

Efficacy of Tranexamic Acid Mouthrinse as a Haemostatic Agent after Extraction in Patients Who are on Anticoagulant and Anti Platelet Therapy

Dr. Abirami .K

Oral and Maxillofacial Surgery

Abstract: Background: Optimal management of patients on anti platelet and anti coagulant who require oral surgery procedure has been controversial. Historically the surgeons have to balance the risk of thromboembolism by reducing or stopping anti platelet and anticoagulant therapy, against the risk of triggering excessive post extraction bleeding if anticoagulation or anti platelet is maintained at therapeutic levels during surgery. Patients on anti platelet and anticoagulants have impaired fibrin formation that is more susceptible to normal fibrinolysis and is believed to be the major cause of post extraction bleeding. In this study the "Efficacy of tranexamic acid mouth rinse as a haemostatic agent after extraction in patients who are on anticoagulant and anti platelet therapy" has been studied. Aims and Objective: The aim of this study was to verify that this technique is a safe, simple, effective and an acceptable method of patient management. The objective was to identify potential risk factors that may increase the likelihood of bleeding. Materials and Methods: One hundred consecutive anti platelet and anti coagulant patients with an International Normalized Ratio (INR) ranges between 1.9 and 3.5 on the day of surgery and who required dental extractions were recruited to this study. Following dental extraction, patients were instructed to use 5 milliliters of 10% tranexamic acid mouth rinse 4 times a day for 7 days, to record bleeding that required pressure to control and their mouth rinse usage. The researcher collected demographic data, details of the state of anti platelet and 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 (16.0). Descriptive statistics were produced for the sample demographics, the pre extraction profile, the post extraction bleeding profile, mouth rinse acceptance and utilization. Identification of potential risks that might increase the likelihood of bleeding was carried out using the paired and unpaired t test appropriate. Results: Of the 100 patients treated, 17 reported bleeding at home on day 1 and 3 patients after day 1. The bleeding reported on these 20 patients was controlled at home only by tranexamic acid pressure pack alone. A further 9 patients reported to the researcher's dental surgery department for bleeding which was then controlled by administering other local haemostatic measures (gelatin foam) with tranexamic acid pressure pack. No patients required hospital admission for systemic management of bleeding. Statistical analysis reveals significant risk factors for post extraction bleeding were as follows: Patients in the age group of 41-60; Pre extraction INR equal to and greater than 2.5 ; Smoking. Factors not statistically significant for an increased risk of bleeding included: The number of teeth removed; Pre-extraction bleeding time and Time on anti platelets and anticoagulants. Conclusion: On the basis of research and statistical analysis, it can be concluded that the post-operative use of tranexamic acid mouth rinses in patients who underwent dental extraction at therapeutic INR levels is a safe, simple, effective and an acceptable method of reducing post extraction bleeding.

Keywords: Antiplatelet, Anticoagulant, Post Extraction Bleeding, Hemostasis, Tranexamic Acid.

1. Introduction

An increasing number of patients requiring oral surgery are on long-term anti platelet and anticoagulant therapy. While a number of dental management protocols had been suggested, but still controversy remains. The clinician must balance the risk of thromboembolism by reducing or stopping anti platelet and anticoagulant therapy against the risk of triggering excessive post extraction bleeding if anti platelet and anticoagulation is maintained at therapeutic levels during surgery.¹

Oral anticoagulants and anti platelets are widely used for primary prevention of thromboembolic events in patients with atrial fibrillation and prosthetic heart valves and secondary prevention after systemic embolism in patients with rheumatic mitral valve disease, mitral valve prolapse, mitral annular calcification, non rheumatic mitral regurgitation, aortic plaques larger than 4 mm.²

However, one of the major drawbacks in the use of oral anticoagulant and anti platelet therapy is the increased risk of bleeding after traumatic injuries and surgical procedures.

Patients receiving OAT are generally older, present with multiple comorbidities, and receive several medications.³

The agents most commonly used to control and prevent thromboembolic events are thrombocyte aggregation inhibitors (such as acetylsalicylic acid (ASA) and clopidogrel) and vitamin K antagonists (such as warfarin, acenocoumarol, and fenprocoumon)⁴.

Antiplatelet Therapy and Oral Surgery

Since platelets provide the initial haemostatic plug at the site of a vascular injury, they are involved in pathological processes and are an important contributor to arterial thrombosis leading to myocardial infarction and ischemic stroke⁵. The common anti platelet drugs are ASA, clopidogrel and dipyridamole.

When platelets are inhibited, it takes longer time for free blood flow from a cut to stop and for primary haemostasis to occur, as a consequence, the bleeding time is prolonged⁶. However, the effect on primary haemostasis is minimal in patients without additional risk factors for impaired clotting. Anti platelet medications can double the baseline bleeding time, but this may still be within or just outside the normal

range. It has been reported that only 20% to 25% of patients using ASA have an abnormal bleeding time⁶.

Anticoagulation Therapy and Oral Surgery: The goal of anticoagulant therapy is to prevent clot formation or expansion and Warfarin is the most common drug used in this therapy⁷. If warfarin therapy is stopped, it would take about four days for INR to reach 1.5 in almost all patients and with this INR, any surgery can be safely performed.⁸ After warfarin therapy is restarted, approximately three days will be needed for the INR to reach 2.0. Therefore, if warfarin is withheld for four days before surgery and treatment is restarted as soon as possible after surgery, patients would have a sub-therapeutic INR for approximately two days before surgery, and two days after surgery increasing the risk of thromboembolism⁹. Besides this, the intensity of anti-coagulation, the perioperative risk of thromboembolism may be increased due to other factors, in particular a rebound hypercoagulable state caused by the discontinuation of warfarin and the prothrombotic effect of the surgery itself¹⁰. Consequently, for patients whose INR returns to normal shortly after stopping warfarin therapy, it can be assumed that the risk of preoperative arterial thromboembolism, postoperative arterial thrombo-embolism, and preoperative venous thromboembolism will be similar to that which is expected in the absence of anticoagulation¹¹.

Bleeding vs Thromboembolic Complications: Even though continuing the antiplatelet or the anticoagulation therapy during dental surgical procedures would increase the risk of postoperative bleeding requiring intervention, stopping them does not guarantee that the risk of postoperative bleeding requiring intervention will be eliminated as serious bleeding can occur in non-anticoagulated patients¹². Most cases of postoperative bleeding can be managed by pressure or repacking and resuturing the sockets. The incidence of postoperative bleeding which could not be controlled by local measures varied from 0% to 3.5% .¹³

Bleeding complications, while inconvenient, do not carry the same risks as thromboembolic complications. Patients are at high risk of permanent disability or even death if they stop anti platelet or anticoagulation medications prior to an any surgical procedure than if they continue it. Thromboembolic events, including fatalities, had been reported after antiplatelet or anticoagulation withdrawal. Although the risk is low, the outcome is serious. This must be balanced against the fact that there is no single report of uncontrollable bleeding when dental procedures had been carried out without stopping anti platelet or anticoagulation medications¹⁴.

It is important to consider the consequences of venous and arterial thromboembolism, and of bleeding, in addition to the rates at which these outcomes occur. Six percent of recurrent episodes of venous thromboembolism were expected to be fatal¹⁵. A small group of patients with recurrent events, perhaps 2%, will have serious permanent disability, though the majority will recover well. The consequences of thromboembolism are much more serious; approximately 20 % of these episodes could be fatal, and 40 % result in serious permanent disability¹⁶.

No cases of permanent disability or death, reported as a consequence of postoperative bleeding associated with a dental surgical procedure in which the patient continued oral anticoagulation, were found. The majority of researches that had considered the risks of stopping versus continuing anti coagulation or anti platelet therapy for dental procedures had concluded that most dental patients can undergo dental procedures without stopping their therapies provided that local haemostatic measures were used to control post operative bleeding¹⁷.

Aim

The aim of this study is to research and observe a sample of 100 patients who are on anti coagulant and anti platelet therapy going for teeth removal while being maintained at therapeutic INR and using tranexamic acid as mouth rinses post operatively to achieve hemostasis.

Objective

- To verify that this technique is a relatively safe, simple, effective and an acceptable method of managing these patients;
- To identify risk factors that may have the potential to increase the likelihood of bleeding.

