ผลของยาทรานเอ็กซามิกแอซิดในการลดปริมาณเลือดที่ออกภายหลังการทำการผ่าตัดขากรรไกรร่วมกับการจัดฟัน
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นางสาวกุศล ตันติวงส์

THE EFFECTS OF TRANEXAMIC ACID ON BLOOD LOSS IN

ORTHOGNATHIC SURGERY

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การแก้ไขความผิดปกติของการสบฟันกระดูกขากรรไกรและใบหน้า โดยการผ่าตัดขากรรไกรร่วมกับการจัดฟันเป็นสาเหตุหนึ่งที่ทำให้เกิดการสูญเสียเลือด วัตถุประสงค์ของการศึกษานี้เพื่อศึกษาผลของยาทรานเอ็กซามิกแอชิด ในการลดปริมาณการสูญเสียเลือดจากการผ่าตัดขากรรไกรร่วมกับการจัดฟัน

การศึกษานี้เป็นงานวิจัยแบบสุ่มเชิงทดลอง โดยกลุ่มตัวอย่างได้จากผู้ป่วยที่ได้รับการผ่าตัดขากรรไกรร่วมกับการจัดฟันแบบ ไบแล็ทเทอเริลแซจจิทอลสปริทเรมัสออสติโอโตมี ที่คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ในช่วงเดือนกุมภาพันธ์ 2549 จนถึงเดือนตุลาคม 2549 ได้จำนวนกลุ่มตัวอย่างทั้งหมดจำนวน 19 คน โดยแบ่งเป็นกลุ่มที่ได้รับยาทรานเอ็กซามิกแอชิด(10 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัม) จำนวน 10 คน และกลุ่มที่ไม่ได้รับยาจำนวน 9 คน ผู้ป่วยทั้ง 2 กลุ่ม มีลักษณะทั่วไป เช่น อายุ น้ำหนัก เพศ ระดับฮีโมโกลบินก่อนผ่าตัดและสภาพร่างกายไม่แตกต่างกัน ผู้ป่วยทั้ง 2 กลุ่มได้รับการผ่าตัดโดยวิธีการมาตรฐาน ผลการศึกษาพบว่าปริมาณการสูญเสียเลือดเฉลี่ยที่ออกระหว่างการผ่าตัดในกลุ่มที่ได้รับยามีค่าน้อยกว่าในกลุ่มที่ไม่ได้รับยาร้อยละ 36.92 แต่เมื่อทำการทดสอบสมมติฐานเพื่อเปรียบเทียบในทั้ง 2 กลุ่ม พบว่าปริมาณการสูญเสียเลือดที่ออกเฉลี่ยของกลุ่มที่ได้รับยาไม่มากกว่ากลุ่มที่ไม่ได้รับยาที่ระดับนัยสำคัญ 0.05 สำหรับปริมาณเลือดเฉลี่ยที่ออกหลังและทั้งหมดของการผ่าตัด ระดับฮีโมโกลบินหลังการผ่าตัดวันที่ 1 และวันที่ 3 และค่าการเปลี่ยนแปลงระดับฮีโมโกลบินก่อนและหลังผ่าตัดวันที่1 และก่อนและหลังผ่าตัดวันที่ 3 ในทั้ง 2 กลุ่มมีค่าความแปรปรวนพอๆกัน และทุกค่าเฉลี่ยของกลุ่มที่ได้รับยามีความแตกต่างกับกลุ่มที่ไม่ได้รับยาอย่างไม่มีนัยสำคัญที่ระดับค่าความเชื่อมั่นที่ 0.05 ไม่มีผู้ป่วยในทั้งสองกลุ่มที่ได้รับเลือดภายหลังการผ่าตัด ไม่พบภาวะแทรกซ้อนและภาวะการติดเชื้อใดๆในผู้ป่วยทั้ง 2 กลุ่ม

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KEY WORD: TRANEXAMIC ACID / ANTIFIBRINOLYTIC AGENT / ORTHOGNATHIC SURGERY / TOTAL BLOOD LOSS

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The surgical correction of dentofacial deformities causes considerable blood loss which complicates the surgical result. The objective of this study is to evaluate the effects of tranexamic acid on the reduction of blood loss in patients underwent bilateral sagittal split ramus osteotomies.

