitamin K reductase, warfarin leads to the accumulation of vitamin K epoxide in the liver and plasma and the depletion of vitamin KH\(_2\). The decrease in vitamin KH\(_2\) limits the γ-carboxylation of the vitamin K-dependent coagulation proteins (prothrombin, factor VII, factor IX and factor X) and anticoagulant proteins (protein C and protein S) and as a result impairs their biologic function in blood coagulation. Through the process of γ-carboxylation, these vitamin K-dependent proteins acquire metal-binding properties so that in the presence of calcium ions they undergo a conformational change that is required for the proteins to bind to their cofactors on phospholipid surfaces. The vitamin K-dependent coagulation proteins normally contain 10 to 13 Gla residues within their amino terminus. Oral anticoagulant agents induce the hepatic production and secretion of partially carboxylated and decarboxylated functionally inert coagulation proteins. Prothrombin molecules with fewer than 6 Gla residues have about 2% of normal activity, whereas those with 9 Gla residues have 70% of normal activity. Warfarin has an elimination half-life of 36 hours due to its slow rate of biotransformation and high amount of plasma protein binding. The half-lives for factors VII, IX, X and II are 6, 24, 40 and 60 hours respectively.

The International Normalised Ratio (INR) (Meehan et al., 1997) is used to monitor the level of oral anticoagulation. The indications and optimum levels are given in Table 1.1.
Table 1.1 The indications and optimal levels for warfarin anticoagulation, as measured by the INR, at Auckland and Greenlane Hospitals (Richardson 1996)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Optimum INR</th>
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<tbody>
<tr>
<td>Lone atrial fibrillation (AF)</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Transient (cerebral) ischaemic attacks (TIA)</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Stroke (CVA)</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Prophylaxis of deep vein thrombosis (DVT)</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Recurrent deep vein thrombosis, pulmonary embolism (DVT/PE)</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>(For some patients with DVT/PE, a more appropriate level is)</td>
<td>(3.0-4.5)</td>
</tr>
<tr>
<td>Prosthetic mechanical cardiac valves</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>(For some patients with prosthetic mechanical cardiac valves, a more appropriate level is)</td>
<td>(3.0-4.5)</td>
</tr>
<tr>
<td>Coronary artery by-pass graft (CABG)</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Rheumatic valvular heart disease</td>
<td>2.5-3.5</td>
</tr>
</tbody>
</table>

Traditionally, physicians have monitored coumarin anticoagulation status by determining the prothrombin time: The length of time for a thromboplastin reagent to induce clotting in a citrated sample of patient's blood. Essentially, the prothrombin ratio is an *in vitro* model for the clotting ability of the blood in which the extrinsic and common pathways are mimicked. Since clotting by these pathways relies on the vitamin K-dependent clotting factors, the vitamin K antagonist coumarin reduces the efficiency of coagulation. A reduction in the activity of the vitamin K-dependent factors will lengthen the prothrombin time. The patient's prothrombin time is standardised by dividing its value by a control prothrombin time for the laboratory, giving the prothrombin time ratio. The use of the prothrombin time ratio as a measure of anticoagulation has a major practical shortcoming in that the sensitivities of the different thromboplastin reagents used are highly variable. Since a broad range of thromboplastin reagents are commonly used, a large element of variability is introduced into the assessment of a given patient's anticoagulation status. This meant that interpretation of prothrombin ratio values among different laboratories, clinical research centres and between different runs at the same laboratory is not possible. In an attempt to standardise interpretation of the anticoagulant effect using the prothrombin ratio, the concept of the International Normalised Ratio (INR) was introduced. The INR is defined as the prothrombin-time ratio raised to the power of the International Sensitivity Index (ISI). The ISI is a thromboplastin reagent-specific value that calibrates a given reagent with a standard reagent established by
the World Health Organization, which, by definition, has an ISI of 1.0. The less sensitive the thromboplastin reagent the higher the ISI value that is assigned to it. The ISI for any given thromboplastin reagent used in Prothrombin Time assays is supplied by the manufacturer. The expression of anticoagulant status using the concept of INR provides a means by which the variability in thromboplastin reagent sensitivities can be corrected. The INR is therefore a universally applicable standard for measuring anticoagulant therapy.

The most common adverse effect of warfarin is haemorrhage (Table 1.2). Brigden (1995) found on an overview of 25 studies of warfarin that the average annual frequencies of fatal, major and minor bleeding were 0.6%, 3% and 9.6% respectively. Regular monitoring of the patient’s level of anticoagulation was mandatory. Within the region of interest to oral surgeons, spontaneous airway-threatening bleeding has been reported in the sublingual space (Cohen and Warman, 1989) and the retropharyngeal space (Owens et al., 1975).

### Table 1.2 Factors that increase the risk of bleeding complications with oral anticoagulant therapy (from Brigden, 1995)

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Intense therapy (especially an INR &gt; 4.0)</td>
</tr>
<tr>
<td>Instability of therapeutic control due to:</td>
</tr>
<tr>
<td>Non-compliance</td>
</tr>
<tr>
<td>Drug interactions</td>
</tr>
<tr>
<td>Changes in dietary vitamin K intake</td>
</tr>
<tr>
<td>Concomitant acetylsalicylic acid or non-steroidal anti-inflammatory therapy</td>
</tr>
<tr>
<td>Newly initiated therapy</td>
</tr>
<tr>
<td>History of bleeding</td>
</tr>
<tr>
<td>Presence of serious co-morbid condition (uraemia, congestive heart failure, myocardial infarction, cerebrovascular vascular accident, atrial fibrilation, liver disease, severe anaemia)</td>
</tr>
<tr>
<td>Age greater than 75</td>
</tr>
</tbody>
</table>

Although there are a number of drugs that have the potential to interact with warfarin, there are several regularly prescribed by dentists that should be mentioned. Aspirin and other non-steroidal anti-inflammatory drugs inhibit platelet function, prolong bleeding time and therefore have the potential to increase the risk of warfarin associated bleeding. Metronidazole inhibits the metabolic clearance of the S-isomer of warfarin, thereby increasing the plasma levels and potentiating its anticoagulant effect. Second and third generation
cephalosporins augment the anticoagulant effect by inhibiting the cyclic inter-conversion of Vitamin K. Erythromycin also potentiates the anticoagulant effect of warfarin. Wood and Deedle (1993) reported several cases of antibiotics interacting with warfarin to produce a high INR and subsequent bleeding. Brandrowsky et al. (1996) reported a case of high INR associated with bleeding problems in an oral surgery patient who was taking amoxycillin.

1.4 The fibrinolytic system

Fibrinolysis is defined as the degradation of fibrin by the enzyme plasmin. A fundamental phase in the activation process is the conversion of the zymogen plasminogen to the active enzyme plasmin. Activation of plasminogen is related to 2 different pathways. The extrinsic fibrinolytic system is dependent on activators bound in the tissues and the intrinsic fibrinolytic dependent on humoral precursors circulating in the blood (Figure 1.4.1).

Figure 1.4.1 A simplified scheme of the activation pathways of fibrinolysis (from Sindet-Pedersen, 1991)
Tissue-type plasminogen activator (t-PA) is the main activator of the extrinsic fibrinolytic system whereby plasminogen is converted to plasmin and this leads to degradation of fibrin. The amount of t-PA incorporated during clotting, together with the amount of plasminogen bound to fibrin, determines the rapidity with which the clot is resolved. In the circulation the majority of t-PA is bound to inhibitors (α2-antiplasmin, C1-inactivator, α1-antitrypsin, plasminogen activator inhibitor). During resting conditions, the inhibitor level in the blood is usually higher than the t-PA level. The amount of t-PA in the blood can be acutely increased by stimuli such as exercise, stress, trauma and surgery when it is released from stores. Recently t-PA has been demonstrated in growth media from cultured epithelial cells from oral mucosa (Sindet-Pedersen et al., 1990). Activation of plasminogen by t-PA is enhanced by fibrin which forms a matrix on which t-PA and plasminogen are brought into contact enabling conformational changes, which favour activation. This allows generation of plasmin at the site of fibrin formation where it is relatively protected from the inhibitory effects of the inhibitors α2 antiplasmin. A high local concentration of plasmin is required for optimal fibrinolysis.

Activation of fibrinolysis is characterised by the conversion of zymogen precursors to activators. Two pathways are involved in the intrinsic system. One is dependent on factor XII. Factor XIIa converts prekallikrein to kallikrein to convert a plasminogen proactivator into a plasminogen activator. The other pathway is factor XII-independent. Activation involves conversion of plasma prourokinase to urokinase. The intrinsic system can be activated by plasmin generated directly from the conversion of plasminogen by tPA. This is the more important of the mechanisms for activation of fibrinolysis.

The major physiologic inhibitors of fibrinolysis are α2-antiplasmin, histidine-rich glycoprotein and plasminogen activator inhibitor. α2-antiplasmin is a fast inhibitor reacting stochiometrically 1:1 with active sites of plasmin to form an inactive complex. It also participates in the regulation of fibrinolysis by interfering with the absorption of plasminogen to fibrin. Induced by factor XIIIa, it is incorporated into fibrin during the cross-linking of fibrin, maintaining its anti-plasmin activity. Histidine-rich glycoprotein is a plasma protein that binds to the lysine binding sites of plasminogen and may be regarded as the physiologic counterpart to the antifibrinolytic solution, tranexamic acid. By this mechanism it may reduce the amount of free plasminogen in the plasma by 50%. Plasminogen activator inhibitor is able to inactivate both tissue plasminogen activator and urokinase. It is incorporated into the clot matrix in its active form and constitutes a significant regulating factor of fibrinolysis.
1.4.1 Pharmacological inhibitors of fibrinolysis

Tranexamic acid, (trans-4-aminomethylcyclohexanecarboxylic acid, AMCA) is an antifibrinolytic drug whose mode of action depends on binding to the lysine-binding sites of plasminogen thus blocking the binding of plasminogen to fibrin in a manner similar to histidine-rich glycoprotein. Sindet-Pedersen (1987) found that after systemic administration of 1 gram tranexamic acid taken orally, the mean plasma concentration of tranexamic acid reached its maximum after 120 minutes at approximately 7ug/ml. However, it is important to note that systemic tranexamic acid was not redistributed to saliva at detectable levels.

After a mouthrinse with 10 ml of 5% aqueous tranexamic acid solution for 2 minutes, there was minimal systemic absorption as plasma concentrations remained below 2 ug/ml. The concentrations of tranexamic acid in saliva were initially very high (after 30 minutes the mean concentration was above 200ug/ml) decreasing to approximately 7 ug/ml of saliva after 120 minutes and to approximately 0.4 ug/ml of saliva after 480 minutes. At a tissue concentration of 10 ug/ml of tranexamic acid, tissue plasminogen activity is reduced by 80% and by 98% at tissue concentrations of 100 ug/ml. An inhibition of 80% is considered sufficient to suppress fibrinolytic activity in tissue. Thus, tranexamic acid administered topically as a mouthrinse remained in saliva at a therapeutic level for more than 2 hours and inhibited fibrinolysis.

Because there is very little systemic absorption of tranexamic acid when it is used as a mouthrinse, systemic side effects of the drug such as nausea, diarrhoea and abdominal discomfort are avoided.

1.4.2 Surgery and fibrinolysis

Following surgery there is an initial increase in fibrinolytic activity due to release of t-PA from the endothelium of vessels. Following this initial activation fibrinolytic activity is depressed due to an increased release of plasminogen activator inhibitor that falls to its minimum levels 24 hours after surgery. The systemic effects of dentoalveolar surgery on the fibrinolytic activity of blood are insignificant when either general anaesthesia or local anaesthesia without vasoconstrictor are employed. However, there is an important increase in fibrinolytic activity within the blood of patients who receive local anaesthetic that contains a
vasoconstrictor. This is due to release of t-PA either through the presence of adrenoreceptors or through a central pathway.

The fibrinolytic activity of the saliva is initially reduced after oral surgery due to the inhibitors in the blood and the wound exudate. When bleeding and exudation cease the fibrinolytic activity of the saliva gradually increases. There is suggestive evidence that local fibrinolysis is initiated at the time of oral surgery by plasminogen and plasminogen activators when fibrin is present in the oral cavity. The degree of local fibrinolysis increases with time after surgery as inhibitors of fibrinolysis, originating from blood and wound exudate, disappear from saliva.

1.5 Traditional management of patients on oral anticoagulants

Until recently, clinicians have had 4 strategies for managing a patient on oral anticoagulants.

1.5.1 Discontinuation of anticoagulant therapy

Ziffer et al. (1957) recommended stopping warfarin therapy for 4 or 5 days prior to oral surgery. This allowed sufficient time for the effects of the anticoagulant therapy to be eliminated. Following surgery anticoagulant therapy was restarted. The advantage of this approach is that at the moment of intervention haemostasis is completely normal and the potential for blood loss is minimised. However, there are a number of disadvantages. Delay in treatment until the anticoagulation activity is completely corrected is unavoidable. There is an increased risk of a thromboembolic event developing in the period of interruption of the anticoagulation. Inconvenience and discomfort occur due to the need for repeated blood sampling to monitor the INR as the anticoagulant level is reduced and later reinstated. Current opinion is that complete stoppage of warfarin therapy is unwarranted (Herman et al., 1997).

1.5.2 Minimum acceptable anticoagulant level protocol

This involves a dose reduction regimen of the anticoagulant therapy before treating the patient. The INR is monitored closely until it falls to a lower, more acceptable range for surgery. The range most commonly considered safe for dental treatment by those who recommend this regimen is an INR of 1.5 to 2.0, although an INR range of 1.5 - 2.5 has been suggested (Mulligan and Weitzel, 1988). More recently, Beine and Koehler (1996) said that
surgery could be carried out up to an INR of 4.0 but made recommendations based on the extent of surgery. Where minimal bleeding is expected, as in a minor surgical procedure, they recommended no modification to the INR provided it was below 4.0 with the use of local measures. Where a moderate degree of bleeding is anticipated, as in multiple extractions or the removal of wisdom teeth, then consideration should be given to reducing the INR and using local measures. Where significant bleeding is expected, as in a full mouth clearance, the INR should be reduced below 3.0 and local measures used.

Warfarin has an elimination half-life of 36 hours due to its slow rate of biotransformation and high amount of plasma protein binding. It takes at least 24 hours following warfarin withdrawal before any change in INR is evident. It has been recommended that a 2 day withholding period is likely to achieve an acceptable coagulation level for most surgical procedures (Mulligan 1987). However, Devani et al. (1998) found the preoperative reduction of the INR is often unpredictable and that its reduction on stopping warfarin for 2 days bears little relationship to the original INR at the initial assessment. In a sample of 32 patients, after stopping warfarin for 2 days, the INR dropped below 1.5 in 44% of patients but in 6% the INR was still above 2.0. These patients needed to discontinue their warfarin for a further day before it was within range of INR 1.5 to 2.0. Thus, after 2 days only 50% of patients had reached their target level of anticoagulation. Using this method the anticoagulant needs to be stopped for an unpredictable period between 1 and 3 days in order to get the INR within the range 1.5-2.0. This period varies between patients irrespective of the initial assessment INR.