2. Review of Literature

Forbes et al (1972) conducted a double-blind trial study using tranexamic acid 1 g three times a day for five days, and he noticed significantly reduced blood loss and transfusion requirements after dental extraction in patients with hemophilia and Christmas disease. No side effects were seen. Screening tests showed no toxic action of tranexamic acid on the liver, kidney, or heart.¹⁸

Sindet-Peterson & Stenbjerg (1986) evaluated 3 groups of patients (56 subjects) all with congenital deficiencies in factor VIII and factor IX. Group 1 received high doses of factor concentrate and systemic TXA. Group 2 received the same therapy as the 1st group with an addition of topical mouth-rinse Tranexamic acid. Group 3 received factor replacement therapy to increase levels to approximately 10 % of the normal value perioperatively, combined with systemic and local Tranexamic acid mouthrinse. The author concluded that local anti fibrinolytic therapy as a supplement to systemic therapy which significantly decreased the incidence of postoperative bleeding. At last, the study results suggested that replacement therapy of deficient clotting factors may be reduced during oral surgery in hemophilia patients with utilization of fibrinolysis inhibitors.¹⁹

Borea et al. (1993) reported 15 of the study group used tranexamic acid mouth rinse postoperatively and maintained oral anticoagulation and anti platelet therapy 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. From this the author concluded that OAT does not need to be withdrawn before any oral surgery provided that local antifibrinolytic therapy was instituted.²⁰

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 was no major bleeding complications.²¹

Bandrowsky et al. (1996) reported the case of a patient with a pre-extraction INR of 3.5 who had 20 teeth removed. On the 4th day after tooth removal, the patient who bleed and required hospital admission, had an INR that had risen to 9. The bleed was thought to be due to the grossly elevated INR that had occurred from the interaction of warfarin with amoxicillin. This adverse event cannot be construed as a primary failure of tranexamic acid related inhibition of fibrinolysis.²²

Gaspar et al. (1997) evaluated 47 patients receiving anticoagulant therapy. 15 members in control group had their surgery carried out after oral anticoagulant and anti platelet medication was reduced. The 32 patients in test group underwent surgery without a change in anticoagulant therapy but used tranexamic acid mouth rinse postoperatively. There was no significant difference in the incidence of bleeding between the 2 groups.²³

Herman et al. (1997) wrote, "In certain situations, primarily those dealing with complex oral surgical procedures, were not sufficient reports to make generalization 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".²⁴

Although **Purcell (1997)** discussed the management of the anticoagulated patient and described the use of tranexamic acid, and he identifies the potential risk factors that may increase the likelihood of bleeding in this group of patients so they are better managed.²⁵

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%. On this basis, it is estimated that stopping an antiplatelet and 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 and anti platelets are stopped. Author estimated that anticoagulation reduced the risk of recurrent venous thromboembolism by about 80%. A patient with non-valvular atrial fibrillation, not on antithrombotic therapy had an average risk of systemic embolism of 4.5% per year. In this situation, anticoagulation and anti platelets reduces the risk of embolism by 66%. It is estimated that the risk of major thromboembolism in patients with mechanical heart valves was 8 % per year. Anticoagulation reduced this risk by 75%. Anticoagulant and anti platelet are therefore highly effective at preventing recurrent²⁶ thromboembolic events in patients receiving this medication for venous and arterial diseases.¹⁸

Wahl (1998) carried out a review of the available literature on dental surgery in anticoagulated patients. He viewed 26 case reports on 774 patients who underwent nearly 2014 invasive 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 received continuation of anticoagulation had no serious bleeding problems after dental surgery. Only 12 patients (<2%) had bleeding problems that required more than local measures.²⁷

Wahl (1998) in his second review of 16 case reports from 493 patients involving 542 procedures was carried out on patients who had continual anticoagulation withdrawn specifically for dental procedures. Five patients (1%) had serious embolic complications, including 4 deaths.²⁷

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 were reported in either group and only 1 patient from each group had mild delayed haemorrhage. This was easily controlled by local measures. There had only been 1 report of a major bleed following this protocol²⁸.

Bernardoni saccarro et al (1998) did a study in Thirty seven dental treatments were performed in 15 patients. Group A: nineteen extractions, treated with oral rinse with tranexamic acid (250 mg dissolved in 10 ml of water). Group B: eighteen extractions, in which oral rinse was utilized. Only in five (13.5%) dental extractions (1 from group A and 4 from B) bleeding prolonged were observed. The results suggested that mouth washing with tranexamic acid prevents excessive oral bleeding in patients treated with oral anticoagulants with an INR between 1.7 and 2.5.²⁹

Blinder et al (1999) reviewed the postoperative bleeding in patients with oral anticoagulant treatment those who were underwent dental extractions without discontinuation of the treatment and he compared the effect of 3 different hemostatic modalities in 150 patients underwent dental extractions were divided into 3 groups. Local haemostasis were carried out as follows: group one (119 extractions), with gelatin sponge and closure with sutures; group two (117 extractions), with gelatin sponge and sutures, and mouth rinse with tranexamic acid; group three (123 extractions), with fibrin glue, gelatin sponge, and closure with sutures.³⁰

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 anti coagulant/ anti platelet was unnecessary provided that the INR is within the therapeutic range."³¹

Ardekian et al (2000) investigated a study regarding stopping versus continuing low-dose ASA prior to dental extraction. 30 patients taking ASA 100mg daily were studied. Nineteen continued ASA as normal, while 20 stopped taking ASA seven days before the planned

extractions. A bleeding time test was performed one hour prior to the procedure. The mean bleeding time was longer in patients who continued ASA compared to those who stopped. Although the difference was statistically significant, none of the patients who continued ASA had a bleeding time outside the normal range in this study (2-10 min). Intraoperative bleeding was controlled in 33 (85%) patients with gauze packing and sutures. Six patients (2 who stopped ASA and 4 who continued ASA) had tranexamic acid added to the local packing. At the end of the study, it was observed that no patient experienced uncontrolled bleeding immediately after the procedure or in the following week.³²

In another study, **Wahl (2000)** also estimated the incidence of serious bleeding problems in 950 patients receiving anticoagulation therapy undergoing 2400 individual dental procedures. Only 12 patients experienced bleeding uncontrolled by local measures and none of the patients were reported to have experienced serious harm. Of these 12 patients, seven had higher than recommended anticoagulation levels; three were given a course of postoperative antibiotics, which may interacted with the warfarin and two were using a placebo mouthwash four times a day immediately after the procedure, which is contrary to standard advice to avoid rinsing for the first 24 h.³³

Campbell et al. (2000) randomized 25 patients to discontinue warfarin 72-96 hours prior to surgery (13 patients) or to continue anticoagulants (12 patients). A further group of ten individuals not receiving anticoagulants served to establish a baseline bleeding risk. No patient in any group had postoperative bleeding sufficiently severe to require therapeutic intervention and there were no significant differences in blood loss between the three groups.³⁴

Blinder et al (2001) reviewed the incidence of postoperative bleeding in patients treated with oral anticoagulant therapy those who underwent dental extractions without interruption of anticoagulant treatment to analyze the incidence of postoperative bleeding according to the (INR) value. The 249 patients who underwent 543 dental extractions were divided into five groups. Of the 249 patients, thirty presented with postoperative bleeding (12%): Group one, 3 patients presented with bleeding (5%), Group two, 10 patients (12.8%), Group three, 9 patients (15.2%), Group four, 5 patients (16.6%) and Group five, 3 patients (13%).¹⁸ The incidence of postoperative bleeding were not significantly different among the 5 groups. The value of the INR at the therapeutic dose does not significantly influence the incidence of postoperative bleeding. Therefore, dental extraction can be performed without interruption of oral anticoagulant and antiplatelet treatment. Local haemostasis with gelatin sponge and silk sutures appears to be sufficient to prevent postoperative extraction bleeding.³⁵

Evans et al (2002) reviewed 109 patients on continuous OAC requiring dental extractions to either continue (57 patients) although if the INR was less than 4 on the day of surgery, the patient was stopped. The control group (52 patients) stopped taking OAT two days prior to

surgery and if the INR was greater than 2 on the day of the procedure this was subsequently rebooked for the following day. From this study the author concluded that the rate of bleeding was higher in the group continuing anticoagulation than in control group but the difference between the two group was not significant.³⁶

Lockhart et al (2003) reviewed that postoperative bleeding was considered to be a significant if it conforms to the following four criteria: the bleeding continues beyond 12 hours; it causes the patient to call or return to the dental department or emergency department; results in the development of a large haematoma or ecchymosis within the soft tissues; and requires a blood transfusion.³⁷

Carter et al (2003) evaluated the use of a prescribed 4.8% TXA post-operative mouthwash over 2 days vs 5 days to prevent bleeding in patients taking anti coagulant who requires dental extractions. Eighty five patients under anticoagulant therapy who requires dental extractions, were randomly divided into 2 groups. Group A postoperatively received a 4.8% TXA mouthwash to be used over 2-day period. Group B received the same TXA mouthwash and postoperatively instructed, to be taken over 5 days. 82 of the 85 patients had no postoperative problems. 2 patients in group A and 1 in group B had minor postoperative bleeds that required minor intervention to control. This study shows that a 2-day postoperative regime of a 4.8% tranexamic acid mouthwash was as equally effective as a 5-day regime in controlling post extraction bleeding.³⁸

Cannon and Dharmar (2003) suggested Growing evidence that anticoagulant treatment does not need to be withdrawn or reduced before oral surgery, as long as local hemostatic measures including suture and irrigation of surgical site with TXA followed by mouthwash were performed for these patients. Other hemostatic agents such as autologous fibrin sealant, absorbable gelatin sponges, and oxidized cellulose polymer had also been indicated in surgical practice.³⁹

Keiani Motlagh et al (2003) did prospective clinical study on use of tranexamic acid mouthwashes in patients taking oral anticoagulants underwent minor oral surgery, without modifying their anticoagulant therapy and he did study on Forty patients (18 men and 22 females) aged from 42 to 81. All patients were under the same anticoagulant, vitamin K antagonist, (Sintrom) for different pathologies. The anticoagulant therapy was modified neither before nor after surgery. Tranexamic acid 5% (Exacyl) mouthwashes were prescribed during and after surgery and no postoperative bleeding was reported. So he stated that Use of tranexamic acid mouthwashes under a specific protocol was an efficient, reliable and economic method in preventing postoperative bleeding in patients under oral anticoagulant therapy.⁴⁰

R. Sacco MD, M. Sacco MD, (2007) reported that One hundred thirty-one patients on OAT were randomized to reduced anticoagulation or to full anticoagulation, and 511 teeth were extracted by the same surgeon. Mild bleeding, but excessive enough to warrant adoption of supplementary local hemostatic measures, were observed in 10 cases (15.1%) in the reduced dosage group and in 6 cases (9.2%) in the unmodified dosage group, which was a non significant

difference. There were no thrombotic complications in either group and he concluded this randomized study showed that, using simple measures for local hemostasis it is not necessary to reduce OAT in patients undergoing routine dental extractions.⁴¹

Aframian et al. (2007) concluded that patients administered low-dose ASA can undergo any type of oral treatment, minor surgery and/or tooth extractions, without having to suspend the antiplatelet medication, and without any added risk for the patients with help of local hemostatic measures being more than enough to secure bleeding control⁴².