The prospective, randomized, controlled trial in patients underwent bilateral saggital split ramus osteotomies to correct the dentofacial deformities at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Chulalongkorn University carried out from February 2006 to October 2006. A total of 19 patients in this study were divided in 2 groups, 10 patients treated with 10 mg/kg TXA and the others as control. Standard bilateral saggital split ramus osteotomies procedures were performed in all patients. The study demonstrated the intraoperative blood loss reduced by 36.92% in the experiment group, but the change was not statistically significant (Sig.>0.05). The postoperative blood loss, total blood loss, hemoglobin level at the 1st and 3rd postoperative day, the difference of hemoglobin level at preoperative and the 1st postoperative day and the difference of hemoglobin level at preoperative and the 3rd postoperative day in the experiment group was similar to that in the control group (p>0.05). No patients in both groups had blood transfusion. There were no reports of thromboembolic events, no post operative infection and any other complications of all cases.

Department Oral and maxillofacial Surgery   Student's signature.........

Field of study Oral and maxillofacial Surgery Advisor's signature......

Academic year 2006   Co-advisor's signature...

ACKNOWLEDGEMENTS

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ABBREVIATIONS

TXA	Tranexamic acid
BSSRO	bilateral sagittal split ramus osteotomies
ADP	Adenosine-5$'$-diphosphate
TXA_2	Thromboxane A_2
TF	tissue factor
$\sum$ACA	$\sum$-amino-caproic acid
IV	Intravenous
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
Hb	Hemoglobin
Hct	Hematocrit

CHAPTER I

INTRODUCTION

1.1 Background & Rationale

Orthognathic surgery is recognized to be a safe operation with minimal morbidities. Most patients are young and generally healthy. The complications following orthognathic surgery are bad spits, nerve injuries, intraoperative and postoperative malposition, condylar resorption, interfragmentary incompatibilities, and etc.[1-3] One of the major complications of orthognathic surgery is the potential for excessive blood loss. There are several reports of life-threatening hemorrhage following orthognathic surgery.[1-5] Nowsaday the standard treatment for significant hemorrhage during operations is the rapid control bleeding by one of the following methods: surgical techniques, packing or tamponading the area, ligation of major vessels leading to the bleeding area, radiological intervention to thrombose the vessels leading to the bleeding area and use of blood-derived products such as platelets, fresh frozen plasma (FFP) and replacement of blood loss by using blood transfusion. The disadvantages of homologous blood transfusion include blood transfusion reaction, mis-matched blood transfusion, transmission of infections such as HIV and hepatitis B virus.[6-9,12] The disadvantages of blood transfusion for the elective surgery include the possibility of blood collection from a poor-risk patient, the presence of microemboli, coagulopathy and may lead to anemia and hypovolemia.[5,7,10-11] The use of erythropoietin and other additional measures to increase the hemoglobin preoperatively has been mentioned. In some patients, the use of recombinant human erythropoietin has induced neutralizing antibodies against endogenous erythropoietin leading to red cell aplasia and the use of erythropoietin is not cost-effective.[6] Hypotensive anesthesia is a well-established and an effective method to reduce blood loss by 44%.[6,8,10,12-14] The disadvantage is brain anoxia, a hazard complication and postoperative bleeding after the end of anesthesia due to ineffective intraoperative hemostasis. Contraindications for the use of hypotensive anesthesia are severe cardiac and respiratory diseases.[12-13] The use of