Mulligan (1987) indicated that it takes 3 to 6 days to re-establish therapeutic anticoagulation levels following surgery. The advantage of this method is that it allows the removal of teeth with relatively small risk of haemorrhage. The disadvantages are that there is a delay in treatment of several days while the INR is reduced. During this time the patient may be in pain or have infection, together with the inconvenience of several visits to monitor the INR and further visits while it is again re-established at a therapeutic level. There is an increased risk of thromboembolism during the prolonged ‘window’ period of 4-6 days when the INR is below the effective therapeutic range. This is especially important in the high risk patients such as those with prosthetic heart valves. It has also been suggested that a rebound hypercoagulable state may occur on cessation of warfarin anticoagulation, possibly due to increased thrombin activity. This has not, however, been confirmed (Mulligan and Weitzel, 1988). Wahl and Howell (1996) found that 26% of physicians were opposed to altering
warfarin levels for any oral surgical procedures.

1.5.3 Heparin substitution protocol

Roser and Rosenbloom (1975) detailed a protocol for managing patients who required extensive dental surgery or who represented a definite medical risk including those with a history of prosthetic valve replacement. This involves a specific routine after hospital admission of stopping the oral anticoagulant, heparin substitution, stopping heparin 8 hours pre surgery, carrying out the surgery, restarting heparin and oral anticoagulant therapy 4-6 hours post extraction and maintaining heparin until the oral anticoagulant levels are again within the therapeutic range. The advantage of this technique is that it allows a good fibrin clot to form that is less susceptible to fibrinolysis and narrows the window of risk of thromboembolism due to stopping the anticoagulant from several days to 12-24 hours. Its disadvantage is that it involves hospitalisation for a minimum of 3-4 days and often 6-7 days. This is expensive both for the hospital system and the patient who is unable to carry out normal activities while in hospital.

1.5.4 No change in anticoagulant level protocol

This leaves the anticoagulant dose unaltered and relies on local haemostatic techniques. The advantages of this technique are that it is simple and the development of systemic thromboembolic events is unlikely. Results of studies (Waldrep and McKelrey, 1968; Bailey and Fordyce, 1983) have shown that the principal complication is postoperative oozing. This is usually controllable by local measures. Advocates of this method (Bailey and Fordyce, 1983) studied the complications of dental extractions in 25 consecutive patients on warfarin referred from an anticoagulant clinic who were compared with a control group matched for age and number of extractions. They found that there was no significant difference in the time taken to achieve immediate haemostasis in the 2 groups. However, the anticoagulated group had a significantly greater tendency to rebleed 1 to 5 days post-operatively than the control group. All episodes of late bleeding were controlled using local measures. They concluded that it appeared clinically unnecessary as well as theoretically dangerous, to stop anticoagulant therapy with its small but potentially serious risk of a systemic thromboembolic episode. They recommended that it was a sensible prophylactic measure to suture sockets following extractions.
1.6 Local measures used to promote haemostasis

Local haemostasis-promoting materials and techniques are widely used if patients have dental extractions with unaltered anticoagulation. Traditional local methods to reduce post surgical bleeding in warfarinised patients have included:

a) Suturing the socket;
b) Use of a glucosic polymer based sterile knitted fabric prepared by the controlled oxidation of regenerated cellulose. Its local haemostatic action depends on the binding of haemoglobin to oxycellulose, allowing the dressing to expand into a gelatinous mass, which in turn acts both as a scaffold for clot formation and a clot stabiliser. Its low pH of 2.8 is also thought to potentiate local vasoconstriction. The material is completely absorbable and does not interfere with healing or bone regeneration;
c) Use of a gelatin based sponge, which is able to hold up to 45 times its weight in coagulating blood and acts as a framework until a stable clot has been formed;
d) Application of topical bovine thrombin is particularly useful in dealing with persistent primary haemorrhage. A piece of gelatin sponge is soaked in the preparation and packed into the bleeding socket. Thrombin bypasses the coagulation cascade by converting endogenous fibrinogen to fibrin;
e) Use of microfibrillar collagen.

More recently, various local haemostatic dressings and tissue adhesives have been used to control bleeding after dental extractions in warfarinised patients. These include:

a) A composite biological tissue adhesive, Beriplast (Behringwerke, Marburg, West Germany) which mimics the final phase of blood clotting. Beriplast contains thrombin, which causes fibrinogen to coagulate; factor XIII, as an adjuvant, provides for the cross linkage and stabilisation of the fibrin clot and aprotinin, an antiprotease prevents early disruption of the clot by fibrinolysis. This is combined with a collagen fleece. Martinowitz (1990) has described the technique;
b) Fibrin glue and human fibrinogen concentrate. These coagulation protein-based dressings induce clot formation by mimicking the final stages in the normal clotting mechanism;
c) Absorbable collagen paste (ACP) and calcium alginate.
1.6 The use of topical tranexamic acid mouthrinse to prevent postextraction bleeding

From the above review, the “traditional methods” of managing dental patients who are on oral anticoagulants and require tooth extraction have significant disadvantages. A safe, effective method is required which causes minimal inconvenience to patients in terms of delay in treatment, management requirements and number of visits. A technique that broadly meets these requirements was first described by Sindet-Pedersen et al. (1989) and subsequently verified by Ramstrom et al. (1993). This technique uses the antifibrinolytic agent, tranexamic acid as a mouth rinse to prevent postextraction bleeding. Initially it is used to irrigate the wound following extraction and then as a mouthrinse 6 hourly for 7 days. Used in this way tranexamic acid syrup acts locally to prevent fibrinolysis of the blood clot in the tooth socket and minimise postextraction bleeding.

The beneficial effect of antifibrinolytic treatment can be explained by the presence of activators of fibrinolysis in saliva. Whole saliva represents a mixture of glandular saliva (parotid, submandibular and sublingual saliva, as well as secretions from the minor salivary glands), crevicular gingival fluid (in dentate individuals), and cellular elements (epithelial cells, leukocytes and bacteria) all of which may influence fibrinolysis in the oral cavity. Human saliva contains plasminogen, the physiological substrate for activators. It has been demonstrated (Sindet-Pedersen et al., 1987) that most of the plasminogen activators in whole saliva are bound to epithelial cells in the sediment. It has been concluded that oral epithelial cells have the potential to produce and release significant amounts of plasminogen activators. The plasminogen activator in whole saliva is t-PA (Sindet-Pedersen et al., 1987). Trace amounts of t-PA have been found in submandibular and parotid saliva. Gingival crevicular fluid may contribute plasminogen activators to whole saliva.

Haemostasis has been defined as a balance between fibrin deposition and fibrin dissolution. Patients who are on oral anticoagulants have impaired fibrin formation and are considered to be more susceptible to normal fibrinolysis. This is believed to be the major cause of postextraction bleeding in these patients. The biological components available for haemostasis in the oral cavity are essentially the same as elsewhere in the body but the oral cavity differs from the situation in other tissues by the presence of the external environment. This external environment contains plasminogen and plasminogen activators and, in the presence of fibrin,
oral fibrinolysis is triggered. This results from the fact that fibrin deposited in the oral cavity can be resolved by both the activation of blood fibrinolysis as well as by fibrinogen activators in the oral environment. One of the most significant pathogenic factors for the development of bleeding after oral surgery is the activation of fibrinolysis in the oral cavity. Topical tranexamic acid mouthrinse prevents fibrin degradation and thus prevents bleeding.

A summary of the technique proposed by Sindet Pedersen et al. (1989) is as follows. When the patient who is on oral anticoagulants and who requires tooth removal presents for treatment, the INR is tested to check that it is within the therapeutic range. If it is within this range, the tooth is removed and the wound irrigated with 5% tranexamic acid solution and then closed by suture. The patient is instructed to rinse the wound with 10ml of 5% tranexamic acid solution for 2 minutes, 4 times a day, for 7 days. The advantages of this method are its simplicity and effectiveness with lack of serious side effects. The incidence of postextraction bleeding is greatly reduced. There is minimum delay between presenting and treatment, with a minimum number of appointments and inconvenience. Because the INR is maintained within the therapeutic range the patient is not placed at an increased risk of thromboembolism. This satisfies physicians who are reluctant to alter the INR to allow extractions to proceed. The principal disadvantage of this technique is that it relies on patient compliance to use the tranexamic acid mouth rinse 4 times a day for 7 days.

1.8 Literature Review

Wahl (1998) carried out a review of the available literature on dental surgery in anticoagulated patients. He reviewed 26 case reports on 774 patients who underwent 2014 dental surgical procedures, including 1964 extractions while receiving continual oral anticoagulant therapy. He observed that although some patients had minor oozing managed with local measures, more than 98% of patients receiving continual anticoagulation had no serious bleeding problems after dental surgery. Only 12 patients (<2%) had bleeding problems that required more than local measures. On close examination of these, none made a good case for withdrawal of warfarin for dental surgery. A second review of 16 case reports from 493 patients involving 542 procedures was carried out on patients who had had continual anticoagulation withdrawn specifically for dental procedures. Five patients (1%) had serious embolic complications, including 4 deaths. Wahl (1998) concluded that it is inappropriate to interrupt warfarin therapy for dental surgery. Although there is a theoretical risk of
haemorrhage in patients at therapeutic levels of anticoagulation, the risk is minimal and is usually easily treated by local measures. The risk of bleeding is greatly outweighed by the risk and morbidity of thromboembolism after withdrawal of anticoagulant therapy.

Following the initial description of the technique by Sindet Pedersen et al. (1989) and verification study by Ramstrom et al. (1993), a number of subsequent studies have supported this technique. Street and Leung (1990) reported they had used the technique without problems on 11 of 12 patients. The twelfth patient who had an infected impacted wisdom tooth removed and had not been compliant with her medication, had a bleed 7 days after her procedure sufficient to warrant hospital admission for observation but not transfusion.

Borea et al. (1993) used this approach in a double blind randomised study. Fifteen members of the study group used tranexamic acid mouthrinse postoperatively and maintained oral anticoagulation at therapeutic levels while the control group reduced their level of oral anticoagulation. There was no significant difference between the 2 groups in the incidence of bleeding after oral surgery. They concluded that oral anticoagulant therapy does not need to be withdrawn before oral surgery provided that local antifibrinolytic therapy was instituted.

Souto et al. (1996) reported that they had carried out oral surgery on over 100 patients who had maintained the level of their oral anticoagulants and used tranexamic acid mouth rinses post operatively. There were no major bleeding complications.

Gaspar et al. (1997) evaluated 47 patients receiving anticoagulant therapy. The 15 members who formed the control group had their surgery carried out after oral anticoagulant medication was reduced. The 32 patients in the test group had surgery without a change in anticoagulant therapy but used tranexamic acid mouthrinse postoperatively. There was no significant difference in the incidence of bleeding between the 2 groups.

Devani et al. (1998) removed teeth in 65 patients on oral anticoagulants. The 32 members who formed the control group had their warfarin reduced for 2 or 3 days while the 33 members of the study group had their INR maintained at therapeutic levels. No immediate postoperative bleeding was reported in either group and only 1 patient from each group had mild delayed haemorrhage. This was easily controlled by local measures.
There has only been 1 report of a major bleed following this protocol. Bandrowsky et al. (1996) reported the case of a patient with a pre-extraction INR of 3.5 who had 20 teeth removed and was prescribed amoxycillin. On the fourth day after tooth removal, the patient who bled and required hospital admission, had an INR that had risen to 9.1. The bleed was thought to be due to the grossly elevated INR that had occurred from the interaction of warfarin with amoxycillin. This adverse event cannot be construed as a primary failure of tranexamic acid related inhibition of fibrinolysis.

Herman et al. (1997) wrote, “In certain situations, primarily those dealing with complex oral surgical procedures, there are not sufficient reports to make generalisations about patient treatment. There is a clear need for focused research in this area. It is inappropriate to group all types of dental treatment into a single category”. Fordyce and Bailey (1999) commented, “What is needed now is a study with large numbers of patients, including adequate numbers with an INR greater than 3.0 before it can be stated with confidence that adjustment to the dose of warfarin is unnecessary provided that the INR is within the therapeutic range.”

Although Purcell (1997) discussed the management of the anticoagulated patient and described the use of tranexamic acid, to date no original work has been published in this area in New Zealand. It is important verify this technique in the New Zealand setting and to identify potential risk factors that may increase the likelihood of bleeding in this group of patients so they are better managed.

1.8 Study Aim

The aim of this study, was, in a sample of 100 patients on warfarin who had teeth removed while being maintained at therapeutic INR and who used tranexamic acid mouthrinses post extraction to inhibit fibrinolysis, to:

a) Verify that this technique is a safe, simple, effective and acceptable method of managing these patients;

b) Identify risk factors that may have potentiated the likelihood of bleeding.
2.1 Ethical considerations

Approval for this study was sought from and approved by the Auckland Ethics Committee. The key ethical considerations for this study were those of informed consent and confidentiality.

All subjects involved in this study were fully informed of the consequences of their participation in the study. Alternative options were explained and it was emphasised that refusal to participate in, or withdrawal from the study, would not penalise their management. A copy of the study information sheet (Appendix A) was given to the patient at their initial appointment to take home and study. If required, the patient was given additional time to consider treatment options. Consent was freely given by signing the study consent form (Appendix B).

Confidentiality was maintained by entering all electronic data under a unique identification code available only to the researcher, ensuring that no person could identify individual subjects.

2.2 Sample recruitment

People recruited into this study presented from 3 principle sources. First, patients referred by other hospital departments. The dental department at Greenlane Hospital has a close working relationship with the both the cardiac and haematology departments who were a major source of referrals. All cardiology inpatients receive a dental review prior to cardiac surgery. Many of these patients require the removal of a number of teeth. The haematology department has a clinic that monitors patients who have had recent deep vein thrombosis or pulmonary embolism. Patients from this clinic are referred to the dental department for extractions. A second group of patients were referred by general medical or general dental practitioners for specialist management of dental extractions due to warfarin use. Finally, there was a significant group of patients on warfarin who presented to the dental department requiring tooth extraction for relief of severe pain.
Between October 1997 and June 1999 100 cases (patient episodes) were recruited to this study. This involved 96 patients, 4 of whom were recruited twice for a separate, independent series of extractions.

2.2.1 Eligible Patients

Eligible patients were those:

a) Who were on oral anticoagulants and required removal of teeth;
b) With an INR between 1.9 and 4.0 on the day of surgery;
c) Aged 18 years or older.

2.2.2 Exclusions

Patients were excluded if:

a) They failed to give informed consent;
b) Their medical practitioner advised them that they should not be managed this way;
c) They had taken acetylsalicylic acid (aspirin) or nonsteroidal anti-inflammatory drugs (NSAIDS) within 7 days of surgery unless surgery was urgent and their bleeding time was less than eight minutes;
d) They had a known bleeding disorder or liver failure;
e) They had an INR less than 1.9 or an INR greater than 4.0;
f) They had an APTT greater than 55 seconds or a bleeding time greater than 8 minutes, unless cleared by advice from a haematologist;
g) They were unable to follow instructions, either because of language difficulties or because of intellectual or physical impairment.