Pototski et al (2007) reviewed that antiplatelet and anticoagulant agents had been extensively researched and developed as potential therapies in the prevention and management of arterial and venous thrombosis. On contrary, anti platelet and anticoagulant drugs were also been associated with an increase in bleeding time and risk of postoperative hemorrhage and he concluded that the optimal INR value for dental surgical procedures is 2.5 because it minimizes the risk of either hemorrhage or thromboembolism so minor oral surgical procedures, such as biopsies, dental extraction and periodontal surgery, can safely be done with an INR lower than 4.0.⁴³

Madrid and sanz (2009) reviewed nineteen studies were identified reporting outcomes after oral surgery procedures. Five studies were randomized-controlled trials, 11 were controlled clinical trials and three were prospective case series. The results of these studies are very homogeneous, reporting minor bleeding in very few patients, without a significant difference between the OAT patients who continue with the vitamin K antagonists vs. the patients who stopped this medication before surgery. These post-operative bleeding events were controlled only with local haemostatic measures: tranexamic acid mouthwashes, gelatin sponges and cellulose gauzes application were effective. In none of the studies was a thromboembolic event reported and they concluded OAT patients those are continue the AC medication does not have a significantly higher risk of post-operative bleeding than non-OAT patients and they also do not have a higher risk of post-operative bleeding than OAT patients who discontinue the medication. In patients with OAT (INR 2-4) without discontinuation, topical haemostatic agents were effective in preventing post-operative bleeding.⁴⁴

Nematullah et al (2009) reported that his recent meta-analysis showed that peri operative continuation of warfarin did not increase the risk of bleeding for patients undergoing minor dental procedures.⁴⁵

Soma et al in 2010 reviewed dental surgical extractions that were performed on 532 patients diagnosed at risk of thromboembolism without interrupting their anticoagulant therapy. And he confirmed that anticoagulant therapy can be modified successfully and no need to be interrupted, which can carry significant risks.⁴⁶

Manuel-Alejandro et al (2010) compiled a sample of 1194 patients selected. Of these patients, a total of 2392 simple, serial surgical extractions were performed; none of the

patients interrupted their anticoagulant treatment with warfarin sodium. Of these eighty three sample presented with a some degree of bleeding; where in seventy seven of samples, the bleeding was controlled with local hemostatic measures, where in six patients required their dose of OAT to be adjusted. There was a higher incidence of post extraction bleeding in patients with periodontal pathology, compared to caries and pericoronitis and the author concluded that there was an increased number of bleeding in patients with periodontal problems, due to the increased presence of inflammation in the soft tissues.⁴⁷

Campell et al (2010) suggested that many patients can undergo surgical treatments safely without interrupting their usual therapeutic anti-coagulation regime and without any additional medical intervention by using TXA locally as a post-operative antifibrinolytic agent for 2 days⁴⁸.

Christian Bacci et al (2010) et al conducted Four hundred fifty-one patients being treated with warfarin who required dental extraction were compared with a control group of 449 non-anticoagulated subjects undergoing the same procedure. In the warfarin-treated group, the OAT regimen was maintained unchanged, such that the patients had an INR ranging between 1.8 and 4, and local haemostatic measures (i.e. gauzes saturated with tranexamic acid) were adopted. Of these 2 groups report was not statistically significant. And he stated that results of this study which applied in large, multicenter study show that dental extractions can be performed easily and safely in an OAT outpatients without any interruption of the ongoing oral anticoagulant therapy, thus minimizing the costs and reducing discomfort for patients.⁴⁹

Ker et al (2013) reviewed 29 trials involving 2612 participants. In this study 28 trials involved patients undergoing surgery without bleeding and only one trial involved patients with epistaxis (nosebleed). Thus Tranexamic acid reduced blood loss by 29% There was uncertainty regarding the effect on death myocardial infarction, deep vein thrombosis and pulmonary embolism TXA reduced the risk of receiving a blood transfusion by a relatively 45%. By this the author concluded that topical application of tranexamic acid reduces bleeding and avoid blood transfusion in surgical patients, however the effect on the risk of thromboembolic events was uncertain.⁵⁰

Sammar tino et al. (2012) stated that cardiovascular disease was the most common cause of mortality in elderly people worldwide, oral anticoagulants are widely used for long-term prevention or treatment of cardiovascular events, including stroke and myocardial infarction. For this reason, the management of patients on OAT requiring surgical procedures remains a challenge due to the risk bleeding if therapy was continued.⁵¹

Wardrop et al. (2013) stated the literature with regard to the use of antifibrinolytics for the prevention of post extraction bleeding in patients with hematologic disorders. The author suggested that TXA and ACA may be useful adjuncts to platelet transfusions so that platelet use, and their complications associated with their use, can be reduced. However, the sample of this study were too small to assess

whether antifibrinolytics which increased the risk of thrombo embolic events.⁵²

Gandhi et al (2013) reported that TXA, a synthetic derivative of the amino acid lysine, was an antifibrinolytic agent that blocks lysine-binding sites on plasminogen, thereby reducing the local degradation of fibrin by plasmin. TXA works to stabilize and to inhibit the degradation of existing clots, and it was widely used to limit bleeding in clinical practice. A series of systematic reviews and meta-analyses were published showing strong evidence that TXA is effective in reducing blood loss and transfusion requirements in knee arthroplasty.⁵³

Micheal Wahl (2014) stated that the physicians and dentists must weigh the bleeding risks in continuing antiplatelet medications versus the thrombotic risks in interrupting antiplatelet medications. However, the risk for thromboembolic complications after interruption of antiplatelet and anti coagulant therapy for dental procedures was apparently significant, although small." Thus there was a small chance that continuing antiplatelet therapy that will result in non fatal bleeding which requiring local measures for hemostasis versus a small but significant chance that interrupting antiplatelet therapy will result in a possibly fatal thromboembolic complication. So the author stated that the decision was simple: "It is time to stop interrupting antiplatelet and anticoagulant therapy for dental surgical procedures."⁵⁴

Ripolles de ramon J (2014) et al. Hypothesis was based on studies of local application of tranexamic acid after maxillofacial interventions as effective therapeutic alternative for the prevention and control of bleeding. With this the author stated that the effectiveness of the application of a tranexamic acid solution after tooth extraction in anticoagulated patients in terms of healing time and degree of healing.⁵⁵

Kammerer et al (2015) reviewed the clinical protocol to reduce the risk of bleeding during surgery or invasive procedures in patients receiving OAT remains controversial. Different recommendations has been proposed, including reduction, complete withdrawal, or substitution of OAT with heparin prior to the surgical procedure, but there was strong evidence that OAT patients undergoing oral surgeries should not discontinue their medication due to the risk of thromboembolic complications.⁵⁶

Wei and Liu (2015) did a series of Systematic reviews and meta-analyses were published showing Strong evidence that TXA was effective in reducing blood loss and Transfusion requirements in knee arthroplasty , hip surgeries, and spinal surgeries without increased. Thromboembolic complications such as myocardial infarction, deep venous thrombosis, and pulmonary embolism.⁵⁷

Lucy et al (2016) investigated the incidence of bleeding after dental extraction without stopping antiplatelet therapy. Postoperative bleeding was assessed in a total of 1271 patients who were divided into 2 groups: a study group comprising 183 patients on antiplatelet therapy who underwent 548 dental extractions on 274 occasions and a

control group comprising 1088 patients who were not receiving any antiplatelet or anticoagulant therapy and underwent 2487 dental extractions on 1472 occasions. However, the differences were not significant. Postoperative bleeding were managed successfully by repacked with Gelfoam impregnated with tranexamic acid powder in 12 patients and by resuturing in three of the control patients undergoing extraction of impacted teeth with flap elevation. Finally author concluded that there was no need to interrupt antiplatelet drugs before dental extraction.⁵⁸