antifibrinolytic drugs to reduce bleeding has also emerged as an additional approach. Pharmacological agents used in this purpose are Aprotinin, Tranexamic acid (TXA) and Desmopressin (dDAVP) and aminocaproic acid.[15] The surgical correction of most dentofacial deformities causes considerable blood loss. The hemorrhage may not be able to control by ligation and cauterization of vessels. A common approach to minimize peri-operative blood loss in cardiopulmonary bypass (CPB) surgery, orthopaedic surgery, upper gastro-intestinal tract surgery, oral surgery in patients with haemophilia and etc. are through the prophylactic use of the antifibrinolytic agents. Aprotinin is an effective antifibrinolytic drug. It has been shown to reduce blood loss in cardiac and hepatic surgery.[16-18] In orthopaedic surgery, the use of Aprotinin has side effects with a high risk of an anaphylactic reaction and possible increasing in thrombosis.[19-20] However Aprotinin is a proteolytic enzyme inhibitor acting on plasma and kallikrein. It is indicated for patients at high risk of major blood loss during and after open heart surgery with extracorporeal circulation and for patients in whom optimal blood conservation during open heart surgery is an absolute priority. Desmopressin (DDAVP) is widely used in patients with coagulopathies such as von Willebrand's disease and some types of hemophilia.[21] Epsilon aminocaproic acid has ten times less potency compared to tranexamic acid (TXA). Previous reports on TXA in most operations demonstrated that TXA significantly reduced intraoperative and postoperative blood loss. There were few reports of thrombotic events in patients who were given TXA during cardiac surgery[22] and joint replacement surgery.[23-37]

1.2 Objective
To study the hemostatic effect of TXA in patients undergo orthognathic surgery.

1.3 Hypothesis
H_0 : Total blood loss in the Tranexamic acid group is equal to the control group.

H_1 : Total blood loss in the Tranexamic acid group is less than the control group.

1.4 Assumption

1.4.1 Patient selection

Patients (ages range from 18 to 40 years) who were generally fit and healthy (ASA I or II) and planned for surgical correction of the dento-facial deformities at the Department of Oral & Maxillofacial Surgery, Faculty of Dentistry , Chulalongkorn University from February, 2006 to October, 2006. The surgical procedure in this study was bilateral sagittal split ramus osteotomies (BSSRO). Patients were excluded if they have any of the following disorders; medical history of hematopoitic disorders, deep vein thrombosis, previous exposure to TXA, currently taking oral contraceptive pills or anticoagulants, ischemic heart disease, renal disease, chronic liver diseases, acquired defective color vision or allergic to TXA. Patients who had injury to major blood vessels during operation and bad splits were also excluded from this study. Those who refused to participate in experiment are excluded, too. Patients were divided into two groups, a study group and a control group. This study was approved by the ethics committee of the faculty. Inform and consents were obtained from all patients participated in the study.

1.4.2 Intraoperative blood loss were evaluated from the blood in the suction container, the blood soaked surgical sponges, gauzes and swabs immediately after the operation.

1.4.3 Postoperative blood loss was evaluated from the blood in the vacuum drains when they were removed on the 3rd postoperative day.

1.4.4 Total blood loss was calculated from the intraoperative blood loss plus the postoperative blood loss.

1.4.5 Hemoglobin evaluation was recorded on the first and the third postoperative day which were compared with the baseline hemoglobin on the day before operation.

1.5 Ethical consideration

Tranexamic acid has a blood-sparing effect in patients undergoing major surgery. The efficiency of this agent in reducing perioperative and postoperative blood loss by administering preoperatively in patients undergoing major operations is well documented. However, there has been speculation about an increased risk of deep vein thrombosis (DVT) in patients who are treated with TXA and also its safety. There are few reports of thrombotic events in patients who were given TXA during cardiac surgery[22] and joint replacement surgery.[23-37] However, the equilibrium between fibrin deposition and fibrinolysis in surgical patients is influenced by several factors other than the use of TXA. Moreover the incidence of DVT in patients who undergo orthognathic surgeries is low because of most patients are young, no or less risk factors for DVT the admission period is short and all patients are encourage to have early mobilization. Furthermore, the incidence of DVT in the Thai population is low. This may be due to genetic and geographic factors.