2.3 Patient management

2.3.1 Standardisation of patient management

All patients in this study were managed surgically by the researcher. This allowed uniform standardised management techniques throughout the study.
2.3.2 Management of the patient at the initial contact appointment

Where possible, all potential patients were referred directly to the researcher. Some patients were initially seen by another clinician with subsequent referral to the researcher. Assessment of the patient's presenting problem was carried out in the normal manner, with a history, examination and special tests as indicated. A diagnosis and a provisional treatment plan were made. Patients who met the eligibility criteria for inclusion into the study were given an explanation of the study and an information sheet (Appendix A) about the dental management of warfarin patients, which they could take home and read. They were invited to join the study. Most patients were recruited at this initial appointment. A few patients wanted time to talk to their family, their medical practitioner and to consider all the facts. The researcher phoned these patients 3 days later and any concerns were discussed. Once the patient had agreed to join the study an appointment was made for the surgery and a letter (Appendix C) was sent to the patient's medical practitioner explaining how the patient would be managed. If the patient was on either an aspirin containing drug or a non-steroidal anti-inflammatory drug (NSAID) the patient's medical practitioner was asked for permission to stop this medication for 7 days prior to surgery and for 7 days after surgery. The patient was instructed accordingly.

Patients who declined to join the study had an appointment made for surgery approximately a week later. The patient's doctor was contacted and asked to reduce the level of anticoagulation below an INR of 2.0 on the day of surgery as this had been the previous practice in this unit.

2.3.3 Management of the patient on the day of surgery (Figure 2.1)

The patient was managed either at Auckland Hospital or Greenlane Hospital. Prior to surgery the patient attended the dental department and any concerns were discussed. Their general medical condition was assessed and the proposed treatment plan confirmed. The patient was then taken to the Haematology Laboratory to have their bleeding time tested. Blood was collected for their INR and APTT. The results of these tests were available within an hour. If the INR was in the range 1.9 – 4.0 the patient was admitted to the study and asked to sign the consent form. If the INR was below 1.9 the patient was managed conventionally using local measures without entering the study and without using tranexamic
Figure 2.1  Patient management on the day of surgery under local anaesthetic

Final Discussion, answer queries, consent.

Sent to Lab for INR, APTT, bleeding time.

INR > 4.0

Yes

Advertise physician to lower INR

Yes

Antibiotics administered

No

Requires prophylactic antibiotics

ANTIBIOTICS ADMINISTERED

INR < 2.0

Yes

Manage as a "normal" patient

No

Enter tranexamic acid study

Remove teeth in groups of 1-3 teeth as atraumatically as possible

Irrigate socket with tranexamic acid solution

Use firm finger pressure to compress the sockets with a swab soaked in tranexamic acid

Carefully suture sockets with 3 O black silk with at least two individual sutures per socket

All teeth planned for extraction have been removed

Yes

Pressure applied to all sockets with swabs socket in tranexamic acid for 10 minutes

Remove swab

Observe for one minute

Bleeding stopped

No

Identify bleeding socket

Insert Suture

Pressure applied to socket with swab soaked in tranexamic acid for 10 minutes

Bleeding stopped

No

Remove sutures from bleeding sockets, identify bleeding point, apply Gelfoam soaked in thrombostat, resuture

Bleeding stopped

Pressure applied to socket with swab soaked in tranexamic acid for 20 minutes

Patient discharged with post operative instructions and Tranexamic acid mouth rinse

Contact haematology registrar and consider administration of fresh frozen plasma and admission to haematology ward.
acid mouthrinse. If the INR was greater than 4.0 the patient’s medical practitioner was advised and the patient booked for another appointment for surgery after the INR had been lowered back into the therapeutic range. Patients with cardiac condition requiring prophylactic antibiotic cover were given intravenous antibiotics according to New Zealand Heart Foundation Guidelines (Appendix D).

Uncomplicated surgery was carried out under local anaesthetic in the dental chair using 2% lignocaine with 1:80,000 adrenalin. Uncomplicated surgery on severely medically compromised patients was carried out in an operating theatre where the patients were monitored by an anaesthetist. In these cases local anaesthesia, 2% lignocaine with 1:80,000 adrenaline, was used with or without sedation. More extensive procedures were carried out in an operating theatre under general anaesthesia supplemented with the use of local anaesthetic, 0.5% Bupivacaine with 1:200,000 adrenaline. Local anaesthetic was administered following the standard dental protocol. Mandibular teeth were anaesthetised using an inferior dental block and buccal infiltration. Maxillary teeth were anaesthetised using buccal and palatal infiltration.

Before starting surgery, the gingival pocket around all teeth being removed was probed, using a World Health Organisation periodontal probe, to measure pocket depth and bleeding (discussed page 29).

The teeth were removed using either forceps and/or elevators. If required, a mucoperiosteal flap was raised and bone removed by bur with saline irritation and the tooth sectioned.

Following delivery of the tooth, the wound was thoroughly irrigated with 10% tranexamic acid solution, care being taken not to suck this out of the socket. The socket wall was compressed using finger pressure over a swab soaked in tranexamic acid solution. The wound was then closed using 3 ‘0’ black silk suture. Generally at least 2 sutures were placed per tooth socket. Where multiple extractions were being carried out, 2 or 3 teeth were removed at a time before irrigating and suturing sockets. At the completion of surgery, the patient was asked to bite on a pressure pad soaked in tranexamic acid solution. After 10 minutes the pack was removed and the wound observed. If bleeding had stopped the patient was discharged with their home-care pack of tranexamic acid mouthrinse and post-operative instructions.
If bleeding had not stopped, the point of bleeding was identified and oxidised regenerated cellulose was placed into the wound at this point. The patient was then asked to bite on a pressure pad soaked in tranexamic acid solution. After 10 minutes the pack was removed and the wound observed. If bleeding had stopped the patient was discharged with their home-care pack of tranexamic acid mouthrinse and post-operative instructions.

If bleeding had not stopped, the point of bleeding was identified. The sutures at that point were removed and the local area around the bleeding site was infiltrated with local anaesthetic containing a vasoconstrictor. The wound was irrigated with 10% tranexamic acid syrup and oxidised regenerated cellulose and/or gelatin sponge soaked in bovine thrombin solution inserted into the base of the oozing socket. The socket was sutured with silk sutures and the patient asked to bite on a pressure pad soaked in tranexamic acid solution. After 20 minutes the pack was removed and the wound observed. If bleeding had stopped the patient was discharged with their home-care pack of tranexamic acid mouthrinse and post-operative instructions.

If the patient continued to bleed, this was recorded. Assistance was then sought from the Haematology Department at Auckland Hospital. Consideration was given to an infusion of fresh frozen plasma or vitamin K. All details of this management and outcome were recorded.

The patient was discharged with the following items:

a) 150ml, 10% tranexamic acid syrup plus 5 ml measure;
b) Post-operative instructions/data collection sheet (Appendix E);
c) Pressure swabs;
d) Laboratory request form for post-extraction INR on day 4;
e) Postextraction antibiotics (if required).

The patient was instructed to use 5ml of 10% tranexamic acid solution as a mouth rinse 4 times a day, ie, on waking in the morning, at midday, at 6 o’clock in the evening and just before going to bed in the evening. The solution was taken into the mouth and gently rinsed over the site of surgery for a minimum of 2 minutes by the clock. The solution was then spat out. The patient recorded the time this mouthrinse was carried out on the data-collection sheet (Appendix E). Apart from using the tranexamic acid mouthrinse, the patient was instructed not to rinse their mouth on the day of surgery. Only soft food was to be eaten during the first 2
days following surgery. No aspirin containing drugs or non-steroidal anti-inflammatory
drugs were permitted. On the fourth day after surgery the patient was instructed to go to their
nearest blood collection service for INR testing. If bleeding occurred the patient was
instructed to identify the point of bleeding, make a gauze ball, place it over the bleeding
socket and firmly bite on it for 20 minutes by the clock before removing the pressure packs.
This incident was recorded on the patient data collection sheet. If after 20 minutes the
bleeding had not been controlled by pressure then the patient was instructed to contact the
researcher who would manage the bleed at his dental surgery.

2.3.4 Management of postextraction bleeding (Figure 2.2)

Any patient presenting to the researcher’s dental surgery with postextraction bleeding was
asked to bring in their tranexamic acid mouthrinse bottle and their data collection sheet. The
patient was seated in a dental chair and any excess blood clot in the mouth was removed. The
bleeding point was identified. Local anaesthetic was administered to this area. A gauze swab
soaked in tranexamic acid solution was placed over the bleeding site. The patient was
instructed to bite on this. A venous blood sample was collected and sent to the haematology
laboratory for an INR. The history of the presenting bleed was reviewed. The contents of the
tranexamic acid mouthrinse bottle were measured and the data sheet reviewed to determine
the degree of compliance to mouthrinse use. After 20 minutes the swab was removed and the
wound observed. If the bleeding had stopped the sutures were reviewed and if necessary extra
sutures placed. If required, oxidised regenerated cellulose was placed in the wound. A gauze
swab soaked in tranexamic acid solution was placed over the bleeding site and the patient was
instructed to bite on this. After 20 minutes the swab was removed and the area observed for
two minutes. If bleeding had stopped the patient was discharged and instructed to continue
using the tranexamic acid mouthrinse and avoid traumatising the area.

If the wound continued to ooze, the sutures were removed and the bleeding point identified.
gelatin sponge soaked in topical bovine thrombin was applied to the area. The socket was then
sutured and pressure applied to the area with a pressure pack soaked in tranexamic acid for 20
minutes. The swab was then removed and the area observed for 2 minutes. If bleeding had
stopped the patient was discharged and instructed to continue using the tranexamic acid
mouthrinse and avoid traumatising the area.
Figure 2.2 Management of postextraction bleeding

- **Postextraction bleed**
  - **Working hours**
    - Contact Dental Department Greenlane Hospital
  - **After hours**
    - Patient contacts researcher
      - **Reply**
        - Patient contacts Emergency Department (ED)
          - ED contacts Dental House Surgeon on call
      - **No reply**
        - Patient contacts Emergency Department (ED)
          - ED contacts Dental House Surgeon on call
  - Patient belongs to study
    - Contact researcher
  - Patient does not belong to study
    - Contact researcher
      - **Researcher contacted**
        - Researcher manages patient in his dental surgery
          - Patient re-examined
            - Bleeding history reviewed
            - Blood clot removed from mouth, bleeding point identified
            - Pressure swab soaked in tranexamic acid patient bites on this for 20 minutes
            - Blood taken for INR, volume of tranexamic acid in bottle recorded
          - **Bleeding continues**
            - Insert local anaesthetic
              - Remove existing suture
              - Irrigate wound with Tranexamic Acid
              - Insert either oxidised regenerated cellulose or gelatin
              - Sponge soaked in thrombostat.
              - Black silk suture
              - Bite on tranexamic acid soaked pad for 20 minutes
          - **Bleeding stops**
            - Observe further 20 minutes, no swab
              - No further bleeding
                - **DISCHARGE**
          - **Bleeding continues**
            - Local measures have failed
              - Contact haematology registrar
              - If appropriate, arrange admission
              - Consider alternative therapy
                - eg. Fresh frozen plasma, Vitamin K, DDAVP.
            - **Bleeding stops**
              - Observe further 20 minutes, no swab
                - No further bleeding
                  - **DISCHARGE**
If the patient continued bleeding the haematology service was consulted and consideration given to admitting the patient to hospital and treating with fresh frozen plasma and/or administering vitamin K.

The procedures carried out and their outcome was recorded.

2.3.5 Suture removal appointment

The suture removal appointment was scheduled 7 days after surgery. The patient was asked to return the data collection sheet together with the bottle of tranexamic acid mouthrinse, containing the remains of the mouthrinse. On the patient’s arrival in the surgery, a quick survey was made of the responses on the data collection sheet. The patient was asked about their use of the mouthrinse. Any problems or adverse effects associated with the mouthrinse were sought. Questions were asked about any bleeding that may have occurred, why it occurred and how it was managed. The sutures were removed and any swelling, bruising or limited opening noted. The patient was then discharged. The volume remaining in the bottle was measured and, knowing the volume that should have remained, the percent compliance of the bottle was calculated. The data collection sheet data was then reviewed in detail. The number of times the mouthrinse was used as entered on the sheet by the patient was divided by the number of times the mouthrinse should have been used, in order to calculate the percent compliance. This data was recorded.

If the patient failed to return the data collection sheet or bottle, the patient was asked whether or not they had had any bleeds so that this data could be collected. In such cases it was not possible to calculate the compliance from either the data sheet or the bottle.

2.4 Trial end point

The study was discontinued after 100 patient episodes were completed. For the individual patient episode, the end point was either 7 days after surgery or earlier if uncontrolled bleeding required systemic management in hospital.

Four levels of bleeding were recorded: No bleeding (normal haemostasis); bleeding controlled at home by the use of a pressure pack; bleeding not controlled at home but controlled in the
researcher’s dental surgery by local measures; bleeding not controlled by local measures but requiring hospital admission for systemic management. Bleeding controlled either at home by pressure or in the researcher’s dental surgery by local means were minor end points and although these events were recorded as such, the patient continued to be included in the trial. Systemic management of bleeding in hospital was a major end point and the event was recorded.

2.5 Compliance

This study relied heavily on patient compliance. Compliance was required in several ways. First, the patient had to follow standard postextraction instructions that helped to reduce the likelihood of bleeding. These included not rinsing on the day of extraction, having a soft diet for first 48 hours after surgery and not using aspirin or NSAID’s for relief of pain. Second, the patient was required to comply with the tranexamic acid mouthrinse regimen. To help improve compliance, time was spent with the patient prior to surgery explaining the reason for and importance of the tranexamic acid mouthrinse. This was reinforced with an information sheet given to the patient. Seven days was not a long time to seek compliance.

2.6 Data collection

On recruitment to the trial the patient was allocated a unique coded number under which all data was collected. This ensured that only the researcher could identify the patient. All data was confidential. Data was initially collected on the clinical data collection sheet (Appendix F) before being entered into a computer for analysis. This included information on possible factors influencing the initiation of bleeding and the management of any rebleeds. Information on patient compliance and attitude to the mouthrinse were also recorded.

2.6.1 Demographic details

Demographic details were collected concerning the patient’s age, sex, smoking history and their relevant medical history. Details of the patient’s medical history were gained either by directly from the patient or if required, from the patient's hospital notes and/or the patient’s general medical practitioner.
2.6.2 Details about the state of anticoagulation

The reason for being on anticoagulants and the length of time on anticoagulants was recorded.

Immediately prior to surgery the patient had their INR, APTT and bleeding time tested. The
INR was normally retested on the fourth day after the extractions, however because
community testing laboratories were closed on Saturdays, Sundays and public holidays,
ocasionally this test was carried out on either the third day or fifth day after the extractions.
A copy of this result was sent to the patient’s medical practitioner who adjusted the warfarin
level if required.

2.6.3 Details about the extraction

The teeth being removed were recorded.

Before starting surgery, the gingival crevice around each tooth being removed was probed,
using a World Health Organisation periodontal probe. The locations around the tooth probed
were, the mesio-buccal, buccal, disto-buccal, mesio-palatal, palatal and disto-palatal gingival
crevices. Light probing pressure was used. If a pocket depth equal to or greater than 5
millimetres (mm) was detected at one or more locations, this was recorded as a periodontal
pocket for that tooth. If bleeding was noted after probing at any one of the probed locations
around a tooth, this was recorded as a periodontal bleed for that tooth. Cardiac patients at risk
of infectious endocarditis, were probed immediately prior to commencement of surgery after
antibiotic prophylaxis had been given.