Quireoz et al (2016) reviewed the increased risk of bleeding observed in patients on oral anticoagulant therapy (OAT) undergoing outpatient oral surgical procedures had been reported in the literature and remains a major concern in the care of these patients. This is still of great concern to dental surgeons that discontinuing OAT medication increases the risk of thromboembolism, while maintaining the therapeutic dose increases the risk of hemorrhage. The author represented 1821 patients receiving OAT, 4116 tooth extractions, and 144 cases of postoperative bleeding. In most studies, there were no differences in the effectiveness of various local hemostatic measures, and only tranexamic acid was proven effective as compared with a placebo group. The reported INR values varied widely among studies; the lowest INR value was 0.9 and the highest was 5.0. All local hemostatic methods showed low rates of bleeding; and when bleeding occurred, the use of these methods was essential for controlling postoperative bleeding. While local hemostatic measures appear to be effective in controlling postoperative bleeding, additional controlled randomized clinical trials were needed to assess the true effectiveness of these measures in patients taking OAT.⁵⁹

Murphy et al (2016) stated that the antifibrinolytic drug tranexamic acid (TXA) was effective in reducing blood loss and transfusion requirements in other fields of elective surgery and its use was emerging in a number of plastic surgical subspecialties. This systematic review and meta-analysis evaluated the current evidence for the efficacy and safety of TXA in craniomaxillofacial, head and neck, breast, aesthetic, burns, and reconstructive microsurgery. Studies were analyzed using standard methodology. A total of 7965 records were screened, of which 14 met the inclusion criteria. Seven were suitable for meta-analysis. In craniofacial surgery, TXA was associated with a mean reduction in blood loss of 18.2 mL/kg (P = 0.00001) and a mean reduction in blood transfusion of 8.7 mL/kg (P = 0.0001). In orthognathic surgery, TXA was associated with a mean reduction in blood loss of 156 mL (P = 0.001). Tranexamic acid may also have a role in reducing drainage output volumes in oncological breast excision and lymph node dissection of the neck. Level-1 evidence for efficacy in aesthetic surgery, burns, and reconstructive microsurgery is lacking. Although no reported complications were attributable to TXA, there remain no phase IV trials published. Level-1 evidence supports the use of TXA in craniofacial and orthognathic surgery. There exists an unmet need for studies in areas, including burns, aesthetic surgery, and reconstructive microsurgery. Phase IV trials in areas of proven efficacy are also required.⁶⁰

Ali Mithiborwala et al (2016) evaluated the post extraction control of haemorrhage with administration of TXA as pressure pack in patients on anticoagulant and antiplatelet therapy. And he reported no instances of post extraction bleeding, except in 1 and whom intravenous TXA was given, which the bleeding was controlled. No TXA allergy was noted. And postoperative control of haemorrhage was there acceptable in all the cases.⁶¹

Sara Juliana et al (2017) suggested that surgical site irrigation with TXA followed by mouthwash during the first postoperative week is safe and may reduce the risk of bleeding after minor oral surgeries in anticoagulated patients. However, additional trials should be conducted to compare TXA efficacy over absorbable hemostatic materials.⁶²

Nishidha et al (2017) summarized the recent evidence or recommendations in the related guidelines related TXA and briefly summarized the evidence for the safety of TXA administration by a systematic review method using observational studies. Consequently, the relative risk for venous thromboembolism was 1.61, indicating a non-significant increase in the venous thromboembolism risk of TXA therapy.⁶³

3. Materials and Methods

A. **Study design:** Comparative interventional study

B. **Study participants (human)**

a) **Inclusion criteria**

- Who were on oral anticoagulants and anti platelets and required removal of teeth;
- With an INR between 1.9 and 3.5 on the day of surgery
- Aged 18 years or older

b) **Exclusion criteria**

- They failed to give informed consent;
- They had a known bleeding disorder or liver failure;
- They had an INR less than 1.9 or an INR greater than 3.5;
- Patients who are on dual anti platelets, dual anti coagulants, antiplatelet and anti coagulant. They had an APTT greater than 55 seconds or a bleeding time greater than 8 minutes, unless cleared by advice from a haematologist;
- They were unable to follow instructions, either because of language difficulties or because of intellectual or physical impairment.

c) **Number of groups to be studied, identify groups with definition : 1 Group**

C. **Sampling**

- a) Sampling population : 100
- b) Sample size calculation

$$N = \frac{4pq}{d^2}$$

P=incidence of bleeding =42.86⁽⁶⁴⁾.

Q=100-P D=20% of P

Sample size = 100

Total sample size of study = 100

c) Sampling technique : Convenient sampling

4. Study Procedure

The patients were managed at Department of Oral and Maxillofacial Surgery OPD in Sree Mookambika Institute of Dental Sciences. Prior to the surgery the patients concerns were discussed. Their general medical conditions were assessed and the proposed treatment plan confirmed. The patients BT, INR and APTT were recorded. If the INR is in the range 1.9 – 3.5 the patient was admitted to the study. If the INR below 1.9 the patient was managed conventionally using local measures without entering the study and without using tranexamic acid mouthrinse. If the INR value was greater than 3.5 they were excluded from the study. Patients with cardiac condition requiring prophylactic antibiotic cover were given oral / intravenous antibiotics according to American Heart Foundation Guidelines.

Uncomplicated extraction was carried out under local anaesthetic in the dental chair using 2% lignocaine with 1:80,000. The teeth were removed using either forceps and /or elevators. 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. After 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 was observed. If the 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 gelatin sponge 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 was observed. If bleeding had stopped the patient were discharged and was provided with their home-care pack of tranexamic acid mouthrinse along with post-operative instructions.

If the 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 solution. The wound was then irrigated with 10 % tranexamic acid mouthrinse 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 along with their home-care pack of tranexamic acid mouthrinse and post-operative instructions. If the patient continues to bleed, this was recorded. Consideration was given to an infusion of fresh frozen plasma/ platelets or vitamin K, DDAVP

All details of this management and outcome were recorded. The patient was discharged with the following items:

a) 500 mg , tranexamic acid tablets plus 5 ml measure;

- b) Post-operative instructions/data collection sheet;
- c) Pressure swabs;
- d) Laboratory request form for post-extraction INR on day 4;
- e) Postextraction antibiotics (if required).

Post-operative instructions: The patient was instructed to crush the 500 mg tablets and dissolved in 5ml sterile water and use 5ml of 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 mouth rinse was carried out on the data-collection sheet. Apart from using the tranexamic acid mouth rinse, the patients were instructed not to rinse their mouth on the day of surgery. Only soft food was to be eaten during first 2days following surgery. On the fourth day after surgery the patients 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 is instructed to contact the researcher who would manage the bleed at dental surgery department.

Management of postextraction bleeding:

Any patient presenting to the researcher's dental surgery with post extraction bleeding was asked to bring in their tranexamic acid mouthrinse 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 hematology laboratory for an INR. The history of the presenting bleed was reviewed. The contents of the tranexamic acid mouth rinse were measured and the data

sheet reviewed to determine the degree of compliance to mouth rinse use. After 20 minutes the swab was removed and the wound was observed. If the bleeding had stopped the sutures were reviewed and if necessary extra sutures placed. If required, gelatin sponge 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 traumatizing the area.

If the wound continued to ooze, the sutures were removed and the bleeding point identified gelatin sponge or oxidized regenerated cellulose 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 the bleeding had stopped the patient was discharged and instructed to continue using the tranexamic acid mouthrinse and avoid traumatizing the area.

Suture removal appointment

The suture removal appointment was scheduled on the seventh days after surgery. The patient was asked to return the data collection sheet together with the tranexamic acid mouth rinse. Once the patients arrival in the department, a quick survey was made of the responses on the data collection sheet. The patient was asked about their use of the mouth rinse. Any problems or adverse effects associated with the mouth rinse were sought out. The sutures were removed and any swelling, bruising or limited opening noted. Then the patient was discharged. The data collection sheet data was then reviewed in detail. The number of times the mouth rinse was used as entered on the sheet by the patient was divided by the number of times the mouth rinse should have been used, in order to calculate the percent compliance. The data were recorded.

Colour Plates



CP 1: Armamentarium



CP 2: Home Care Pack



CP 5: Irrigated with 10% tranexamic acid over the extracted site



CP 3: Extraction of Lower Anterior using Forceps



CP 6: Pressure Pack given by Gauze Soaked in Tranexamic Acid



CP 4: Immediate post extraction bleeding



CP 7 : Haemostasis achieved after 20 minutes



CP 8 : Post Extraction Bleeding after Day 2 of Another Patient



CP 9: Irrigated with 10% tranexamic acid over the bleeding socket



CP 10: Haemostasis achieved after 20 minutes

5. Results and Observation

Statistical analysis:

The data was expressed in number, percentage, mean and standard deviation. Statistical Package for Social Sciences (SPSS 16.0) version used for analysis. Unpaired and Paired t test applied to find the statistical significant between the groups. P values less than 0.05 ($p < 0.05$) considered statistically significant at 95% confidence interval.

Description

One hundred individual patients were recruited into this study. There were 60 males and 40 females. The mean age was 57.1 years with a standard deviation of 15.6 years (range 23- 87 years). The duration of anti platelet and anti coagulant prophylaxis varied between **2 weeks** to 20 years. The median length of therapy was 2 years. The indications for anticoagulant / anti platelet prophylaxis are shown Table 5. The majority, (59 %) were smokers. 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, penicillin, augmentin and cephalosporin. Perioperative antibiotics were prescribed for 62 patient episodes (generally for infective endocarditis prophylaxis). Agents used were amoxycillin, cephalosporin and gentamicin . Amoxycillin was necessary to control postoperative infection in 75 patient episodes.