1.6 Expected Benefit & Application

There will be less total blood loss and the need for blood transfusion is reduced in patients undergoing BSSRO by given TXA preoperatively.

1.7 Limitation

Owing to the very short period of this study, the number of patients participated in this study were small. More studies which larger group of patients should be done to confirm our results.

CHAPTER II
REVIEW OF BASIC KNOWLEDGES

2.1 Review of hemostasis

The term "hemostasis" (hemo= blood; sta= remain) refers to mechanisms that minimize or prevent the loss of blood when a blood vessel is severed. When blood vessels are damaged, bleeding may occur. Four interrelated events constitute hemostasis: (1) local vasoconstriction, (2) formation of a platelet aggregate (clump), (3) formation of a blood clot and (4) clot retraction and dissolution. [38-39]

2.1.1 Local vasoconstriction

When a blood vessel is injured, its immediate response is vasoconstriction and therefore reduces blood flow. This initial vasoconstriction is due to local spasm of the smooth muscle in the wall of blood vessels and the sympathetic reflexes. In smaller vessels, vasoconstriction can be maintained by the release of vasoconstricting chemicals from platelets that begin to accumulate at the damaged site.

2.1.2 Formation of a platelet aggregate

Injury to the endothelium of a blood vessel causes platelets to adhere to the site of injury. Damaged cells of the injured blood vessels release adenosine diphosphate (ADP) which attracts platelets and causes them to clump together at the damaged site. Platelets are coming in contact with exposed collagen of the vascular wall degranulate (releasing stored chemicals), releasing ADP, serotonin (5-hydroxytryptamine) which enhances vasoconstriction, and thromboplastin which hastens blood coagulation. The release of ADP attracts more platelets and causes them to be swollen and become sticky; they adhere in increasing numbers to the damaged site and form a plug called a *platelet aggregation*. Activated platelets also produce thromboxane A_2, a powerful vasoconstrictor and platelet aggregator derived from platelet prostaglandin H_2. In addition, the spherical platelets extend pseudopodia (footlike extensions of their

cytoplasm) to nearby exposed collagen, anchoring the platelet plug and establishing a framework on which coagulation can proceed. Platelets are prevented from aggregating along the length of a normal vessel by the antiaggregation action of prostacyclin. This substance is released from the normal endothelial cells in the adjacent, uninjured part of the vessel.

2.1.3 Formation of a blood clot

Coagulation is the process by which some of the blood loses its fluid consistency and becomes a clot (a semisolid mass similar in consistency to gelatin). Clotting of blood is a complex process consisting of the sequential activation of various factors in the blood. In the formation of a clot, an enzyme called thrombin converts fibrinogen, a soluble plasma protein, into an insoluble plasma protein and fibrin. Fibrin is a threadlike protein. Fibrin aggregates to form a meshlike network at the site of vascular damage, traps red blood cells and plasma, and forms a clot (Fig.1). The complex sequence of chemical events that produce fibrin are divided into three phases or stages, designated as stage I, stage II and stage III (Fig. 2). Common synonyms for blood clotting factors involved in each stage are given in Table 1.

Stage I: Formation of a Prothrombin Converting Factor

Stage I may begin when blood comes in contact with injured tissue (the extrinsic pathway) or it may be initiated in the absence of tissue damage (the intrinsic pathway).

When blood comes in contact with injured tissue, clotting is initiated via the extrinsic pathway, owing to the release of the tissue lipoprotein thromboplastin (factor III). Tissue thromboplastin interacts with a plasma protein, proconvertin (factor VII) and calcium ions to form an agent that activates the Stuart factor (factor X). The activated Stuart factor, in the presence of calcium ions, forms complexes with accelerin (factor V) on phospholipid micelles provided by tissue thromboplastin to form the prothrombin-converting factor.