Whether or not a mucoperiosteal flap was raised and whether or not bone was removed was
recorded. Raising a flap was defined as raising the mucoperiosteum with a periosteal elevator.
Bone removal was defined as removal of bone by means of a handpiece and bur. An
exception to this definition occurred when the extracted tooth was attached to a significant
piece of buccal plate. The tooth could only be delivered after dissecting bone from
mucoperiosteum and delivering the tooth and attached bone in one piece. This was recorded
as both raising a flap and bone removal.

Antibiotic use was recorded for 3 separate time periods. Preoperative antibiotics were
antibiotics taken in the week before surgery, either as part of long term prophylaxis or as
treatment of an existing infection. Perioperative antibiotics were antibiotics administered at
the time of surgery either for infection or as prophylaxis against infectious endocarditis. Postoperative antibiotics were antibiotics taken following surgery.

Any complications that might have had a bearing on the outcome of the operation were recorded, eg. the creation of an oroantral fistula, interference with the inferior dental neurovascular bundle.

2.6.4 Details collected by the patient

After being discharged from surgery, patients were asked to take home and fill in a "data collection sheet" (Appendix E) to record the time they used their tranexamic acid mouthrinse and record any bleeding that occurred at home. Bleeding was defined as a bleed that required that they bite on a pressure swab to control. The mouth was divided into 6 sites. Top right (upper right molars and premolars), top front (upper canines and incisors), top left (upper left molars and premolars), bottom right (bottom right molars and premolars), bottom front (lower incisors and canines) and bottom left (lower left molars and premolars). The site of bleeding and the length of time the bleed lasted were recorded. The event which precipitated bleeding was recorded as either traumatic (if initiated by a specific event) or spontaneous (if not related to a specific event).

Tranexamic acid mouthrinse use was measured in 2 ways. First, the patient was asked to fill in a “data collection sheet” on which they recorded the time they used the mouthrinse. If they did not use the mouthrinse they were asked not to enter an imagined time. Second, the tranexamic acid syrup was given to the patient in a bottle containing a known volume, 150 millilitre (ml), together with a 5-ml measure. The patient was told to use 5 ml 4 times a day for 7 days and record the time of each dose on a time sheet. At the end of the trial on the eighth day when the sutures were removed the patient was required to bring with them the bottle of tranexamic acid plus the filled in data collection sheet. The residual contents of the bottle were measured and knowing the amount that should have been used, compliance was calculated. Both the results of the sheet and the bottle were recorded as a percent of the maximum expected compliance.

If the patient failed to return either the data collection sheet or bottle, they were asked whether or not they had any bleeds, where and when the bleeds occurred, so that this data could be recorded. In this situation it was not possible to calculate the compliance from either the data sheet or the bottle.
In order to judge mouthrinse acceptance patients were asked how they found using the mouthrinse and what problems they had with its use. These results were recorded.

2.6.5 Details concerning management of bleeding

On presentation at the researcher’s dental surgery for control of a bleed, the patient was asked how and why the bleeding restarted and whether or not the start of bleeding was related a particular event. The site, type of bleeding, presence of local infection, oedema or haematoma was noted. The INR was tested and recorded. The procedures carried out to achieve haemostasis were recorded.

2.7 Statistical analysis

Data entry and analysis were conducted using the statistical computer programme SPSS. Descriptive statistics were produced for the sample demographics, the haemostasis screen, post-operative bleeding profile, the teeth removed and mouthrinse compliance.

For statistical analysis, bleeding was defined as bleeding that was not controlled at home by pressure and as a result the patient had presented to the researcher’s dental surgery for control by local measures.

Bivariate analysis was carried out using the chi-square test for categorical data and the independent-samples $t$ test for continuous data. These tests were used to explore the data and select the potential variables for multivariate analysis.

Multivariate analysis was carried out using logistic regression. The goal of a logistic regression analysis is to find the best fitting, least complicated and yet biologically reasonable model to describe the relationship between an outcome (bleeding) and a set of predictor variables (Armitage and Colton, 1998). The advantage of multivariate analysis over bivariate analysis is that it controls for the interaction between the many variables in the model. In this study, four conceptual models were proposed.

The first conceptual model (Table 3.6.3) relates 6 predictor variables associated with patient episodes to the bleeding outcome of patient episodes.
The second conceptual model (Table 3.7.2) uses 6 predictor variables associated with individual teeth to the bleeding outcome of those teeth.

The third conceptual model (Table 3.7.3) uses 11 predictor variables associated with the removal of individual teeth. Five patient episode predictor variables used in the first model are related back to each individual tooth removed from that patient and these are analysed together with the 6 individual tooth predictor variables used in model 2.

The fourth conceptual model (Table 3.7.4) is a simplification of the third model. This was derived from the third model by carrying out a manual, backward, stepwise selection of variables based on the Wald statistic, removing and entering variables until the best fitting, least complicated, biologically reasonable model was reached.
3.1 Description of the sample

Ninety-six individual patients were recruited into this study between October 1997 and June 1999. Four patients were recruited twice, resulting in 100 separate series of extractions. There were 57 males and 43 females. The mean age was 57.1 years with a standard deviation of 15.6 years (range 23 – 87 years). The duration of warfarin prophylaxis varied between 1 month and 25 years. The median length of therapy was 2 years. The indications for anticoagulant prophylaxis are shown Table 3.1.1. The majority, (85%) were non-smokers. Twenty-four patients were on aspirin therapy at the time of enrolment. This was discontinued 7 days prior to the extraction and recommenced 1 week after the extractions.

Preoperative antibiotic therapy was involved in 12 of the 100 patient contacts for either intercurrent infection or long term prophylaxis. The antibiotics used were amoxycillin (5), penicillin (4), augmentin (2) and cephalosporin (1). Perioperative antibiotics were prescribed for 62 patient episodes (generally for infective endocarditis prophylaxis). Agents used were clindamycin (26), amoxycillin (18), amoxycillin and gentamicin (17) and vancomycin (1). Amoxycillin was necessary to control postoperative infection in 5 patient episodes.

Table 3.1.1 Indications for anticoagulant prophylaxis

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of patient episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical heart valves</td>
<td>51</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>17</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>10</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>10</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>7</td>
</tr>
<tr>
<td>Transient ischaemic attacks</td>
<td>2</td>
</tr>
<tr>
<td>Mitral incompetence</td>
<td>1</td>
</tr>
<tr>
<td>Left ventricular thrombus</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
3.2 Laboratory Haemostatic Investigations

The pre-extraction INR results are shown (Figure 3.2.1). The mean INR was 2.5 with a range from INR 1.9 to INR 3.7.

Figure 3.2.1 Histogram of pre-extraction INR

The pre-extraction APTT results are shown (Figure 3.2.2). The mean APTT was 41 seconds with a standard deviation of 7 seconds and a range of 26 to 65 seconds.

Figure 3.2.2 Histogram of pre-extraction APTT (seconds)
The mean bleeding time was 4.4 minutes with a standard deviation of 2.2 minutes and a range of 2.0 to 14.0 minutes as shown (Figure 3.2.3).

**Figure 3.2.3** Histogram of the pre-extraction bleeding time (minutes)

A postextraction INR was carried out on the fourth day after the extractions. The mean INR was 3.0 with a standard deviation of INR 0.9. The median was INR 2.7. Fifteen (16.1%) of results were outside the therapeutic range (INR 2.0 – 4.0). Eight (8.6%) were above INR 4.0 with a maximum of INR 6.7. Seven were below INR 2.0 with a minimum of INR 1.6.

The difference between the pre-extraction INR and the postextraction INR had a mean of 0.46 and a standard deviation of 0.9. The median difference was INR 0.3 and a range of −1.1 to + 4.3. Sixteen cases had a rise greater than 1.0 and 5 cases a rise greater than 2.0.
3.3 Postextraction bleeding

The patients recorded postextraction bleeding on the patient data collection sheet. Significant bleeding, defined as bleeding requiring management in the researcher’s dental surgery was observed in only 8% of patient episodes (Figure 3.3.1).

Table 3.3.1 Frequency of postextraction bleeding

<table>
<thead>
<tr>
<th>Type of Bleed</th>
<th>Number of patient episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bleeding</td>
<td>62</td>
</tr>
<tr>
<td>Managed at home on day one, only</td>
<td>22</td>
</tr>
<tr>
<td>Managed at home, after day one with pressure</td>
<td>8</td>
</tr>
<tr>
<td>Managed in the researcher’s dental surgery with local treatment</td>
<td>8</td>
</tr>
<tr>
<td>Managed in hospital by systemic treatment</td>
<td>0</td>
</tr>
</tbody>
</table>

The pattern of patients that presented to the researcher’s dental surgery for control of bleeding by local measures is shown (Table 3.3.2). Six patients presented once. One patient presented on 2 separate days and another patient presented on 3 separate days.

Table 3.3.2 Pattern of postextraction bleeding

<table>
<thead>
<tr>
<th>Day of Presentation</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients presenting to the researcher’s dental surgery</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

It should be noted that 3 patients, with late bleeds, reported to the researcher’s dental surgery after the 7 day period of the investigation. At this time they had stopped using tranexamic acid mouthrinses. Two patients, each with previous dental surgery managed bleeds, returned to the researcher’s dental surgery with bleeding on day eight. One of these patients also returned with a bleed on day ten. The third patient, without previous bleeding, reported to the researcher’s dental surgery on day eight. All 3 patients had been off tranexamic acid mouthrinses for at least 24 hours, at the time they reported to the researcher’s dental surgery.
3.4 Description of the teeth removed

All 100 patient episodes involved tooth removal. The number of teeth removed per patient episode ranged from 1 tooth to 27 teeth (Table 3.4.1). The mean number of teeth removed was 4.5 with a median of 2 teeth. One patient who had a full dental clearance also had a large torus removed from the palate without complications.

Three patients who had 2 teeth removed, 4 patients who had 4 teeth removed and 1 patient with 15 teeth removed returned to the researcher’s dental surgery with a bleed managed by local measures.

Table 3.4.1  Number of teeth extracted per patient episode by the number of patient episodes

<table>
<thead>
<tr>
<th>Number of teeth extracted per patient episode</th>
<th>Number of patient episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>
A total of 448 individual teeth were removed during 100 patient episodes. Twenty-one teeth were involved in a significant bleed requiring management in the researcher’s dental surgery. Eighteen of these teeth were in the maxilla of which 16 were in the maxillary molar region (Table 3.4.2). Three bleeds occurred in the mandibular molar region.

**Table 3.4.2**  Tooth location by number of teeth removed from that location and the number from this location involved in dental surgery managed bleeds

<table>
<thead>
<tr>
<th>Tooth location</th>
<th>Number of teeth removed</th>
<th>Number of teeth involved in dental surgery managed bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary central incisors</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Maxillary lateral incisors</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Maxillary canines</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>Maxillary first premolars</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>Maxillary second premolars</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Maxillary first molars</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Maxillary second molars</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Maxillary third molars</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Mandibular central incisors</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Mandibular lateral incisors</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Mandibular canines</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Mandibular first premolars</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Mandibular second premolars</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Mandibular first molars</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Mandibular second molars</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Mandibular third molars</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>448</strong></td>
<td><strong>21</strong></td>
</tr>
</tbody>
</table>
3.5 Mouthrinse acceptance and utilisation

One patient refused to join the study requesting admission to hospital for heparin therapy. This level of management was not required so the INR was reduced below 2.0 and the tooth removed. Every patient's medical practitioner readily accepted the study.

In response to the question, "Did you mind using the mouthrinse?" 3 patients said they would rather be managed some other way. The different reasons given included: The taste of the mouthrinse; difficulty fitting in with work and the mouthrinse caused a pain in the face (left and right temporomandibular joint and temporal regions).

For the remaining 97 patient episodes there were no major objections to using the mouthrinse. These patients were asked if they had any minor problems associated with using the mouthrinse. 80 patients had no minor problems. In only 17 patient contacts was there any comment. These comments were: Discomfort, slight pain or ache (5); taste (5); inconvenient (4); remembering (1); fitting in with meals (1); caused chest pain (1) and caused bleeding (1).

Data collection sheets measuring patient compliance were not returned for analysis in 3% of the patient episodes. Of the remainder, 59 (60.8%) were fully compliant, 6 (6.2%) missed 1 mouthrinse, 3 (3.1%) missed 2 mouthrinses, 3 (3.1%) missed 3 mouthrinses and 5 (5.2%) missed 4 mouthrinses (Figure 3.5.1).

**Figure 3.5.1** Compliance as measured by the patient data collection sheet
In 8 patient episodes the mouthrinse bottle was not returned. Of the remaining 92 patients who did return their bottle, 53 (57.6%) were 100% compliant, 7 (7.6%) missed 1 mouthrinse, 2 (2.2%) missed 2 mouthrinses, 1 (1.1%) missed 3 mouthrinses and 4 (4.3%) missed 4 mouthrinses (Figure 3.5.2).

**Figure 3.5.2** Compliance as measured by the residual contents of the bottle

There was a strong correlation between compliance as measured by the patient data sheet and compliance as measured by the residual contents of the bottle, with a highly significant Pearson correlation between the 2 variables of 0.863 (p<0.0005). The adjusted R square (goodness of fit), was 0.741.

Only 2 of 8 bleeding events managed in the researcher's dental surgery were associated with a failure to comply fully with the prescribed mouthrinse regimen. Of the non-compliant patients who had a bleed managed in the researcher's dental surgery, 1 patient was 33% compliant and the other patient was 85% compliant. The remaining 6 patients with bleeding managed by local measures in the researcher's dental surgery were fully compliant.
3.6 Analysis of patient episode predictor variables

Bivariate analysis of categorical patient episode predictor variables (Table 3.6.1) that might have cause bleeding managed in the researcher’s dental surgery was carried out using the chi-square test. Because of the low expected count in 1 or more cells, Fisher’s Exact Test was used to calculate significance.

Table 3.6.1 Results of chi-square tests of patient episode predictor variables for bleeding managed in the researcher’s dental surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bleed Managed in the dental surgery</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%)</td>
<td>No (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (11.6%)</td>
<td>38 (88.4%)</td>
<td>43</td>
</tr>
<tr>
<td>Male</td>
<td>3 (5.3%)</td>
<td>54 (94.4%)</td>
<td>57</td>
</tr>
<tr>
<td>Smoke</td>
<td>3 (23.1%)</td>
<td>10 (76.9%)</td>
<td>13</td>
</tr>
<tr>
<td>Non smoke</td>
<td>5 (5.9%)</td>
<td>80 (94.1%)</td>
<td>85</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4 (16.7%)</td>
<td>20 (83.3%)</td>
<td>24</td>
</tr>
<tr>
<td>No Aspirin</td>
<td>4 (5.3%)</td>
<td>72 (94.7%)</td>
<td>76</td>
</tr>
<tr>
<td>INR above 2.4</td>
<td>6 (10.7%)</td>
<td>50 (89.3%)</td>
<td>56</td>
</tr>
<tr>
<td>INR below 2.5</td>
<td>2 (4.5%)</td>
<td>42 (95.5%)</td>
<td>44</td>
</tr>
<tr>
<td>INR above 2.9</td>
<td>3 (27.3%)</td>
<td>8 (72.7%)</td>
<td>11</td>
</tr>
<tr>
<td>INR below 3.0</td>
<td>5 (5.6%)</td>
<td>84 (94.4%)</td>
<td>89</td>
</tr>
<tr>
<td>More than 4 teeth removed</td>
<td>1 (4.0%)</td>
<td>24 (96.0%)</td>
<td>25</td>
</tr>
<tr>
<td>Less than 5 teeth removed</td>
<td>7 (9.3%)</td>
<td>68 (9.3%)</td>
<td>75</td>
</tr>
</tbody>
</table>

* Indicates a significant effect
Bivariate analysis of continuous patient episode predictor variables (Table 3.6.2) that might cause bleeding managed in the researcher’s dental surgery was carried out using the independent-samples *t* test.