Of these 100 patients treated, 17 reported bleeding at home on day 1 and 3 patients after day 1 that was controlled only by tranexamic acid pressure pack. A further 9 patients reported to the researcher's dental surgery where bleeding was controlled by local measures using gelatin sponge. No patients required hospital admission for systemic management of bleeding.

Statistical analysis reveals significant risk factors for postextraction bleeding were: those patients on age between 41-60; pre extraction INR equal to greater than 2.5; smoking.

Factors not statistically significant for an increased risk of bleeding included: The number of teeth removed; pre-extraction bleeding time; time on anti platelets and anticoagulation.

Finally concluded that the post-operative use of tranexamic acid mouthrinses in patients who underwent teeth removal at therapeutic INR levels is a safe, simple, effective and acceptable method of reducing postextraction bleeding.

Data Collection

On recruitment to the trial the patient was allocated a patient OP and a unique serial 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 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.

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.

Details about the state of anticoagulation/ antiplatelets:

The reason for being on anticoagulants and antiplatelets and the length of time on anticoagulants / anti platelets was recorded. Immediately prior to surgery the patient had their INR, APTT and bleeding time tested.

Details about the extraction

The teeth being removed were recorded.

Details collected by the patient

After being discharged from surgery, patients were asked to take home and fill in a "data collection sheet" to record the time they used their tranexamic acid mouth rinse 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 (maxillary right molars and premolars), top front (maxillary canines and incisors), top left (maxillary left molars and premolars), bottom right (bottom right molars and premolars), bottom front (mandibular incisors and canines) and bottom left (mandibular left molars and premolars). The site of bleeding and the length of time the bleed lasted were recorded. The event which caused bleeding was recorded as traumatic (if initiated by a specific event) or spontaneous (if not related to a specific event).

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 to 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.

6. Tables and Graphs**Table 1:** Distribution of patients based on age

Age (Years)	Number	Percentage (%)
20-40 years	10* (p=0.03)	10.00*
41-60 years	64	64.00
61-80 years	36* (p=0.04)	36.00*
Total	100	100.00

(*p<0.05 significant compared 41-60 years with others)

Table 2: Distribution of patients based on gender

Gender	Number	Percentage (%)
Male	60	60.00
Female	40* (p=0.03)	40.00*
Total	100	100.00

(*p<0.05 significant compared male with female)

Table 3: Distribution of patients based on smoking

Smoking	Number	Percentage (%)
Yes	59	59.00
No	41* (p=0.05)	41.00*
Total	100	100.00

(*p<0.05 significant compared yes with no)

Table 4: Mean values of blood parameters pre extraction

Blood parameters	MEAN±SD
INR	2.29±0.35
Platelet count	2.32±0.24
Bleeding time	3.54±0.32

Table 5: Distribution of patients based on reason for being on anti-coagulant medication

Reason for being on anti-coagulant medication	Number	Percentage (%)
CAD	72* (p=0.01)	72.00*
RHD	12	12.00
AVR	1	1.00
IHD	4	4.00
Atrial fibrillation	7	7.00
TVD	1	1.00
ACHD	1	1.00
CAD+IHD	1	1.00
CHD/ASD	1	1.00
Total	100	100.00

(*p<0.05 significant CAD with others)

Table 6: Distribution of patients based on time on anti-coagulant medication

Time on anti-coagulant medication	Number	Percentage (%)
Days	2* (p=0.02)	2.00
Weeks	73	73.00
Months	19* (p=0.04)	19.00
Years	6* (p=0.04)	6.00
Total	100	100.00

(*p<0.05 significant compared weeks with others)

Table 7: Distribution of patients based on post extraction bleeding

Post extraction bleeding	Number	Percentage (%)
Yes	28	28.00
No	72* (p=0.03)	72.00
Total	100	100.00

(*p<0.05 significant compared yes with no)

Table 8: Mean values of blood parameters

Blood parameters	MEAN±SD
INR	2.37±0.58

Table 9: Distribution of patients based on day of post operative bleeding

Day of post operative bleeding	Number	Percentage (%)
No	71* (p=0.03)	71.00
1 st day	17 [#]	17.00
2 nd day	8	8.00
3 rd day	3	3.00
4 th day	1	1.00
Total	100	100.00

(*p<0.05 significant compared no with others,

[#]p<0.05 significant compare Nil with others)

Table 10: Distribution of patients based on event which caused bleeding

Event which caused bleeding	Number	Percentage (%)
No	71* (p=0.01)	71.00*
Spontaneous	26	26.00
Trauma	3	3.00
Total	100	100.00

(*p<0.05 significant compared no with others)

Table 11: Distribution of patients based on degree of bleeding

Degree of bleeding	Number	Percentage (%)
No	71* (p=0.01)	71.00
Slight ooze	24	24.00
Frank ooze	5	5.00
Total	100	100.00

(*p<0.05 significant compared no with others)

Table 12: Distribution of patients based on post operative bleeding and INR

Degree of bleeding	Number	Percentage (%)
No	71*(p=0.01)	71.00
Present	29	29.00
Total	100	100.00
INR (MEAN±SD)	2.91±3.74	

(*p<0.05 significant compared no with others)

Table 13: Distribution of patients based on treatment to achieve hemostasis

Degree of bleeding	Number	Percentage (%)
No	71*(p=0.01)	71.00
Pressure	20	20.00
Hemostat	9	9.00
Total	100	100.00

(*p<0.05 significant compared no with others)

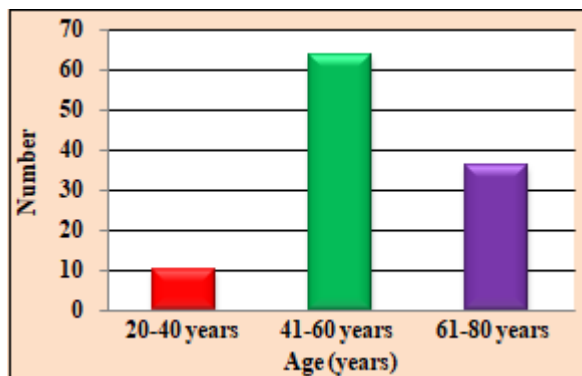
Table 14: Comparison of pre and post operative INR

Status	INR (MEAN±SD)	P value
Pre operative	2.29±0.35	0.89
Post operative	2.37±0.58	

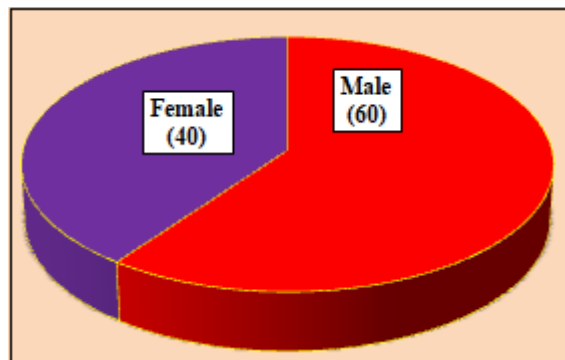
(p>0.05 no significant difference compared pre operative with post operative)

Table 15: Distribution of patients based on frequency of post extraction bleeding and its management

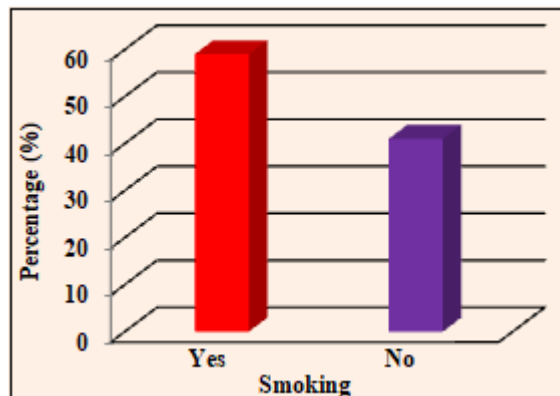
Type of bleed and management	Number	Percentage (%)
No bleeding	71	71.00
At home on day one, only	17	17.00
At home, after day one with pressure	3	3.00
At researcher's dental surgery with local treatment	9	9.00
At hospital by systemic treatment	0	0.00
Total	100	100.00



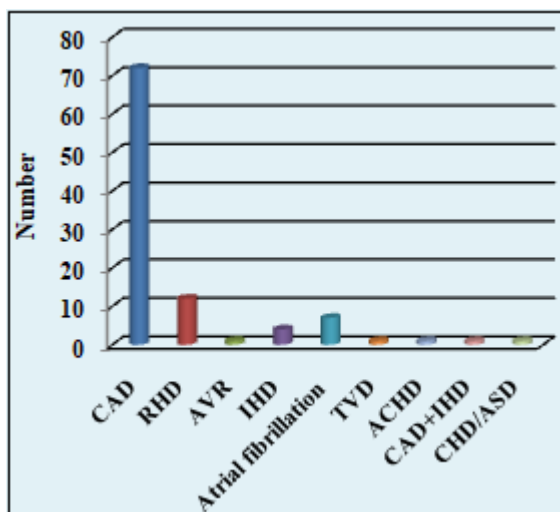
Graph 1: Distribution of patients based on age