Intrinsic coagulation may occur inside or outside the body. In either case, the first step is the activation of the Hageman factor (factor XII). In the body, activation of the Hageman factor may occur from collagen, fibrin or platelet membrane during platelet

aggregation. In addition, it can apparently be activated under conditions of stress, anxiety, fear and other states. Outside the body (e.g., in a test tube), activation of the Hageman factor occurs when blood comes in contact with foreign substances whose common property appears to be a negative surface charge.

The Hageman factor activates the plasma enzyme, plasma thromboplastin antecedent (PTA; factor XI) which activates a plasma protein in the presence of calcium ions, the Christmas factor (factor IX). Activated Christmas factor interacts with another protein, antihemophilic factor (factor VIII) is on the surface of phospholipids and in the presence of calcium and forms a complex that activates the Stuart factor. The succeeding steps in the formation of prothrombin- converting factor are the same as for the extrinsic mechanism.

Stage II: Conversion of prothrombin to thrombin

Prothrombin is a plasma globulin manufactured by the liver and normally present in circulating plasma. It is the active precursor of an active enzyme called thrombin. Thrombin does not normally present in plasma unless blood is clot. In the presence of calcium ions and the prothrombin-converting factor, prothrombin is enzymatically split into two fragments-one inert and the other possessing the properties of thrombin. Initially, the conversion of prothrombin proceeds too slowly to produce significant amounts of thrombin needed for coagulation. Thrombin itself, however, increases its own rate of formation by converting an unstable plasma protein, proaccelerin (factor V), into accelerin, which then accelerates the formation of thrombin. Thrombin also activates the antihemophilic factor and is needed to activate a fibrin-stabilizing factor in stage III.

Stage III: Conversion of fibrinogen to fibrin

Fibrinogen is a soluble plasma protein produced by liver and circulating in plasma. Thrombin converts fibrinogen to fibrin by cleaving two pairs of small polypeptides (fibrinopeptides) from each fibrin molecule, leaving a fibrin monomer (a single link in a chain of molecules that make up fibrin). Fibrin monomers spontaneously polymerize, forming the insoluble, threadlike protein and fibrin. In addition, thrombin activates another plasma enzyme, fibrin-stabilizing factor (factor XIII), which, in the