**Table 3.6.2** Results of independent-samples *t* tests of patient episode predictor variables for bleeding managed in the researcher’s dental surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bleed Managed in the dental surgery</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Yes</td>
<td>8</td>
<td>47.3</td>
<td>20.9</td>
<td>.062</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>92</td>
<td>58.0</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>APTT</td>
<td>Yes</td>
<td>8</td>
<td>44.1</td>
<td>4.1</td>
<td>.162</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>91</td>
<td>40.8</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Time on anticoagulants</td>
<td>Yes</td>
<td>7</td>
<td>4.6</td>
<td>3.2</td>
<td>.880</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>88</td>
<td>4.2</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Pre-extraction INR</td>
<td>Yes</td>
<td>8</td>
<td>2.7</td>
<td>0.4</td>
<td>.218</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>92</td>
<td>2.5</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Post-extraction INR</td>
<td>Yes</td>
<td>8</td>
<td>3.2</td>
<td>0.8</td>
<td>.352</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>85</td>
<td>3.3</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Bleeding time</td>
<td>Yes</td>
<td>7</td>
<td>4.9</td>
<td>3.3</td>
<td>.584</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>90</td>
<td>4.3</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Compliance (sheet)</td>
<td>Yes</td>
<td>8</td>
<td>89.8</td>
<td>23.3</td>
<td>.904</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>89</td>
<td>90.1</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Compliance (bottle)</td>
<td>Yes</td>
<td>7</td>
<td>92.6</td>
<td>15.4</td>
<td>.641</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>85</td>
<td>89.2</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>Total teeth extracted</td>
<td>Yes</td>
<td>8</td>
<td>4.6</td>
<td>4.3</td>
<td>.937</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>92</td>
<td>4.5</td>
<td>5.9</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.6.3  Results of the logistic regression analysis of the conceptual model of patient
episode predictor variables for bleeding managed in the researcher’s dental surgery

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>B</th>
<th>Standard error of B</th>
<th>T</th>
<th>Significance of T</th>
<th>Odds Ratio</th>
<th>95% C. I. Lower</th>
<th>95% C. I. Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-.0385</td>
<td>.0267</td>
<td>2.0878</td>
<td>.1485</td>
<td>.96</td>
<td>.91</td>
<td>1.0</td>
</tr>
<tr>
<td>Sex</td>
<td>.2894</td>
<td>.8956</td>
<td>.1044</td>
<td>.7466</td>
<td>1.3</td>
<td>.23</td>
<td>7.7</td>
</tr>
<tr>
<td>Smoke</td>
<td>.7795</td>
<td>.9568</td>
<td>.6638</td>
<td>.4172</td>
<td>2.2</td>
<td>.33</td>
<td>14.2</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.3261</td>
<td>.8676</td>
<td>2.3360</td>
<td>.1264</td>
<td>3.8</td>
<td>.69</td>
<td>20.6</td>
</tr>
<tr>
<td>Total extraction</td>
<td>.0280</td>
<td>.0761</td>
<td>.1349</td>
<td>.7134</td>
<td>1.0</td>
<td>.89</td>
<td>1.19</td>
</tr>
<tr>
<td>Pre-ext. INR split 3.0</td>
<td>2.2112</td>
<td>1.0053</td>
<td>4.8377</td>
<td>.0278*</td>
<td>9.1</td>
<td>1.3</td>
<td>65.5</td>
</tr>
<tr>
<td>Constant</td>
<td>-4.1494</td>
<td>2.6901</td>
<td>2.3901</td>
<td>.1230</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates a significant effect

The Hosmer and Lemeshow Goodness-of-Fit Test has a significance of 0.4800. Because the observed significance level is high the model fits the data well.

The probability of bleeding is given by the formula: Logit (p) = -4.1494 - 0.0385 (Age in years) + 0.2894 (sex) + 0.7795 (smoke) + 1.13261 (aspirin) + 0.0280 (number of teeth extracted) + 2.2112 (pre-extraction INR above 2.9).

This formula correctly predicts 98.9% (89/90) of non-bleeds but predicts only 12.5% (1/8) of bleeds correctly. Overall, 91.8% percent of outcomes are correctly predicted.
3.7 **Analysis of individual tooth predictor variables**

Bivariate analysis of categorical individual tooth predictor variables (Table 3.7.1) that might cause bleeding managed in the researcher’s dental surgery was carried out using chi-square tests.

**Table 3.7.1**  Results of chi-square tests of patient episode predictor variables for bleeding managed in the researcher’s dental surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bleed managed in dental surgery</th>
<th>Total</th>
<th>P Value</th>
<th>Relative Risk</th>
<th>95% C.I. Max</th>
<th>Min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxillary teeth</td>
<td>18 (8.1%)</td>
<td>205 (91.9%)</td>
<td>223</td>
<td>0.001*</td>
<td>6.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Mandibular teeth</td>
<td>3 (1.3%)</td>
<td>222 (98.7%)</td>
<td>222</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molar teeth</td>
<td>19 (10.55%)</td>
<td>162 (89.5%)</td>
<td>181</td>
<td>&lt;.0005*</td>
<td>14.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Premolar, canine, incisor</td>
<td>2 (0.7%)</td>
<td>265 (99.3%)</td>
<td>267</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxillary molar</td>
<td>16 (16.2%)</td>
<td>83 (83.8%)</td>
<td>99</td>
<td>&lt;.0005*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandibular molar</td>
<td>3 (3.7%)</td>
<td>79 (96.3%)</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premolar, canine, incisor</td>
<td>2 (0.7%)</td>
<td>265 (99.3%)</td>
<td>276</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periodontal bleed</td>
<td>18 (18.2%)</td>
<td>201 (91.8%)</td>
<td>219</td>
<td>0.001*</td>
<td>6.3</td>
<td>1.9</td>
</tr>
<tr>
<td>No periodontal bleed</td>
<td>3 (1.3%)</td>
<td>226 (98.7%)</td>
<td>226</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periodontal pocket</td>
<td>18 (15.0%)</td>
<td>102 (85.0%)</td>
<td>120</td>
<td>&lt;.0005*</td>
<td>16.4</td>
<td>4.9</td>
</tr>
<tr>
<td>No periodontal pocket</td>
<td>3 (0.9%)</td>
<td>325 (99.1%)</td>
<td>328</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remove bone</td>
<td>2 (3.8%)</td>
<td>51 (96.2%)</td>
<td>53</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No bone removed</td>
<td>19 (4.8%)</td>
<td>376 (95.2%)</td>
<td>395</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raise flap</td>
<td>2 (3.8%)</td>
<td>50 (96.2%)</td>
<td>52</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No flap raised</td>
<td>19 (4.8%)</td>
<td>377 (95.2%)</td>
<td>396</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates significant effect
Table 3.7.2  Results of a logistic regression analysis of the conceptual model of predictor variables associated with individual teeth that may have caused bleeding that was managed in the researcher’s dental surgery by local measures

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>B</th>
<th>Standard error of B</th>
<th>T</th>
<th>Significance of T</th>
<th>Odds ratio</th>
<th>95% C. I. Lower</th>
<th>95% C. I. Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raise flap</td>
<td>.3411</td>
<td>1.3315</td>
<td>.0656</td>
<td>.7978</td>
<td>1.4</td>
<td>.10</td>
<td>19.1</td>
</tr>
<tr>
<td>Remove bone</td>
<td>-.5955</td>
<td>1.2997</td>
<td>.2100</td>
<td>.6468</td>
<td>.55</td>
<td>.04</td>
<td>7.0</td>
</tr>
<tr>
<td>Periodontal pocket</td>
<td>2.0639</td>
<td>.7995</td>
<td>6.6647</td>
<td>.0098*</td>
<td>7.9</td>
<td>1.6</td>
<td>37.7</td>
</tr>
<tr>
<td>Periodontal bleed</td>
<td>.7309</td>
<td>.8102</td>
<td>.8138</td>
<td>.3670</td>
<td>2.1</td>
<td>.42</td>
<td>10.2</td>
</tr>
<tr>
<td>Mandibular molar</td>
<td>1.0048</td>
<td>.9466</td>
<td>1.1267</td>
<td>.2885</td>
<td>2.7</td>
<td>.43</td>
<td>17.5</td>
</tr>
<tr>
<td>Maxillary molar</td>
<td>2.7700</td>
<td>.7907</td>
<td>12.2721</td>
<td>.0005*</td>
<td>16.0</td>
<td>3.4</td>
<td>75.2</td>
</tr>
<tr>
<td>Constant</td>
<td>-6.1887</td>
<td>.9209</td>
<td>44.5794</td>
<td>.0000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates a significant effect

The Hosmer and Lemeshow Goodness-of-Fit Test has a significance of 0.7515. Because the observed significance level is high the model fits the data well.

The probability of bleeding is given by the formula: Logit (p) = -6.1887 + 0.3411 (raise flap) - 0.5955 (bone removed) + 2.0639 (periodontal pocket) + 0.7309 (periodontal bleed) + 1.0048 (mandibular molar) + 2.7700 (maxillary molar).

This formula correctly predicts 100% (427/427) non-bleeds but predicts no bleeds (0/21) correctly. Overall, 97.06% of outcomes are correctly predicted.
Table 3.7.3 Results of logistic regression analysis of the conceptual model of patient episode predictor variables related to each individual tooth removed plus individual tooth predictor variables for that tooth, related to the bleeding outcome of that tooth

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>B</th>
<th>Standard error of B</th>
<th>T</th>
<th>Significance of T</th>
<th>Odds ratio</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.0264</td>
<td>0.0362</td>
<td>0.5310</td>
<td>0.4662</td>
<td>0.97</td>
<td>0.91</td>
<td>1.0</td>
</tr>
<tr>
<td>Sex</td>
<td>1.5216</td>
<td>0.7880</td>
<td>3.7280</td>
<td>0.0535</td>
<td>4.8</td>
<td>0.98</td>
<td>21.5</td>
</tr>
<tr>
<td>Smoke</td>
<td>3.4417</td>
<td>1.5283</td>
<td>5.0712</td>
<td>0.0243*</td>
<td>31.2</td>
<td>1.5</td>
<td>624</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3.1467</td>
<td>3.1467</td>
<td>12.5196</td>
<td>0.0004*</td>
<td>23.3</td>
<td>4.1</td>
<td>133</td>
</tr>
<tr>
<td>Pre-ext.INR split 3.0</td>
<td>2.8996</td>
<td>1.0797</td>
<td>7.2127</td>
<td>0.0072*</td>
<td>18.2</td>
<td>2.2</td>
<td>151</td>
</tr>
<tr>
<td>Raise flap</td>
<td>0.0301</td>
<td>1.7295</td>
<td>0.0030</td>
<td>0.9861</td>
<td>1.03</td>
<td>0.03</td>
<td>30.6</td>
</tr>
<tr>
<td>Remove bone</td>
<td>0.1223</td>
<td>1.7335</td>
<td>0.0050</td>
<td>0.9438</td>
<td>1.13</td>
<td>0.04</td>
<td>33.8</td>
</tr>
<tr>
<td>Periodontal pocket</td>
<td>3.2228</td>
<td>1.3667</td>
<td>5.5602</td>
<td>0.0184*</td>
<td>25.1</td>
<td>1.7</td>
<td>366</td>
</tr>
<tr>
<td>Periodontal bleed</td>
<td>2.5533</td>
<td>1.5806</td>
<td>2.6094</td>
<td>0.1602</td>
<td>12.8</td>
<td>0.58</td>
<td>284</td>
</tr>
<tr>
<td>Mandibular molar</td>
<td>0.6904</td>
<td>1.5861</td>
<td>0.1895</td>
<td>0.6634</td>
<td>1.99</td>
<td>0.09</td>
<td>44.7</td>
</tr>
<tr>
<td>Maxillary molar</td>
<td>3.8180</td>
<td>1.4356</td>
<td>7.0732</td>
<td>0.0078*</td>
<td>45.5</td>
<td>2.7</td>
<td>758</td>
</tr>
<tr>
<td>Constant</td>
<td>-11.036</td>
<td>3.1514</td>
<td>12.2630</td>
<td>0.0005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates a significant effect

The Hosmer and Lemeshow Goodness-of-Fit Test has a significance of 0.9715. Because the observed significance level is high the model fits the data well.

The probability of bleeding is given by the formula: Logit (p) = -11.036 - 0.264 (Age in years) + 1.5216 (sex) + 3.4417 (smoke) + 3.1467 (aspirin) + 2.8996 (pre-extraction INR above 2.9) + 0.0301 (raise flap) - 0.1223 (bone removed) + 3.2228 (periodontal pocket) + 2.5533 (periodontal bleed) + 0.6904 (mandibular molar) + 3.8180 (maxillary molar).

This formula correctly predicts 52.4% (11/21) of bleeds and 99.3% (418/421) of non-bleeds. Overall, 97.1% of outcomes are correctly predicted.
Table 3.7.4  Results of logistic regression analysis of the conceptual model of predictor variables derived from Table 3.7.3

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>B</th>
<th>Standard error of B</th>
<th>T</th>
<th>Significance of T</th>
<th>Odds ratio</th>
<th>95% C. I.</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2.9069</td>
<td>.6803</td>
<td>18.2606</td>
<td>.0000*</td>
<td>18.3</td>
<td>4.8</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Pre-ext.INR split 3.0</td>
<td>3.1756</td>
<td>.8293</td>
<td>14.6622</td>
<td>.0001*</td>
<td>23.9</td>
<td>4.7</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Periodontal pocket</td>
<td>3.1643</td>
<td>.7900</td>
<td>16.0447</td>
<td>.0001*</td>
<td>23.7</td>
<td>5.0</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>Maxillary molar</td>
<td>3.0013</td>
<td>.6858</td>
<td>19.1522</td>
<td>.0000*</td>
<td>20.1</td>
<td>5.2</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-8.0347</td>
<td>1.1268</td>
<td>50.8442</td>
<td>.0000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates a significant effect

The Hosmer and Lemeshow Goodness-of-Fit Test has a significance of 0.6114. Because the observed significance level is high the model fits the data well.

The probability of bleeding is given by the formula: Logit (p) = -8.0347 + 2.9069 (aspirin) + 3.1756 (pre-extraction INR above 2.9) + 3.1642 (periodontal pocket) + 3.0013 (maxillary molar).