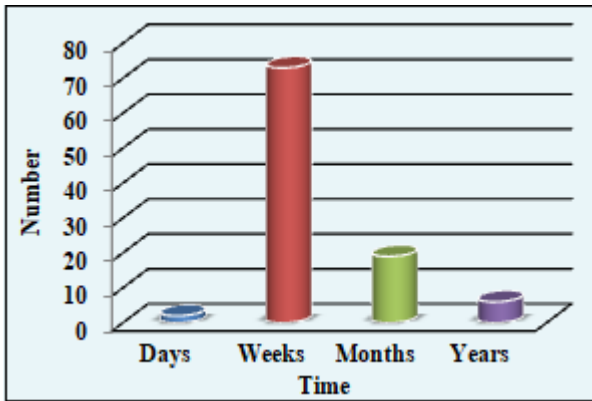
Graph 2: Distribution of patients based on gender



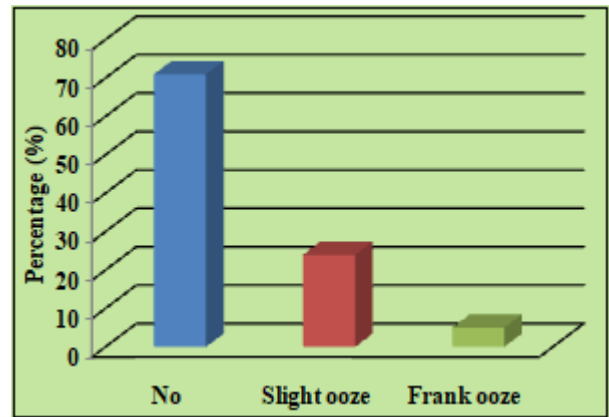
Graph 3: Distribution of patients based on smoking



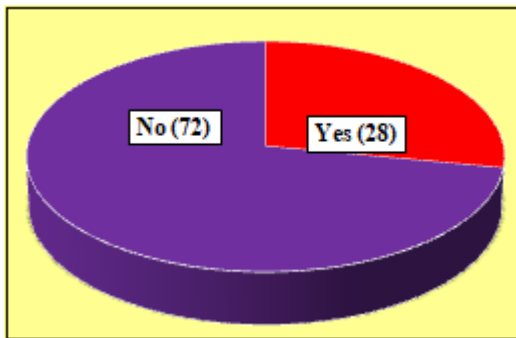
Graph 4: Distribution of patients based on reason for being on anti-coagulant medication



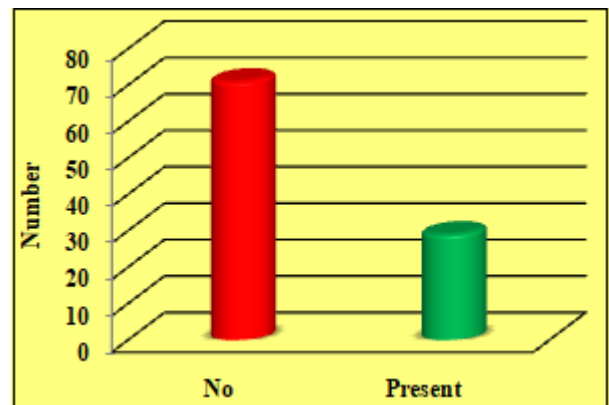
Graph 5: Distribution of patients based on time on anti-coagulant medication



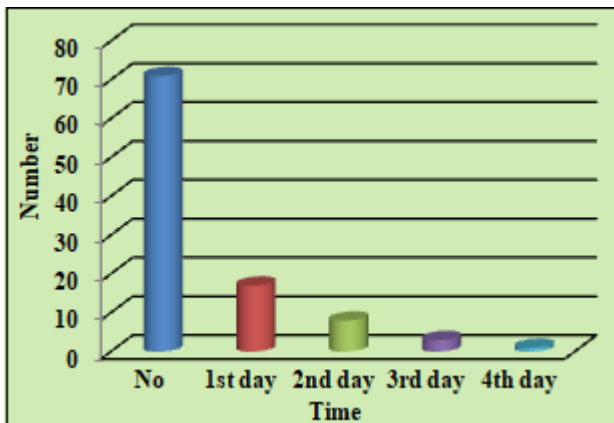
Graph 9: Distribution of patients based on degree of bleeding



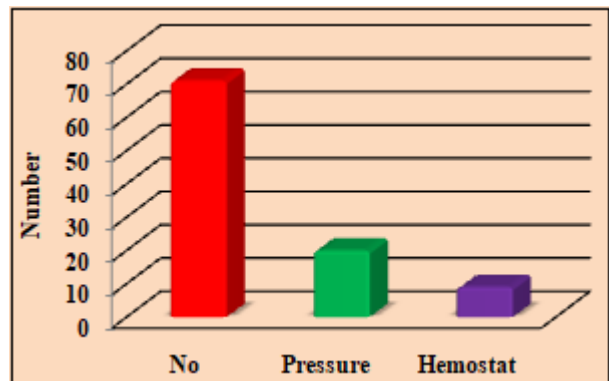
Graph 6: Distribution of patients based on post extraction bleeding



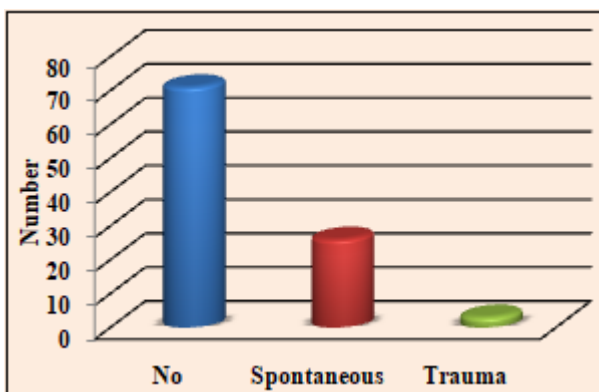
Graph 10: Distribution of patients based on post operative bleeding and INR



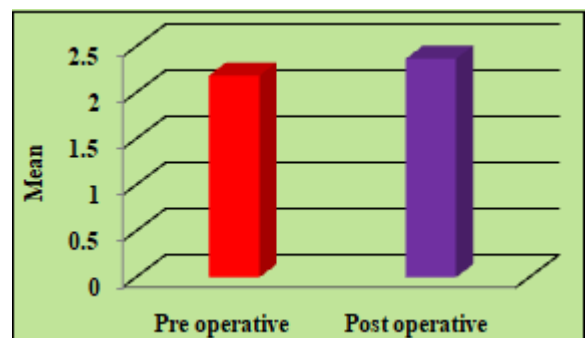
Graph 7: Distribution of patients based on day of post operative bleeding



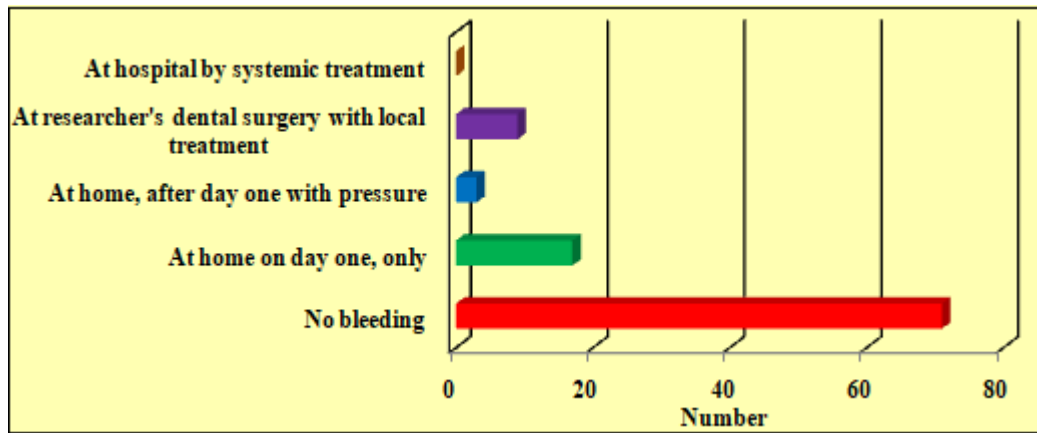
Graph 11: Distribution of patients based on treatment to achieve hemostasis



Graph 8: Distribution of patients based on event which caused bleeding



Graph 12: Comparison of pre and post operative INR



Graph 13: Distribution of patients based on frequency of post extraction bleeding and its management

7. Discussion

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.

Local haemostasis-promoting materials and techniques are widely used if patients have dental extractions with unaltered anti platelet / anticoagulation.

Traditional local methods to reduce post surgical bleeding in anti platelet and anti coagulant patients have included:

- Suturing the socket;
- 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 stabilizer. 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;
- 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;
- 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;
- Use of microfibrillar collagen.

Martinowitz (1990) described various local haemostatic dressings and tissue adhesives had been used to control bleeding after dental extractions in anti platelet and anti coagulant patients. These include:

- 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 stabilization of the

fibrin clot and aprotinin, an antiprotease prevents early disruption of the clot by fibrinolysis.