presence of calcium ions, stabilizes the fibrin polymer through covalent bonding of the fibrin monomers.
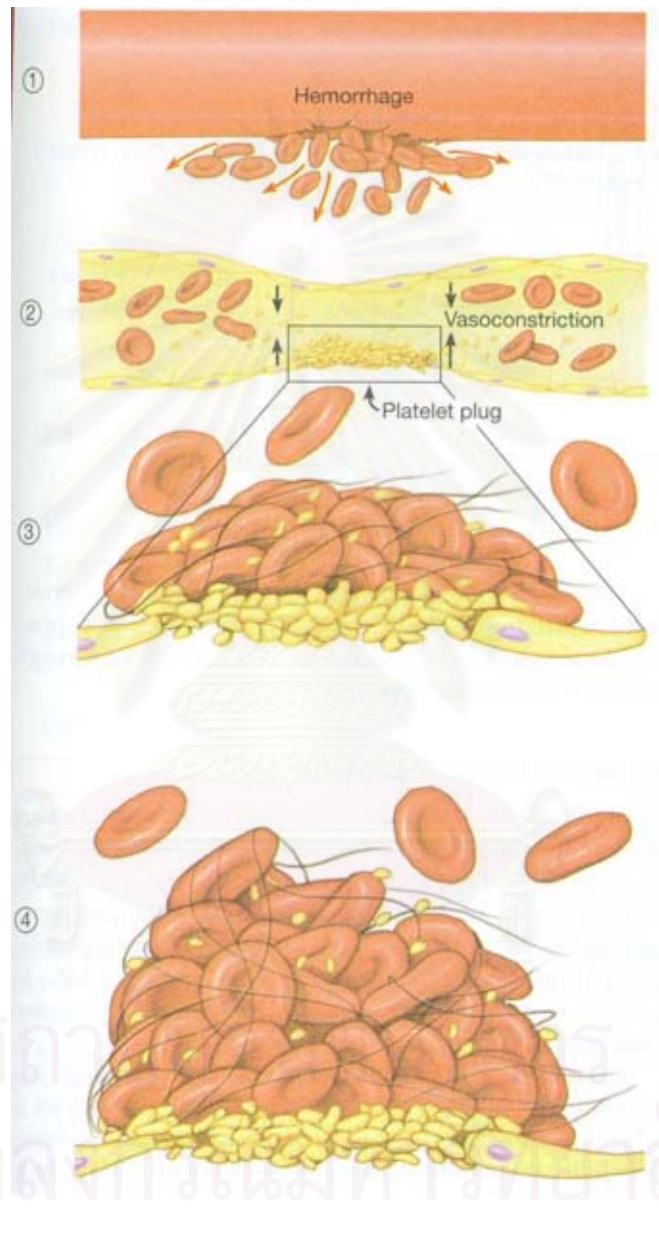
Figure1. Formation of a clot. Fibrin forms long threads in which blood cells, platelets and plasma become trapped.[38]
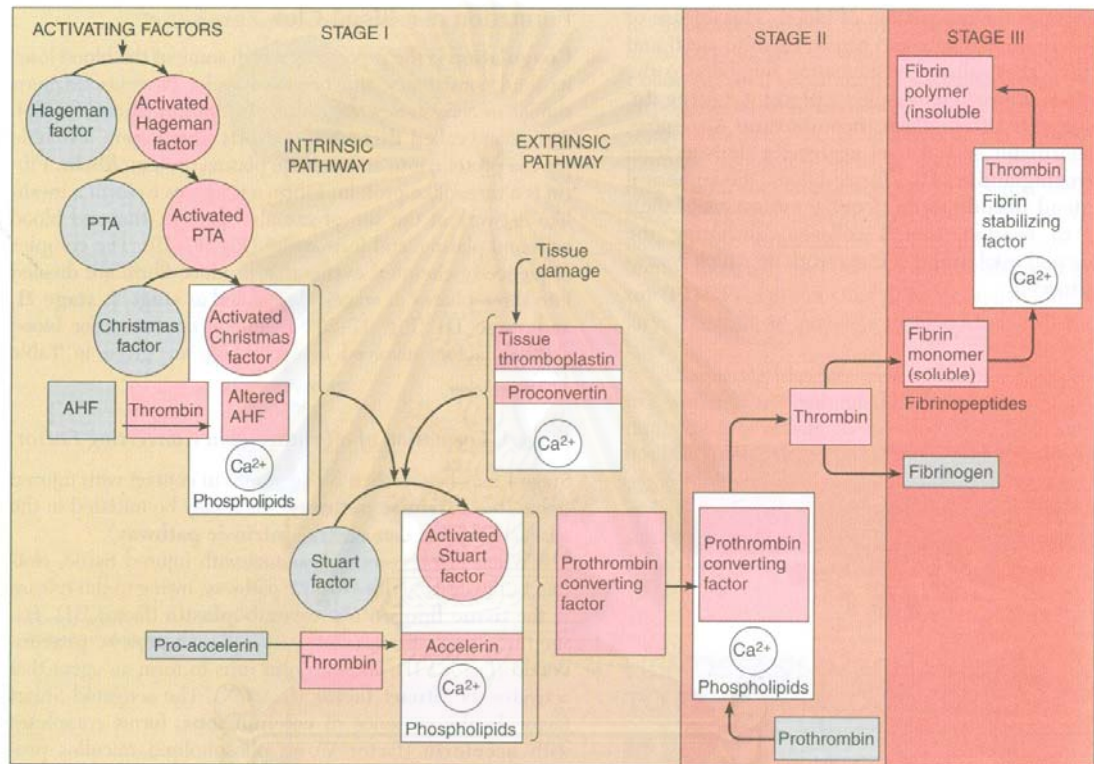
Figure2. A schema of blood coagulation.[38]