This formula correctly predicted 52.4% (11/21) of bleeds and 99.1% (423/427) of non-bleeds. Overall, 96.9% of outcomes are correctly predicted.
CHAPTER 4  DISCUSSION

4.1 Design

This study was undertaken to verify that using tranexamic acid mouthrinse is a safe, effective and acceptable method of managing anticoagulated patients in the New Zealand setting. A novel aspect of this investigation was the evaluation of potential risk factors associated with the removal of the teeth and the identification risk factors for bleeding. This has not previously been reported in this group of patients. It must be recognised that because this study did not have a control group it does not provide a high level of evidence and does no more than enable the building of a hypothesis about the possible causes of post-operative bleeding in warfarin patients managed post-operatively with tranexamic acid mouthrinse. It is important that this limitation is borne in mind otherwise it is likely that observed associations could be misinterpreted or overstated. In addition, there was an inherent bias in the study design because it could not be double blinded. The possibility of information bias by both the researcher and patient may have influenced the results. This bias was minimised by collecting data on relevant variables in advance of the bleeding endpoint.

The 2 problems associated with data collection were missing data and recording data. Missing data occurred either because pre-extraction tests were not carried out as requested, e.g. pre-extraction APTT (1 missing) and bleeding time (3 missing) or because the patient overlooked postextraction investigations. Seven patients did not have their postextraction INR tested while 8 patients did not return the bottle containing residual tranexamic acid. Three patients failed to return their data collection sheet. Data collection in the operating theatre under general anaesthetic presented problems especially when multiple teeth were removed. The researcher was scrubbed and using a ‘no touch surgical technique’. Therefore, data had to be entered at the end of the procedure with a potential for recall error. Every effort was made to achieve accuracy.

All previous studies have used 10ml of 4.8% tranexamic acid mouthrinse. This study used 5ml of 10% tranexamic acid mouthrinse. The reason for this decision was that 10mls of 4.8% tranexamic acid solution contains the same amount of active solution as 5mls of 10% solution. Tranexamic acid is supplied as a 10% solution in New Zealand and New Zealand law does not allow hospital pharmacies to dilute and repackage pharmaceuticals except under
controlled conditions at high cost. The main advantage of the larger volume used in other studies is that it maybe easier to rinse around the mouth, especially the upper jaw.

Defining bleeding had its problems. Two levels of bleeding were initially considered for analysis. First, bleeding managed either at home after day 1 or in the researcher’s dental surgery and second, bleeding managed in the researcher’s dental surgery only. Each of these levels had its advantages and disadvantages. The advantage of recording home bleeds after day 1 was that more bleeds were captured for endpoint analysis. However, there were several significant disadvantages. This relied on the patient accurately reporting and recording any bleeding that occurred at home. Different patients had different thresholds for reporting bleeding. This led either to either under-reporting or to over-reporting depending on the individual patient’s threshold. In an attempt to standardise home bleed reporting, patients were asked to only record bleeding that required a pressure swab to control. Bleeding requiring control at home is common following dental extractions, even in patients with normal coagulation. When multiple teeth were removed from the same region of the mouth it was impossible for the patient to identify and accurately record which tooth socket was bleeding. Therefore, when bleeding was recorded in a region by the patient, all tooth sockets in that region were recorded as having bled. By this definition, 26 sockets were recorded as having bled although it was unlikely that all these sockets had actually bled. This may have led to an over-estimation of the incidence of home bleeding. For statistical analysis, only “dental surgery bleeds” were used as these represented the most objective endpoint. A further advantage of using dental surgery-managed bleeds was that the number and position of the bleeding sockets could be accurately recorded. A disadvantage of this approach was that relatively few endpoint bleeds were available for analysis (8% of patient episodes involving 21 of 448 teeth). There was also variability in the threshold at which patients presented themselves to the dental surgery. One anxious patient presented with a relatively minor bleed. In contrast, other patients had persistent bleeding at home and did not present to the dental surgery.

Compliance is an issue in any treatment study. This effect was offset because warfarin requires a high level of compliance and regular monitoring to avoid serious complications. The study population was perhaps more motivated to comply. Compliance was assessed by 2 methods. First, the patient was asked to record mouth rinse use on the patient data collection
sheet. This relied on patient honesty not to record when they missed their mouthrinse and diligence to record when they did use it. Patients were encouraged to be honest, to only record definite mouthrinse use and not enter factitious data. Second, patients were asked to return the mouthrinse bottle containing unused residual tranexamic acid. This assumed patients accurately measured the amount of mouthrinse used and did not discard any medication prior to returning the bottle. Demonstrating a reasonably good correlation between the 2 methods of measurement with an adjusted R-square of 0.741 validated accuracy of compliance. Theoretically the residual contents of the bottle gave the more accurate measure of compliance, as it did not rely on patient diligence to record mouthrinse use. One of the 2 patients who recorded bleeds and poor compliance bled over several days. There was also a problem with some patients who lived in a rest home. While some rest homes were excellent with administering the mouthrinse, it was surprising that several showed poor compliance. Language and old age were not a barrier to compliance as it was possible to recruit either a family member or a friend to take responsibility for informing and assisting the patient.

To achieve maximum compliance, the patient was fully informed about the need to use the mouthrinse and encouraged to believe its use was important. Despite this effort, only 60% of patients were fully compliant and 21% of patients missed more than 4 of 27 mouthrinses. Overall compliance was 90%. Two of 8 patients who reported to a dental surgery with bleeding were non-compliers. Although disappointing, this level of compliance was probably representative of the population treated and very good for an intervention study. Ramstrom et al. (1993) reported 4 (8.7%) of 46 patients were not fully compliant. Adverse comments about the mouthrinse in their study included were taste (3), nausea (1), slight burning feeling (1) and tedious (1). These comments were similar to those made in the present study. Most study subjects accepted the mouthrinse without reservation with only 1 refusal and 3 not wishing to repeat the experience. Negative reactions were generally of a minor nature. Some patients were relieved not to have to reduce their warfarin. Patients were encouraged to involve their family and discuss treatment with their family doctor. Whenever possible the patient’s medical practitioner was contacted in the patient’s presence and a letter sent to their doctor. This minimised patient anxiety and improved acceptance of the study regimen.

The major risks associated with removal of teeth in these anticoagulated patients were either uncontrolled bleeding or a thromboembolic event. Only minor bleeding occurred and this was controlled either at home with pressure or in the researcher’s dental surgery by local
measures. No bleeding required systemic therapy or admission to hospital. No thromboembolism occurred. No medical emergencies occurred to patients during the period of the study. Because tranexamic acid mouthrinse has minimal systemic absorption (Sindet-Pedersen, 1987) and was spat out after 2 minutes, it was very safe. If accidentally swallowed it does not have any significant adverse effect. The results obtained in this study are consistent with a review of the literature by Wahl (1998). He reported that 98% of 774 patients who underwent dental extractions while on warfarin and were managed by a number of different techniques had either no bleeding or insignificant bleeds that were managed by local measures. Only 12 (2%) cases required hospitalisation for a short period. It was concluded that this was a safe method of managing patients.

As part of the present study, the INR was tested 4 days postextraction. At this time, 15 (16.1%) patients were outside the therapeutic range of INR 2.0 to 4.0. Eight (8.6%) had an INR above 4.0 with a maximum of INR 6.7 and 7 (7.5%) had a sub therapeutic INR below 2.0 with a minimum of INR 1.6. The difference between the pre-extraction and postextraction INR values was greater than 1.0 in 17.3% of cases and exceeded 2.0 in 5.4% of cases. This is an important observation, as an INR greater than 4.0 increases the risk of unwanted bleeding. Although only 1 patient with a postextraction INR greater than 4.0 returned with bleeding, this interval test, performed at day 4, is potentially important as it allows the patient’s medical practitioner an opportunity to intervene and adjust the level of anticoagulation before complications develop. Possible explanations for this change in INR include: Normal INR instability; a change of diet associated with tooth extractions leading to decreased dietary vitamin K; antibiotics interfering with the enteric recirculation of vitamin K. The only account in the literature reporting a serious bleed following dental extractions in patients on warfarin managed postextraction with antifibrinolytic mouthrinses is by Bandrowsky et al. (1996) who reported an INR of 9.2 4 days postextraction. The high INR may have been intercepted earlier had closer monitoring been in place.

In only 8 of the 100 patient treatment episodes was it reported that minor bleeding at home after day 1 required pressure for control. This involved up to 44 (9.8%) of a total of 448 tooth sockets. The incidence of home bleeds in this group of patients has not been previously reported. In addition, 8 of 100 patients involving 21 (4.7%) sockets presented at the researcher’s dental surgery with bleeding that was not controlled at home. This bleeding was readily controlled after infiltration of the adjacent mucosa with 2% lignocaine solution
containing 1:80,000 adrenaline, removal of the clot, irrigation of the wound with 10% tranexamic acid solution, application of pressure with a swab soaked in tranexamic acid solution and resuturing the socket. No patients required hospital admission for systemic management of bleeding.

The incidence of bleeding that was controlled in the researcher’s dental surgery by local measures was slightly higher in this study than that previously reported. Sindet-Pedersen et al. (1989) reported 1 bleed in 19 (5.3%) cases. Ramstrom et al. (1993) reported no bleeds requiring treatment in 46 patients. Borea et al. (1993) reported 1 bleed out of 15 (6.7%) requiring treatment. Gaspar et al. (1997) reported 2 bleeds in 32 patients (6.3%) requiring treatment. Devani et al. (1998) reported 1 case in 33 (3%) with bleeding requiring treatment. There are several possible explanations for these observed differences in bleeding. Patients in the present study had stopped their aspirin for 7 days whereas patients in the other studies discontinued their aspirin for at least 14 days before surgery. Aspirin was a factor identified in the logistic regression as being a significant contributor to bleeding. This study used 5ml of 10% tranexamic acid solution whereas other studies used 10ml of 4.8% tranexamic acid. It is possible that the smaller volume of tranexamic acid did not effectively reach the upper sockets, where the majority of bleeds occurred and was therefore less effective at preventing fibrinolysis.

The present study with a bleeding rate of 8% requiring additional treatment, while slightly higher than other studies using a comparable technique, is considerably less than studies involving extraction of teeth at therapeutic INR without topical antifibrinolytic mouthrinses. These report an incidence of bleeding between 21% and 50% (Bailey and Fordyce, 1983; Sindet-Pedersen et al., 1989; Ramstrom et al., 1993). It may therefore be concluded that topical tranexamic acid mouthrinses effectively reduce postextraction bleeding.

A particular benefit of this technique is its simplicity. Provided the patient has an INR below 4.0 at the time of surgery and has not taken aspirin or NSAID’s within the preceding 7 days, teeth maybe removed without significant risk. Surgery can be confidently scheduled with a definite date that avoids loss of operating time due to cancellations resulting from variable INR correction enabling tooth removal to proceed with minimum delay and inconvenience. The procedure can be undertaken with parenteral antibiotic support and any difficulty in re-establishing a stable postextraction warfarin level is avoided.
Other techniques for managing patients on warfarin requiring tooth extraction are potentially more complicated. An INR reduction below 2.0 cannot be guaranteed 2 days after stopping warfarin (Devani et al. 1998) and often takes 3 days. This delays treatment, increases the risk of thromboembolism, involves the patient’s medical practitioner in reducing warfarin and necessitates extra tests to re-establish the INR following surgery. If the INR on the planned day of surgery is still above 2.0, surgery maybe further delayed and requires rescheduling the operation. Removal of teeth with an INR greater than 2.0, without using antifibrinolytic mouthrinses is associated with increased bleeding and this has the potential to cause further inconvenience. Heparin substitution of warfarin requires 4 or 5 days hospitalisation (Roser and Rosenbloom, 1975). This is both expensive and inconvenient.

4.2 Statistical Modelling

Bivariate analysis was used to explore the different variables that might influence the incidence of bleeding and was also used to help select variables that were later used in models for multivariate analysis.

The advantage of multivariate analysis over bivariate analysis is that it controls for the interaction between the many variables in the model. In this study, 4 conceptual models were proposed. The first conceptual model (Table 3.6.3) used predictor variables associated with patient episodes. Previous studies have considered certain “patient” variables a possible risk for bleeding. In these controlled studies (Sindet-Pedersen et al. 1989, Ramstrom et al. 1993), the authors matched what they considered were potential risk factors for bleeding, between the experimental and control groups. This logistic regression model using predictor variables associated with patient episodes predicted 98.9% of non-bleeds correctly but only correctly predicted 12.5% of bleeds, which was the outcome of interest.

The second conceptual model Table (3.7.2) related 6 predictor variables associated with individual teeth to the bleeding outcome of those teeth. The model derived from these variables correctly predicted 100% of non-bleeds but was unsatisfactory because it did not predict any that bled.

Because neither variables derived from patient episodes nor variables derived from individual teeth could explain the bleeding that occurred, it was decided to combine these variables and
form a third conceptual model. The third conceptual model Table (3.7.4) used 11 predictor variables associated with the removal of individual teeth. Five patient episode predictor variables used in the first model were related back to each individual tooth that was removed from that patient and these were analysed together with the 6 individual tooth predictor variables used in model 2. The model derived from these variables accurately predicted 52.4% of tooth sockets that bleed requiring dental surgery management and accurately predicted 99.3% of those that didn’t bled. An advantage of this model was that it controlled for a large number of variables. However this model was complicated because there were relatively few bleeds (21 teeth out of 448 removed) and too many predictor variables. This led to the formation of the fourth conceptual model.

The fourth conceptual model (Table 3.7.4) was a simplification of the third model and was the best fitting, least complicated, biologically acceptable model. The model equation for probability of bleeding managed in a dental surgery is, Logit (p) = -8.0347 + 2.9069 (aspirin) + 3.1756 (pre-extraction INR = or > 3.0) + 3.1643 (periodontal pocket = or > 5mm) + 3.0013 (maxillary molar). This model correctly predicts 52.4% of tooth bleeds and correctly predicts 99.1% of non-bleeds.

It is important to note that there were very few bleeding endpoints (8 patient episode bleeds out of 100 patient episodes and 21 individual tooth socket bleeds out of 448 teeth removed) on which to carry out statistical analyses and from which to make a hypothesis about possible risk factors for bleeding. Furthermore, 2 patients in which bleeding occurred, contributed 12 individual tooth sockets that bled, to the analysis. The data of these 2 patients may have biased the analysis in conceptual models 3 and 4.

4.3 Risk Factors for bleeding requiring management in the researcher’s dental surgery

Regardless of the method of statistical analysis used, there were several predictor variables strongly associated with an increased risk of bleeding managed in the researcher’s dental surgery by local measures. These were a tooth with a periodontal pocket equal to or greater than 5 millimetres, a maxillary molar tooth, an INR equal to or greater than 3.0 and a person who was on long term aspirin therapy that was stopped 7 days prior to surgery.
Factors not statistically significant for an increased risk of bleeding requiring management in the researcher's dental surgery included: The number of teeth removed; raising a mucoperiosteal flap; removing bone; pre-extraction INR equal to or above 2.5; pre-extraction APTT; pre-extraction bleeding time; time on anticoagulants and compliance with tranexamic acid mouthrinses.

The significance of age, gender and smoking was inconclusive, being significant in some results and not significant in others.