- Fibrin glue and human fibrinogen concentrate. These coagulation protein-based dressings induce clot formation by mimicking the final stages in the normal clotting mechanism;
- Absorbable collagen paste (ACP) and calcium alginatease.⁶⁶

This study was undertaken to verify that using tranexamic acid mouthrinse was a safe, effective and acceptable method of managing anticoagulation and anti platelet patients in Sree Mookambika Institute of Dental Science. 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 had not previously been reported in this group of patients. It must be recognized that because this study did not have a control group it does not provide a high level of evidence and does not more than enable the building of a hypothesis about the possible causes of post-operative bleeding in anti coagulant and anti platelet patients managed post-operatively with tranexamic acid mouthrinse. It is important that this limitation was borne in mind otherwise it was 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 minimized by collecting data on relevant variables in advance of the bleeding endpoint.

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.

All previous studies have used 10 ml 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. The main advantage of the larger volume used in other studies is that it may be 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 under-reporting or to over-reporting depending on the individual patient's threshold. In an attempt to standardize 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 bleeding 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 point. 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. There was also variability in the threshold at which patients presented themselves to the dental surgery.

The major risks associated with removal of teeth in these anticoagulated and anti platelet 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 effect⁶³. The results obtained in this study are consistent with a review of the literature by Wahl (1998)²⁷. He reported that 98% of 774 patients who underwent dental extractions while on anti coagulant / anti platelets patients 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 hospitalization for a short period. It was concluded that this was a safe method of managing patients.

Of these 100 patients treated, 17 reported bleeding at home on day 1 and 3 patients after day 1 that was controlled only by tranexamic acid pressure pack. A further 9 patients reported to the researcher's dental surgery where bleeding was controlled by local measures using gelatin sponge. No patients required hospital admission for systemic

management of bleeding. 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 gelatin sponge placed in socket and resuturing the socket. No patients required hospital admission for systemic management of bleeding.

This study used 5ml of 10% tranexamic acid solution whereas other studies used 10 ml 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 3.5 at the time of surgery the teeth can be 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.

Other techniques for managing patients on anti coagulants / anti platelets requiring tooth extraction are more potentially complicated. An INR reduction below 2.0 cannot be guaranteed 2 days after stopping anti platelets / anti coagulants (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 may be further delayed and required 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 requires 4 or 5 days hospitalization (Roser and Rosenbloom, 1975)⁶⁸. This was both expensive and inconvenient.

Statistical Interpretation:

The data was expressed in number, percentage, mean and standard deviation. Statistical Package for Social Sciences (SPSS 16.0) version used for analysis. Unpaired and Paired 't' test applied to find the statistical significant between the groups. P values less than 0.05 (p<0.05) considered statistically significant at 95% confidence interval.

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 maxillary molar tooth, an INR equal to or greater than 2.5. This study also indicated that some areas of the mouth were especially prone to post extraction bleeding while other areas were relatively immune. Upper teeth bleed more than lower teeth. Molar teeth bleed 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 was 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 was wide (bucco-palatally) it was generally not possible to close the wound and support the blood clot. Second, the maxilla was more vascular than the mandible.

Traditionally, the INR had 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 was concluded that the incidence of bleeding does not greatly increase as the INR rises from 2.0 to 2.5 but with an INR of 2.5 and above the incidence of bleeding significantly increases. This finding was consistent with clinical experience and was biologically reasonable as anti coagulant and anti platelet causes impaired fibrin formation. The higher the INR, the more impaired the fibrin formation, therefore the more susceptible it was to fibrinolysis. The bleeding time test was not a significant determinant of post extraction bleeding. This was consistent with other evidence indicating that bleeding time was a poor predictor of surgical bleeding risk.

8. Recommendations

On the basis of this study, several proposals can be made about the management of patients on anticoagulant / anti platelet. Of the 100 patients treated, 17 reported bleeding at home on day 1 and 3 patients after day 1. The bleeding reported on these 20 patients was controlled at home only by tranexamic acid pressure pack alone. A further 9 patients reported to the researcher's dental surgery department for bleeding which was then controlled by administering other local hemostatic measures (gelatin foam) with tranexamic acid pressure pack. No patients required hospital admission for systemic management of bleeding.

Statistical analysis reveals significant risk factors for postextraction bleeding were as follows:

- Patients in the age group of 41-60;
- Pre extraction INR equal to and greater than 2.5 ;

- Smoking.

Factors not statistically significant for an increased risk of bleeding included:

- The number of teeth removed;
- Pre-extraction bleeding time and
- Time on anti platelets and anticoagulants.

9. Summary and Conclusion

In the past, optimal management of patients on anti coagulants / anti platelets who require oral surgery had been controversial. However, the technique described by Sindet-Pedersen *et al.* (1989) and used in this study provides a method of management that was 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 9% 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.

A unique aspect of this study was the identification of factors that may predispose the patient to an increased risk of postextraction bleeding. These factors were: pre extraction INR equal to greater than 2.5; smoking. Factors not statistically significant for an increased risk of bleeding included: The number of teeth removed; pre-extraction bleeding time; time on anti platelets and anticoagulants. 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 might 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. 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.

Finally concluded that the post-operative topical use of tranexamic acid mouthrinses in patients who underwent teeth removal at therapeutic INR levels was a safe, simple, effective and acceptable method of reducing postextraction bleeding.

References

- [1] Ramstrom G, Pedersen S, Hall G, Blomback M, Alander U. Prevention of post surgical bleeding in oral surgery using tranexamic acid without dose modification of oral anticoagulants. *J Oral Maxillofac Surg.*1993; (51):1211-16.
- [2] Schulman S. Clinical practice:care of patients receiving long-term anticoagulant therapy. *N Engl J Med* 2003;349: 675-83,
- [3] Baillargeon J, Holmes HM, Lin Y-L, Raji MA, Sharma G *et al.* Concurrent use of

- [4] warfarin and antibiotics and the risk of bleeding in older adults. *Am J Med* 2012; 125:183e- 189.
- [5] Broekema F, Minnen B, Jansma J, Bos RM. Risk of bleeding after dentoalveolar surgery in patients taking anticoagulants. *Br J Oral Maxillofac Surg* 2014;(52): e15-e19.
- [6] Merritt JC, Bhatt DL. The efficacy and safety of perioperative antiplatelet therapy. *J Thromb Thrombolysis* 2002; (13): 97-103
- [7] Owens CD, Belkin M. Thrombosis and coagulation: operative management of the anticoagulated patient. *Surg Clin North Am* 2005; (85):1179-89
- [8] Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D. Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;(119): 8S-21S
- [9] Little JW, Miller CS, Henry RG, McIntosh BA. Antithrombotic agents: implications in dentistry. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; (93):544-51
- [10] White RH, McKittrick T, Hutchinson R, Twitchell J. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. *Ann Intern Med* 1995 ; (122):40-47
- [11] Grip L, Blomback M, Schulman S. Hypercoagulable state and thromboembolism following warfarin withdrawal in post-myocardial-infarction patients. *Eur Heart J* 1991; J12.
- [12] Genewein U, Haeberli A, Straub PW, Beer JH. Rebound after cessation of oral anticoagulant therapy: the biochemical evidence. *Br J Haematol* 1996;(92):479-85.
- [13] Wahl MJ. Myths of dental surgery in patients receiving anticoagulant therapy. *J Am Dent Assoc* 2000;(131):77-81.
- [14] Beirne OR. Evidence to continue oral anticoagulant therapy for ambulatory oral surgery. *J Oral Maxillofac Surg* 2005; (63):540-545
- [15] Evans IL, Sayers MS, Gibbons AJ, Price G, Snooks H, Sugar AW. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. *Br J Oral Maxillofac Surg* 2002; (40) : 248-52
- [16] Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Larfars G, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995; (332):1661-65.
- [17] Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for 1 year among different subtypes of stroke. Results from the Perth Community Stroke Study. *Stroke* 1994;(25):1935-44.
- [18] Dodson TB. Strategies for managing anticoagulated patients requiring dental extractions: an exercise in evidence-based clinical practice. *J Mass Dent Soc* 2002; (50):44-50.
- [19] Forbes D, Barr R, Reid G, Thomson C, prentice R, et al. Tranexamic acid in control of haemorrhage after dental extraction in haemophilia and Christmas disease. *Br Med J* 1972; 2(5809): 311-3.
- [20] Sindet-Pedersen S, Stenbjerg S. Effect of local antifibrinolytic treatment with tranexamic acid in hemophiliacs undergoing oral surgery. *J Maxillofac Surg* 1986; 44 (9):703-7.
- [21] Borea G, Montebugnoli L, Capuzzi P, et al. Tranexamic acid as a mouthwash in anticoagulant-treated patients undergoing oral surgery (An alternative method to discontinuing anticoagulant therapy). *Oral Surg Oral Med Oral Pathol* 1993; (75) : 29-32
- [22] Souto , Oliver A , Zuazu-Jausoro ,Vives A, Fontcuberta J. Oral surgery in anticoagulated patients without reducing the dose of oral anticoagulant: A prospective randomized study. *J Maxillofac Surg*; 1996; 54(1): 27-32.
- [23] Bandrowsky T, Vorono A., Borris T, Hank W. Amoxicillin-related postextraction bleeding in an anticoagulated patient with tranexamic acid. *Oral Surg Oral Med Oral Path* 1996 ; 82(6): 610-12.
- [24] Gaspar R, Brenner B, Ardekian L, Peled M, Laufer D. Use of tranexamic acid mouthwash to prevent post-operative bleeding in oral surgery patients on oral anticoagulant medication. *Quintessence Int* 1997; 28: 375-78.
- [25] Herman W, Joseph L, Stephen H. Current perspectives on dental patients receiving coumarin anticoagulant therapy. *J Am Dent Assoc* 1997; 128(3): 327-35.
- [26] Purcell, C. Dental management of the anticoagulated patient. *New Zealand Dent J.* 1997 (93): 87-92
- [27] Kearon C, Hirsh J. Management of anti coagulation before and after elective surgery. *The New Eng J Med* 1997; 336(21):1506-11.
- [28] Wahl MJ. Dental surgery in anticoagulated patients. *Arch Intern Med* 1998; 158: 1610-1616
- [29] Davies R, Sindet-Pedersen , Devani et al. Dental extractions in patients on warfarin: is alteration of anticoagulant regime necessary?. *Br J Oral Maxillofac Surg*; 1998 ; 36(6):480
- [30] Bernardoni SC, Vizcaino AM, Villamizar Y, Diez-Ewald M, Salazar G et al. Mouth-washing with tranexamic acid in patients treated with oral anticoagulants subjected to oral surgery procedures. *Invest Clin* 1998 ; 39: e77- e83.
- [31] Blinder D, Manor Y, Martinowitz U, Taicher S, Hashomer T. Dental extractions in patients maintained on continued oral anticoagulant: comparison of local hemostatic modalities. *Oral Surg Oral Med Oral Pathol Oral Radiol Endo.* 1999 ;88(2):137-40
- [32] Fordyce, A, Bailey B. Letters to the Editor. Re: Devani et al. Dental extractions in patients on warfarin: is alteration of anti-coagulant regime necessary? *Br J Oral Maxillofac Surg* 1999;37:150.
- [33] Ardekian L, Gaspar R, Peled M, Brener B, Laufer D. Does low-dose aspirin therapy complicate oral surgical procedures? *J Am Dent Assoc* 2000; 131: 331-35
- [34] Wahl MJ. Myths of dental surgery in patients receiving anticoagulant therapy. *J Am Dent Assoc* 2000; 131:77-81.
- [35] Campbell J H, Alvarado F, Murray R A. *Anticoagulation and minor oral surgery: should the anticoagulation regimen be altered?* *J Oral Maxillofac Surg* 2000; 58: 131-136.
- [36] Blinder D, Martinowitz U, Ardekian L, Peleg M, Taicher S: Oral surgical procedures during anticoagulant therapy. *Int J Oral and Maxillofac Surg* 2001; 30(6): 518-2.
- [37] Evans I L, Sayers M S, Gibbons A J, Price