Clotting factors

International Committee Designation	Synonyms	Location
Factor 1	Fibrinogen	Plasma
Factor 2	Prothrombin	Plasma
Factor 3	Tissue thromboplastin	Tissue cells
Factor 4	Calcium ion	Plasma
Factor 5	Proaccelerin	Plasma
	Prothrombin accelerator	
	Accelerator globulin	
	Labile Factor	
Factor 6	Obsolete	
Factor 7	Serum prothrombin conversion accelerator (SPCA)	Plasma
	Proconvertin	
	Autoprothrombin 1	
	Stable factor	
Factor 8	Antihemophilic factor (AHF)	Plasma
	Platelet cofactor 1	
	Thromboplastinogen	
	Antihemophilic factor A	
Factor 9	Plasma thromboplastin component (PTC)	Plasma
	Christmas factor	
	Platelet cofactor 2	
	Antihemophilic factor B	
	Autoprothrombin 2	
Factor 10	Stuart-Prower factor	Plasma
	Stuart factor	
	Autoprothrombin 3	
Factor 11	Plasma thromboplastin antecedent (PTA)	Plasma
Factor 12	Hageman factor	Plasma
	Contact factor	
Factor 13	Fibrin-stabilizing factor	Plasma
	Plasma transglutaminase	
	Laki-Lorand factor	
Platelet factor	Platelet factor 3	Platelets

Table 1. Common synonyms for blood clotting factors.[38]

2.1.4 Clot retraction and dissolution

After a clot forms, the actin and myosin of the platelets trapped in the fibrin mesh interact in a manner similar to that in muscle. The contraction pulls the fibrin strands toward the platelets and thereby extrudes the serum (plasma without fibrinogen) and shrinks the clot. The process is called clot retraction. Retraction serves to draw wound surfaces together and open the vessel if it has been occluded by the clot, thereby increase blood flow and promoting tissue repair and clot dissolution. Several cofactors are required for blood coagulation (Fig.2); the most important are Ca^{++}. If Ca^{++} in the blood is removed or bound, coagulation does not occur. Retraction is caused by a platelet factor, thrombosthenin, a contractile protein that is shortened requires the presence of thrombin and adenosine triphosphate (ATP).

Blood clots are not permanent. After hemorrhage has been ceased and tissue repair is well underway, the clot is gradually dissolved by breaking down fibrin (fibrinolysis) into soluble fragments by the enzyme plasmin. Plasmin is derived from plasminogen, an inactive β –globulin normally present in plasma. The formation of plasmin from plasminogen requires an enzyme called activator. Activator is normally absent from plasma but its precursor, proactivator, is present and may be converted into activator by cytofibrokinase (a tissue enzyme); staphylokinase and streptokinase (bacterial enzymes); plasma kinase (Hageman factor); and other enzymes in the body excreted in urine (urokinase), tear and saliva. Tissue plasminogen activator (TPA) formed by endothelial cells appears to be responsible for most of the physiological fibrinolysis. A balance between deposition of fibrin and fibrinolysis limits coagulation to the area of vascular injury.

2.2 Review of Tranexamic acid

Tranexamic acid (TXA), a synthetic antifibrinolytic drug released in 1970s[33] , used to inhibit plasminogen activation and fibrinolysis. It is white, odorless powder that forms white crystals which are soluble in water, acids, alkalis and slightly soluble in alcohol, but remains insoluble in organic solvents. It may be useful when hemorrhage cannot be staunched e.g. in prostatectomy, dental extraction in hemophiliacs or menorrhagia. It is a trans-stereo isomer of a synthetic amino acid, introduced to inhibit the formation of plasmin, preserves platelet function and reduces perioperative blood loss and thus reduces the need for blood transfusions.[20]