Deep periodontal pockets are often associated with granulation tissue and infection. The soft tissue walls of these pockets are ulcerated and bleed on light probing due to trauma of the underlying acutely inflamed tissue. The granulation tissue is very hyperaemic and vascular. Inflammation increases the fibrinolytic response in the operated area. It is interesting to note that while periodontal bleeding on probing was significant in the bivariate analysis it was not significant in the multivariate analysis which controls for the interaction of variables. The reason was that all periodontal pockets with a depth equal to or greater than 5mm bled on probing but not all periodontal bleeds were associated with deep pockets. Indeed, a number of bleeds on probing were associated with inflamed gingival margins and minimal pocketing. This led to the conclusion that it is the large, ulcerated, inflamed surface area associated with deep periodontal pocketing that predisposes a patient to postextraction bleeding.

This study also indicated that some areas of the mouth are especially prone to postextraction bleeding while other areas are relatively immune. Upper teeth bled more than lower teeth. Molar teeth bled more than all other teeth combined. The most common area for bleeding was the maxillary molar region and the least common the mandibular premolar, canine and incisor regions. Increased bleeding from the maxillary molar region is biologically plausible. First, maxillary molars are generally 3 rooted teeth and their removal leaves a wound with a large surface area. This is especially important if there is periodontal disease present with a large amount of granulation tissue. Because the wound is wide (bucco-palatally) it is generally not possible to close the wound and support the blood clot. Second, the maxilla is more vascular than the mandible. Finally, it maybe argued that 5ml of tranexamic acid solution is an insufficient volume to effectively reach the maxillary sockets and prevent fibrinolysis. Only a few studies of warfarinised patients have stated where bleeding occurred in the mouth. Ziffer et al. (1957) reported the case of an upper third molar and a second case of a mandibular first
molar with prolonged postextraction bleeds. Devani et al. (1998) reported oozing from an upper and a lower third molar.

Traditionally, the INR has been used to determine how a patient on oral anticoagulants requiring dental extractions should be managed. Management has been based on the assumption that the higher the INR the more likely a patient is to bleed. The present study found that there was no statistical difference between the incidence of bleeding below an INR of 2.5 and an INR equal to or above 2.5. However, this study confirmed that bleeding was significantly greater when the INR exceeded 3.0. From these results it maybe concluded that the incidence of bleeding does not greatly increase as the INR rises from 2.0 to 2.9 but with an INR of 3.0 and above the incidence of bleeding significantly increases. This finding is consistent with clinical experience and is biologically reasonable as warfarin causes impaired fibrin formation. The higher the INR, the more impaired the fibrin formation, therefore the more susceptible it is to fibrinolysis.

Aspirin appears to influence the incidence of postextraction bleeding. This is consistent with its known effect on platelet adhesion because it prolongs the bleeding time and, in the presence of oral anticoagulants, may increase the probability of postoperative bleeding. On average, platelets have a lifespan of 10 days. In the present study, patients on long-term aspirin were asked to stop taking their aspirin 7 days prior to surgery. While this leaves 70% of the total population of platelets unaffected by aspirin, 30 percent of platelets are still affected by aspirin. This result supports the argument that aspirin should be stopped for a minimum of 10 to 14 days before tooth removal for patients on warfarin, as recommended by Sindet-Pedersen et al. (1989) and Ramstrom et al. (1993), rather than the 7-day protocol used in the present study. This allows the total population of platelets to be replaced and free of the effects of aspirin. The decreased risk of bleeding must be balanced against the risk of further delay in treatment.

Proportionately more women (11.6%) bled than men (5.9%) but this was not statistically significant in the bivariate analysis. However, by multivariate analysis statistical significance was almost achieved. A possible reason is that females on oral contraceptives induce a higher level of fibrinolytic activity of their saliva than females with a normal menstrual cycle or males (Sindet-Pedersen, 1991).
Fibrinolytic activity of saliva maybe influenced by smoking (Sindet-Pedersen, 1991). When smoking people suck on their cigarette. A vacuum is created in the mouth, which has a similar effect to sucking the socket, and this increases the likelihood of bleeding. Further, smokers tend to have a higher plaque score and a decreased resistance to periodontal disease.

The bleeding time test was not a significant determinant of postextraction bleeding. This was consistent with other evidence indicating that bleeding time is a poor predictor of surgical bleeding risk (De Rossi and Glick, 1996). During the course of the study, 2 patients had a prolonged bleeding time greater than 20 minutes. One patient was using diclofenac diethylammonium (Voltaren Emulgel). On stopping this for 1 week the bleeding time had reduced to 12 minutes and the extractions were carried out without problems. The second patient had a repeat bleeding time exceeding 20 minutes and was given Desmopressin (DDAVP) which reduced the pre-extraction bleeding time to 5 minutes and enabled the extractions proceeded without complication. It could perhaps be argued that both these patients might have potentially had a significant postextraction bleed, but screening had identified the possible complication and allowed preventive intervention.

The APTT is used to assess the integrity of the intrinsic coagulation pathway. Warfarin decarboxylates Factor IX of the intrinsic pathway and both Factor X and Prothrombin of the common pathway. It is therefore reasonable to expect that a prolonged APTT may affect the prevalence of postextraction bleeding. The mean APTT for those that bled was 44 seconds while the mean for those that did not bleed was 41 seconds. Although close, this did not reach statistical significance and this was expected because the APTT is relatively insensitive to warfarin. One patient with a pre-extraction APTT of 75 seconds was excluded from the study for further coagulation investigations.

It is highly relevant to note that neither the bivariate nor the multivariate analyses support the hypothesis that the more teeth removed the greater the likelihood the patient will present to a dental surgery with a postextraction bleed. This was a surprise finding as one would expect that the greater the number of teeth removed, the greater the wound area, the greater the incidence of significant bleeding. This current study had more patient episodes and more teeth removed per case than has been previously reported. The implications of this finding are important in the management of this group of patients. Some clinicians have advocated that multiple extractions should be staged to reduce the likelihood of bleeding. This is clearly not
required. Multiple treatments are expensive in terms of time and resources for the clinician and inconvenient for the patient.

Another surprising result of this study was that raising a mucoperiosteal flap and removing bone did not contribute significantly to the incidence of bleeding either in the bivariate analysis or the multivariate analysis. It might be argued that the increased trauma of a surgical extraction would have been significant enough to affect the likelihood of bleeding. Also, plasminogen activators have been demonstrated in alveolar bone, the cells of the buccal and palatal mucosa and the subepithelial blood vessels of the gingivae (Sindet-Pedersen, 1991) and would have been released during surgery and increased the likelihood of fibrinolysis. A possible explanation may be that immediately following surgery the wound was irrigated with tranexamic acid solution thereby reducing fibrinolysis. The wound was then sutured to protect the clot from trauma and isolate it from saliva.

4.4 Recommendations

On the basis of this study, several proposals can be made about the management of patients on warfarin. First, deep periodontal pocketing is a significant indicator of postextraction bleeding. Raising a flap and bone removal are not significant risk factors. When teeth with deep periodontal pockets are removed, the associated granulation tissue should be excised, especially from the interproximal region. If necessary, a flap should be raised, the area curetted, and grossly inflamed tissue removed. Alternatively, a week before their removal, teeth should be scaled to remove infected deposits from their root surface. This allows resolution of the inflamed periodontal tissues prior to surgery. These procedures may reduce the likelihood of bleeding, especially if molar teeth are being removed. Second, because some patients had an unstable INR following removal of their teeth, consideration should be given to testing the INR 4 days post extraction. This is most important if postoperative antibiotics have been prescribed. Finally, because 3 patients returned with later bleeds after the 7 day period of investigation with bleeding, consideration should be given to extending the period of tranexamic acid mouthrinse use from 7 days to 10 days if the clinician believes the patient has a higher risk of bleeding.
CHAPTER 5  SUMMARY AND CONCLUSIONS

In the past, optimal management of patients on warfarin who require oral surgery has been controversial. However, the technique described by Sindet-Pedersen et al. (1989) and used in this study provides a method of management that is safe, simple, effective and acceptable. The anticipated incidence of postextraction bleeding requiring management by local measures of 21-50% without the use of antifibrinolytic mouthrinses was reduced to 8% by using the antifibrinolytic mouthrinse tranexamic acid, 4 times a day for 7 days. Mouthrinse use was widely accepted with only 3% of patients strongly objecting to its use. Overall, mouthrinse compliance was high (90%) although only 60% of patients were fully compliant with 21% missing five or more rinses.

A unique aspect of this study is the identification of factors that may predispose the patient to an increased risk of postextraction bleeding. These factors are: Teeth with a periodontal pocket equal to or greater than 5 mm in depth; patients with an INR equal to or greater than 3.0 on the day of surgery; removal of maxillary molar teeth and removal of teeth from patients who have been on long term aspirin therapy that was stopped only 7 days before surgery. This study also found that upper sockets were more likely to bleed than lower sockets and that molar sockets were more likely to bleed than premolar, canine or incisor sockets.

Identification of these factors gives a clinician an opportunity to implement strategies to reduce the likelihood of bleeding. These strategies may include either pre-extraction scaling of teeth to reduce gingival inflammation associated with deep periodontal pockets or excision of excess granulation tissue at the time of the extractions. Consideration should be given to stopping long-term aspirin therapy for a minimum of 10 days before extractions. Patients with factors that increase the risk of postextraction bleeding may require tranexamic acid mouthrinses for 10 days after extractions rather than the normal 7 days. Postextraction INR instability may mean the INR should be tested after 4 days, especially if postoperative antibiotics are prescribed.

Surprisingly, neither the number of teeth removed, nor the raising of a mucoperiosteal flap and removing bone to surgically remove teeth were statistically significant for the incidence of bleeding requiring management by local measures.
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Information Sheet

The use of Cyklokapron mouthrinse to prevent bleeding after dental extractions

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Introduction
You are invited to take part in this study which uses a mouthrinse (Cyklokapron) to prevent post dental extraction bleeding. If you decide to take part you will be required to use a mouthrinse four times a day for a week and record on a sheet any bleeding that may occur, the time you use your mouth rinse, the level of pain you are experiencing and the pain relief you use. Please take this information sheet home with you, study it and consider whether or not you would like to join the study. I will contact you by phone on........................ at........... and answer any queries you may have regarding the study and to seek your consent. Your decision to take part is entirely voluntary. Should you decide not to take part you will still continue to receive dental treatment.

What are the aims of the study?
At the present time you are on anticoagulant medication which thins your blood to stop clots from forming. You also need to have some teeth removed. Because of your blood thinning medication there is a greater risk of bleeding following tooth removal. Recent studies have shown that a major cause of this rebleeding is due to breakdown of the blood clot in the mouth. This can be prevented by using regular Cyklokapron mouthrinses without the need to reduce your blood thinning medication. To date, studies have shown this to be effective but have not given full details of the types of patients who can and can't be treated this way. In this study volunteers will use Cyklokapron mouthrinses to prevent postoperative bleeding without reducing their level of anticoagulant medication. Information will be collected about yourself, your medication and the surgery, to find out if there are any common factors which may lead to post-extraction bleeding. From these results we will develop a protocol for treating patients who are on anticoagulants.
What is involved

We are seeking to enrol 100 patients over two years through the Dental Departments at Greenlane and Auckland Hospitals. Patients who are older than 18 years of age and who are on oral anticoagulants and who require tooth removal will be included. If you are on aspirin or one of the non steroidal anti-inflammatory drugs, you and your doctor will be asked to stop the aspirin or nonsteriodal anti-inflammatory drug for seven days before the extraction and for seven days after the extraction as this increases the likelihood of bleeding.

You will require a minimum of two blood tests to measure the degree of anticoagulation in your blood, i.e. the day of surgery and four days after your dental extraction. (Since you are taking blood thinning medication you will require these blood tests regardless of whether you are in the trail or not).

You are also required to use Cyklokapron mouthrinse four times a day for 2 minutes each time, for seven days. You will also be asked to record the time you mouth rinse, any pain relief you use and level of pain you have.

What are the risks and/or inconveniences of the study?

Your involvement in this study is similar to other methods of managing tooth extraction for patients who are on anticoagulants. This is due to the need to attend the dental department a number of times plus the need to undergo blood tests. The prevention of bleeding depends on you using the Cyklokapron mouthrinse four times a day for seven days.

Because you have not stopped taking your anticoagulant medication there is a small risk of bleeding. Biting on a pressure pack for ten minutes can normally control this bleeding. Occasionally it is possible that you may have to return to the dental department to have bleeding stopped by restitching the socket. On the rare occasion that these methods do not control bleeding you will be admitted to hospital and the bleeding controlled by an infusion of fresh frozen plasma.

Other risks include the very small possibility of bruising or difficulty in opening your mouth following surgery. Again this is a risk associated with any dental extraction.

Provided the Cyklokapron is used as a mouthrinse and spat out after holding in the mouth for 2 minutes, there is minimal adsorption into the body and therefore no risk of side effects. It has a somewhat bitter taste.

What are the benefits of the study?

There are four main advantages of treating you by this method are:

1) Because your level of anticoagulation is maintained at an effective level there is no greater risk of forming blood clots during and after your treatment than normal.
2) Because your level of anticoagulation does not have to be adjusted you may be treated without delay. This is important if you are in pain or have an infection.
3) Because the level of anticoagulation is not altered you do not have the inconvenience of having your dose reduced and then re-established. This can be difficult.
4) The risk of bleeding is similar to other methods of management.

Will taking part cost anything, and will participants receive any payment, or reimbursement of expenses?

Costs involved are the same, regardless of whether you are in the study or not. If appropriate, you will be expected to pay normal hospital dental charges for treatment. You will be given an estimate of this prior to treatment commencing

Participants will not receive any payment for taking part nor will they receive reimbursement of expenses, associated with treatment or attending treatment.
Are there other treatments available? What are the advantages/disadvantages of these?
Yes, there are, depending on your condition, three other possible ways to manage you.

Method 1
This involves reducing the level of anticoagulation so that the risk of bleeding is reduced. This takes several days. When this level is reached the teeth are removed and later that day the anticoagulant medication is restarted and adjusted to re-establish an effective level of blood thinning.

The disadvantages of this method are:
1) Your level of blood thinning is reduced and there is a minimum period of 3-4 days when it is below the recommended level. During this time there is an increased risk of forming thromboemboli.

2) Because of the delay in getting the level of blood thinning to a safe level to prevent excessive bleeding you may have to wait several days before tooth removal can be carried out.

3) When the level of blood thinning is altered it maybe difficult to re-establish the level of blood thinning at a stable level.

Method 2
If you are at high risk of forming clots you may be admitted to hospital, your oral anticoagulant stopped, and an alternative anticoagulant, heparin given by injection. After two days you have your teeth removed and the oral anticoagulant is restarted and the heparin continued until the oral anticoagulant reaches therapeutic level to prevent blood clots. You are then discharged from hospital. The advantage of this method is that you are only exposed to a short period of 12-24 hours where you are at an increased risk of clot formation. The disadvantage is that you are in hospital for 4-7 days.

Method 3
Finally, you may have your teeth removed without any change in your medication. The advantage of this is that there is no increase in the risk of clot formation. The disadvantage is that there is an increased risk of bleeding. It is estimated that one in four patients treated this way may have to return to hospital to have a minor bleed treated.