- G, Snooks H et al. *Can warfarin be continued during dental extraction? Results of a randomized controlled trial.* Br J Oral Maxillofac Surg 2002; 40:248–52.
- [38] Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy. Part 1: coagulopathies from systemic disease. Br Dent J 2003; 195: 439-45.
- [39] Carter G, Goss A. Tranexamic acid mouthwash prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. Int J Oral Maxillofac Surg 2003; 32: e504- 7.
- [40] Cannon PD, Dharmar VT. Minor oral surgical procedures in patients on oral anticoagulants a controlled study. Aust Dent J 2003 48: 115e- e118.
- [41] Keiani MK, Loeb I, Legrand W, Daelemans P, Reck V : Prevention of postoperative bleeding in patients taking oral anticoagulants. Effects of tranexamic acid. J Rev Stomatol Chir Maxillofac 2003;104 (2):77-9.
- [42] Sacco R, Sacco M, Carpenedo, Mannucci. Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different intensity targets. Oral Surg Oral Med Oral Pathol Oral Rad Endo 2007; 104(1) , e18-e2.
- [43] Aframian J, Rajesh V, Peterson D. Management of dental patients taking common hemostasis-altering medications. Oral Surg Oral Med Oral Pathol Oral Rad Endo 2007; 103: S45.e1- S45.e1.
- [44] Pototski M, Amenábar JM. Dental management of patients receiving anticoagulation or antiplatelet treatment. What influence do anticoagulants have on oral implant therapy? A systematic review. J Oral Sci 2007 ;49(4):253-8.
- [45] Madrid C, Sanz M. Dental extractions in patients maintained on continued oral anticoagulant: comparison of local hemostatic modalities. Clin Oral Implants Res 2009;20(4) :96-106.
- [46] Nematullah A, Alabousi A, Blanas N, Douketis JD, Sutherland SE. Dental surgery for patients on anticoagulant therapy with warfarin: a systematic review and meta-analysis. J Can Dent Assoc 2009; 75: 41-5.
- [47] Somma F, Nicola M, Plotino G, Pameijer H. Conservative approach to dental extractions in patients on anticoagulant therapy. A clin S Gen Dent 2010; e30-35.
- [48] Alejandro R, Cristina B, Isabel L, Gerardo G , Jose M . Extractions without eliminating anticoagulant treatment: A literature review Manuel: Med Oral Patol Oral Cir Bucal. 2011;16 (6): e800-4.
- [49] Campbell J H, Alvarado F, Murray R A. *Anticoagulation and minor oral surgery: should the anticoagulation regimen be altered?* J Oral Maxillofac Surg 2010; 58: 131–136.
- [50] Bacci C, Michele M, Lorenzo F, Alessandro P, Roberto D et al. Management of patients undergoing anticoagulant treatment Results from a large, multicentre, prospective, case-control study; Thromb Haemost 2010; 104-108.
- [51] Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. Cochrane Database of Systematic Reviews 2013;(7): CD010562.
- [52] Sammartino G, Marenzi G, Miro A, Ungaro F, Nappi A, Sammartino JC, et al. Local delivery of the hemostatic agent tranexamic acid in chronically anticoagulated patients. Craniofac Surg 2012; 23: e648- e652.
- [53] Wardrop D et al. Antifibrinolytics (lysin analogues) for the prevention of bleeding in patients with haematological disorders (review). Cochrane Database Syst Rev 2013;7:CD009733
- [54] Gandhi R, Evans HMK, Mahomed SR, Mahomed NN. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. BMC Res Notes 2013; (6): 184-89.
- [55] Michael J. Wahl. Dental Surgery and Antiplatelet Agents: Bleed or Die ; J Am Dent Assoc 2014 ; 127(4): 260– 67.
- [56] Ramon R J, Munoz M, Bravo LC, Bascones M; A Tranexamic acid gel in patients treated with oral anticoagulants. Med Clin (Barc) 2014; 143 (11):484-8.
- [57] Kammerer PW, Frerich B, Liese J, Schiegnitz E, Al-Nawas B. Oral surgery during therapy with anticoagulants-a systematic review. Clin Oral Investig 2015; 19:e171- e180.
- [58] Wei Z, Liu M. The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: a meta-analysis of 2720 cases. Transfus Med 2015; 25: e151- e162.
- [59] Lu SY. Dental extraction without stopping single or dual antiplatelet therapy: results of a retrospective cohort study. Int J Oral Maxillofac Surg. 2016 45(10):1293-8.
- [60] Qeiros SA, Helenilton M, Assis D, Gleysson, S. Conceicao et al. An Evaluation of the Efficacy of Local Hemostatic Measures in Dental Patients Taking Oral Anticoagulants: A Critical Review of the Literature Over the Past Two Decades . Cur Clin Pharmacol 2016; 11(4): 230-40.
- [61] Murphy GR, Glass GE, Jain A. The Efficacy and Safety of Tranexamic Acid in Cranio-Maxillofacial and Plastic Surgery. J Craniofac Surg 2016 ;27(2) :374-9.
- [62] Ali Mithiborwala1, Navin Shah, Amit Mahajan, Isha Kaur Bagga, Dipen Doshi, Darshan Sanghvi; Control of Post Extraction Haemorrhage by Tranexamic Acid Pressure Pack in Patients on Anticoagulant and Antiplatelet Therapy: A Prospective Clinical Study. J Craniofac Res 2016;1(1):6-10.
- [63] Juliana SA, Thiago D, Daniele R, Andrew L, Faria S et al. Topical application of tranexamic acid in anticoagulated patients undergoing minor oral surgery: A systematic review and meta-analysis of randomized clinical trials. J Cranio Maxillofac Surg 2017; 45: e20-6.
- [64] Nishida T, Kinoshita T, Yamakawa K. Tranexamic acid and trauma-induced coagulopathy. J Intensive Care. 2017; 20: 5-10.
- [65] Kdihonsari RH, Razouk O, Goudot P. Management of dental extraction in patients undergoing anticoagulant oral direct treatment: A pilot study. Oral Surg Oral Med Oral Path 2016.122(5):e146-e55.
- [66] Sindet-Pedersen S. Distribution of tranexamic acid to

plasma and saliva after oral administration and mouth rinsing: a pharmacokinetic study. *J Clin Pharmacol* 1987; 27(12):1005-8.

- [67] Martinowitz S, David V, Sanford N, Ramot B, Meir R. Dental extraction for patients on oral anticoagulant therapy: *Oral Surg Oral Med Oral Path* 1990. 70(3):274-77.
- [68] Sindet-Pedersen S, Ramstrom G, Bernvil S, Blomback M. Haemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. *N Engl J Med* 1989;320:840-843.
- [69] Roser SM, Rosenbloom B. Continued anticoagulation in oral surgery procedures. *Oral Surg Oral Med Oral Path* 1975; 40(4):448-57.