PARTICIPATION
1. Your participation is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part you will receive the usual treatment. (Normally Method 1 as outlined above).
2. If you do agree to take part you are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your future health care. Participation in this study will be stopped should any harmful effects appear or if the doctor feels it is not in your best interests to continue.

GENERAL
Your doctor will be informed that you are in this study
An interpreter will be provided if required

If you have any queries or concerns about your rights as a participant in this study you may wish to contact a Health and Disability Services Consumer Advocate, telephone 623 5799
CONFIDENTIALITY

Normal departmental and Hospital notes will be taken and stored according to normal hospital procedures.

Once recruited to the study you will be given a study number and all information from the study will be collected and entered under that number so that **no material which could personally identify you will be used in any reports on this study.** These information sheets will be stored in a locked filing cabinet and will be destroyed at the end of the study.

This study and its results will be audited by the study supervisors and may be audited by the Auckland Area Ethics Committee.

RESULTS

The results of this study will be written up as a thesis for the University of Otago degree, Master of Dental Surgery in Hospital Dentistry. They will also be submitted for publication in an internationally refereed dental journal. If you wish to receive a copy of the results my may indicate this on the consent form.

COMPENSATION

If you suffer **physical** injury as a result of your participation in this clinical trial, you may be covered by ARCIC. You should note, however, that eligibility for **cover** is not automatic.

Your claim for **cover** may be accepted by ARCIC but your **entitlement** to compensation will depend on a number of factors such as whether you are an earner or a non-earner. You should note that in most cases ARCIC provides only partial reimbursement of costs and expenses and there is no lump sum compensation payable under the current ARCIC legislation.

If you have suffered only mental injury, there will be no ARCIC compensation available.

You should also be aware that if you have cover under the ARCIC legislation your right to sue the researcher(s) or anyone else involved in the clinical trial is extremely limited.

If you have any questions about cover or entitlements under the ARCIC scheme you should contact your nearest ARCIC branch office for further information before you consent to participate in this trial.

STATEMENT OF APPROVAL

This study has received ethical approval from the Auckland Ethics Committee.

**If you have any questions about this study, please feel free to contact the researcher** Mr Bob Gibbs, Dental Surgeon, Oral Health Unit, Greenlane Hospital ph 6236494 during normal working hours.
CONSENT FORM

The use of Cyklokapron mouthrinse to prevent bleeding after dental extractions

1) I have read and I understand the information sheet for volunteers taking part in the clinical series which will report on the use of Cyklokapron mouth rinses to prevent post dental extraction bleeding. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

2) I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.

3) I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.

4) I understand that the treatment, will be stopped if it should appear harmful to me.

5) I understand the compensation provisions for this study.

6) I have had time to consider whether to take part.

7) I know who to contact if I have any side effects to the study.

8) I know who to contact if I have any questions about the medication or the study.

I agree to an auditor appointed by the Auckland Ethics Committee reviewing my relevant medical records for the sole purpose of checking the accuracy of this information recorded for the study. YES/NO

I wish to receive a copy of the results. YES/NO

I give consent for my medical practitioner (doctor) to allow the researcher(s) to have access to my medical records for the purpose of obtaining information relevant to this study. YES/NO

I consent to my doctor being informed of my participation in this study and the results of my participation in this study. YES/NO

If you have any concerns about the study, you may contact the researcher: Robert (Bob) Gibbs, Oral Health Unit, Greenlane Hospital, ph 6236494

I................................................................. (full name) hereby consent to take part in this study.

Date Signature

Witnessed
Appendix C: Letter to medical practitioner

Dear Doctor,

RE: ..............................................................D.O.B....../...../.....

I understand that the above person is a patient of yours. At the present time he/she is on oral anticoagulants but requires the removal of teeth. Traditionally this situation has been managed by reducing the oral anticoagulant level below INR 2.0. While the risk of bleeding is reduced there may be an increased risk of thromboembolism and problems associated with re-establishing a therapeutic level of anticoagulation. Recently an alternate method has been described where patients are maintained on a therapeutic dose of oral anticoagulant, the surgery is carried out, and post extraction rebleeding is prevented by the use of topical antifibrinolytic mouthrinses. The process is well described and works, however no profile envelope has been given as to the type patient who can be managed this way. We propose to fully document 100 cases looking at factors connected to anticoagulation, the surgery and rebleeding to determine which factors predispose to an increased risk of rebleeding and hence develop a profile of patients who can be managed by this method.

............................................................... has consented to join this study and is booked for tooth extraction on ......................

- Please maintain the patient on warfarin within their normal therapeutic range.
- I will arrange a pre-operative INR, APTT, FBC, BT followed by an INR four days post operation. Copies of these results will be sent to you.
- Ideally the patient should not take aspirin, or NSAID's for seven days before the operation and for seven days after the operation due to the greatly increased risk of bleeding. If you do not agree to stopping either of these drugs please contact me.
- The patient is instructed to use Cyklokapron mouthrinse, 5ml, four times a day for seven days to prevent fibrinolysis. The solution is spat out after two minutes.
- If bleeding occurs post-operatively the patient is instructed to bite on a swab for 20 minutes by the clock, if bleeding continues, then, during working hours they contact the Oral Health Unit, Auckland Hospital ph 307 2835, or after hours the Emergency Department ph 379 7740.

If you have any concerns about your patient being included in this study, or wish to have further information, please contact me at the Oral Health Unit, Greenlane Hospital, ph 623 6494. Thank you for your help.

Yours sincerely

Robert Gibbs
BDS, FRACDS
Dental Surgeon
Appendix D. Specific recommendations for prophylaxis during dental procedures:
(current recommendations and guidelines of the New Zealand Heart Foundation)

1. Standard regimen
   Amoxicillin 2.0g orally, 1 hour before procedure
   Amoxicillin 1.0g orally, 6 hours late
   NB. Oral penicillin V is an alternative to oral amoxycillin. Regimens using parenteral benzylpenicillin are an alternative to all parenteral amoxycillin recommendations.

2. Patients who have allergy to the penicillins; who have had recent penicillin treatment (ie any penicillin or cephalosporin within the last month); or are on long term penicillin prophylaxis.
   Erythromycin stearate 1.0g orally 1-2 hours before procedure.
   Erythromycin stearate 0.5g orally, 6 hours later.
   or
   Clindamycin 300mg orally 1 hour before the procedure.
   Clindamycin 150 mg orally, 6 hours later.

3. (a) High risk patients. (prosthetic, heterograph or homograph valves; those with severe lesions of their own mitral valves; those with a history of bacterial endocarditis)
   Amoxycillin 1.0g IV plus gentamycin 120 mg IV, immediately before the procedure then 1.0g IV, 6 hours later.
   (b) High risk patients allergic to the penicillins; have had recent penicillin treatment; or are on long term penicillin treatment.
      Vancomycin 1.0g IV, infused over 1 hour before the procedure.
      or
      Clindamycin 300mg IV, immediately before the procedure then Clindamycin 150 mg IV or orally 6 hours later.

4. (a) Intravenous regimen for those unable to take oral medications. (eg those under general anesthetic)
   Amoxycillin 1.0g IV, immediately before the procedure
   Amoxycillin 1.0g IV or orally, 6 hours later.
   (b) Intravenous regimen for patients who are allergic to the penicillins; have had recent penicillin treatment; or are on long-term penicillin prophylaxis
      Vancomycin 1.0g IV, infused over 1 hour before the procedure
      or
      Clindamycin 300mg IV, immediately before the procedure then Clindamycin 150mg IV or orally, 6 hours later.
Appendix E: Postextraction instructions

The use of Cyklokapron mouth rinses to
prevent bleeding after dental extractions

Post operative instructions.
1) Apart from using Cyklokapron mouth rinse, do not rinse the mouth out for 12 hours after your tooth removal
2) Eat only soft food for the first 48 hours (2days) following tooth removal
3) After the first 24 hours start using warm salt rinses after meals to gently rinse the sockets, (ie. half a tea spoon salt to a glass of warm water) after meals for two weeks. This will help keep the tooth sockets clean and help healing.
4) Continue your warfarin as directed by your doctor
5) You may use paracetamol, panadeine or digesic for pain relief as directed. Do not use aspirin or any of the NSAID’s.

| The NSAIDS drugs which may NOT be used for pain relief include: |
|---------------------|---------------------|---------------------|---------------------|
| Anafen               | Anfenax             | Ansal               | Apo-Diclofenac      |
| Arthrexin            | Butazolidine        | Brufen              | Cataflam            |
| Clinoril             | Dalcin              | Diclax              | Dolobid             |
| Froben               | Indocid             | Kefen               | Lederfen            |
| Mefic                | Motrin              | Naprosyn            | Nexen               |
| Noflam               | Nurofen             | Orudis              | Oruvail             |
| Ponstan              | Rheumacin           | Surgam              | Synflex             |
| Tilcotil             | Voltaren            |                     |                     |

| The aspirin containing drugs which may NOT be taken for pain relief include: |
|---------------------|---------------------|---------------------|
| Aspirin             | Aspec               | Aspro               | Cardiprin           |
| Cartia              | Disprin             | Ecotrin             |                     |

The use of Cyklokapron mouthrinse

It is very important you use your Cyclokapron mouthrinse as directed below. Cyklokapron is used to prevent bleeding and unless you use it as directed there is a greater chance you may have a post operative bleed.

Starting 6 hours post extraction, gently rinse 5 ml of 10% Cyclokapron mouthrinse over the sockets for **2 minutes** by the clock then **spit it out.** Do not to eat or drink for the first hour after using the mouth rinse. Carry this procedure out four times a day, that is:
- first thing in the morning when you get up,
- 12.00am,
- 6.00pm
- late as possible before going to bed.

Please fill in your time sheet to say what time you used your mouth rinse.
If bleeding occurs:

1) Make a pressure pad from gauze, place it over the bleeding socket and bite firmly on it for 20 minutes by the clock. If bleeding has stopped then record the date and time of this incident on your time sheet.

2) If bleeding has not stopped then keep biting on a pressure swab and contact Auckland Hospital:

8 am - 5 pm Monday to Friday, telephone Oral Health Unit 6236494
After hours, First phone the hospital paging system, 358 0825, when asked, enter my pager number, 4481, when asked enter your contact phone number and I will contact you back as soon as possible.

If I do not reply within 15 minutes then phone Auckland Hospital, Accident and Emergency, 379 7440, please explain:

- You are a patient of the Oral Health Unit
- You are on anticoagulants and have had teeth extracted
- Explain you are bleeding and have been asked to contact the on call dental surgeon.

Please bring in your bottle of Cyklokapron Syrup plus your data collection sheet

Blood Tests:

On ....................................................... you are required to report to your nearest Diagnostic Laboratory to have the level of your anticoagulation tested.

Suture removal appointment

An appointment has been made for you on ....................................................... at .................. for a post operative check and removal of sutures.

When you come in for this appointment please bring in your Data Sheet and the bottle of Cyklokapron syrup.

INSTRUCTIONS FOR FILLING IN YOUR DATA COLLECTION SHEET:

Please fill in you Data Collection Sheet as follows:

MOUTHRINSE TIME: Enter the time you use your Cyklokapron mouth rinse, eg. 7.00 am, midday, 6.00 pm, 10.00 pm

PAIN SCORE: Record your pain level at the time of your mouthrinse by a “X” on the line where your pain level is, 0 = no pain, 10 = the worst possible pain.

PAIN RELIEF: Whenever you require pain relief please enter the type of pain relief you use, eg. paracetamol, the dose, eg. 2 Tabs and the time taken eg. 3 pm

BLEEDING: Whenever you have a bleeding episode please enter the site, where are you bleeding from? eg, Top right (TR), top front (TF), top left (TL), bottom right (BR), bottom front (BF), bottom left (BL). How long it lasted, eg. 5min, 10 min, 15 min, 20 min, etc. The event, that caused the bleeding, either trauma (T), or spontaneous (S).

Please bring both your Data Collection Sheet and the remains of your Cyklokapron bottle if you come back to hospital with a bleeding episode and at the end of the study when you return to have your stitches removed.

If you have any concerns you wish to discuss you may contact the researcher, Bob Gibbs ph 6236494 during working hours.
<table>
<thead>
<tr>
<th>DAY</th>
<th>MOUTH RINSE TIME</th>
<th>PAIN SCORE</th>
<th>PAIN RELIEF</th>
<th>BLEEDING</th>
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<tbody>
<tr>
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<td></td>
<td>0</td>
<td>10</td>
<td>SITE</td>
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<td>DAY</td>
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<td>PAIN RELIEF</td>
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MOUTH RINSE TIME: Enter the time you use your Cyklokapron mouth rinse, eg. 7.00 am, midday, 6.00 pm, 10.00 pm

PAIN SCORE: Record your pain level at the time of your mouthrinse by a “X” on the line where your pain level is, 0 = no pain, 10 = the worst possible pain.

PAIN RELIEF: Enter the type, eg. paracetamol, the dose, eg. 2 Tabs and the time taken eg. 3 pm

BLEEDING: site, where are you bleeding from? Eg. Top right (TR), top front (TF), top left (TL), bottom right (BR), bottom front (BF), bottom left (BL). How long, eg. 5min, 10 min, 15 min, 20 min, etc. Event, either trauma (T), or spontaneous (S).
APPENDIX F: CLINICIAN DATA COLLECTION SHEET

PATIENT:

GMP:

PATIENT NUMBER SEX AGE CIGARETTE SMOKED/DAY

MEDICAL HISTORY

REASON FOR BEING ON ANTICOAGULANTS:

TIME ON ANTICOAGULANTS

PRE-EXTRACTION

<table>
<thead>
<tr>
<th>INR</th>
<th>APTT</th>
<th>PLATELETS</th>
<th>BT</th>
</tr>
</thead>
</table>

DATE ( )

INR FOUR DAYS POST EXTRACTION

VOLUME REMAINING

How did you find using the mouthrinse?

Where there any problems?

DAY POST EXTRACTION BLEEDING STARTED

TREATMENT REQUIRED TO ACHIEVE HAEMOSTASIS

EVENT WHICH CAUSED BLEED

DEGREE BLEEDING

BLEEDING PRESENTATION INR

<table>
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<th>LA</th>
<th>Suture</th>
<th>Haemostat</th>
<th>Pressure</th>
<th>LA</th>
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<th>Haemostat</th>
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<th>LA</th>
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<td>trauma</td>
<td>Spontaneous</td>
<td>trauma</td>
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<td>slight ooze</td>
<td>frank ooze</td>
<td>slight ooze</td>
<td>frank ooze</td>
</tr>
</tbody>
</table>
THE USE OF TRANEXAMIC ACID MOUTHRISE TO PREVENT POSTEXTRACTION BLEEDING DATA COLLECTION SHEET

| TEETH | 18 | 17 | 16 | 15 | 14 | 13 | 12 | 11 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 48 | 47 | 46 | 45 | 44 | 43 | 42 | 41 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 |
|-------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| REMOVED |
| PERIO BLEED |
| POCKET |
| METHOD |
| FLAP |
| BONE REMOVAL |
| SUTURE |
| HAEMO-STAT |
| DIFFICULTY |
| COMPLICATIONS |
| TOTAL TIME TAKEN | min |
| ANTIBIOTICS: INTRAOPERATIVE | | | |
| POST OPERATIVE | | | |