Defective formation or excessively rapid dissolution of fibrin results in excessive or recurrent bleeding. The dissolution of hemostatic fibrin can be prevented by antifibrinolytic drugs that stabilize fibrin structures. Two synthetic derivatives of the amino acid lysine, TXA [4-(aminomethyl)cyclohexanecarboxylic acid] (Fig.3) and $\sum$-amino-caproic acid (EACA; 6-aminohexanoic acid) have antifibrinolytic activity in humans. In the status of the drug in the management of surgical and other conditions, antifibrinolytic therapy is appropriate.
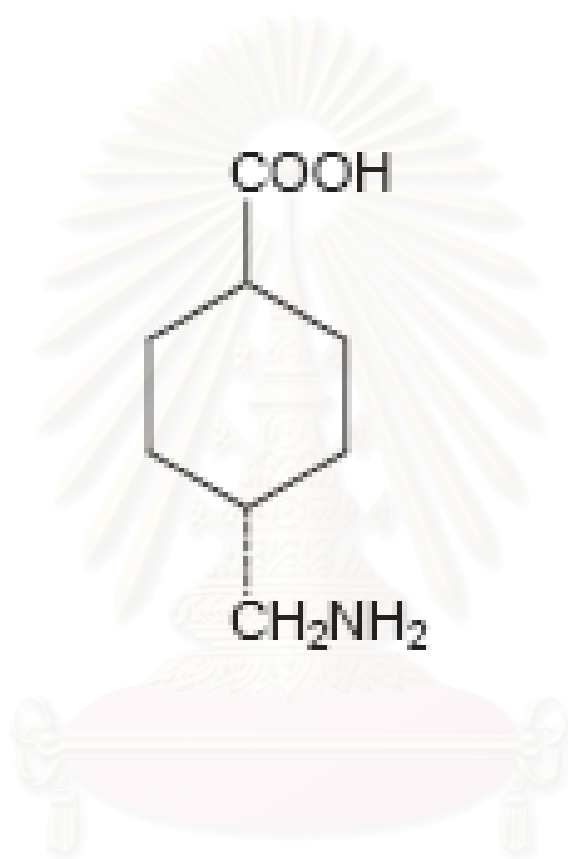
Figure3. Tranexamic acid (TXA) [4-(aminomethyl)cyclohexanecarboxylic acid] [41]

2.2.1 Overview of pharmacodynamic properties

The antifibrinolytic effect of TXA results from the formation of a reversible complex of the drug with plasminogen. Human plasminogen contains lysine binding sites that are important for interactions not only with synthetic antifibrinolytic amino acid derivatives but also with α_2-antiplasmin and fibrin. One of these binding sites has a high affinity for TXA [dissociation constant (K_d)=1.1 µmol/L]; the others have low affinity only [(K_d)=750 µmol/L]. TXA almost completely blocks the interaction of plasminogen and the heavy chain of plasmin with the lysine residues of fibrin monomer, primarily through its binding to the high affinity lysine binding site of plasminogen. .[43-44] Saturation of this site with TXA prevents binding of plasminogen to the surface of fibrin (Fig.4). This process retards fibrinolysis. Although plasmin is still formed, it is unable to bind to fibrinogen or fibrin monomer. Conversely, when the binding site of plasmin is blocked by TXA, inactivation by α_2-antiplasmin cannot proceed.

A comparison of the binding potencies of TXA and EACA in fibrinolytic test systems has shown TXA to be more potent by a factor between VI and X. TXA competitively inhibits the activation of trypsinogen by enterokinase. At concentration 4 times greater, TXA noncompetitively inhibits the proteolytic action of trypsin. The drug also weakly inhibits thrombin.[43] The noncovalent interactions between plasminogen/plasmin and other macromolecules such as fibrin are mediated by a series of 5 triple disulphidebonded plasminogen domains called kringles, each of which has a single binding site for lysine analogues. The pharmacodynamic effects of TXA, vary according to the indication in which the drug is being used; observations from patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), women with menorrhagia, patients undergoing total knee arthroplasty and recipients of orthotopic liver transplants, are summarized in Table 2. In these studies, suppression of fibrinolysis by TXA was manifested by reductions in blood levels of D-dimer (a breakdown product of cross-linked fibrin) relative to those in untreated patients and the drug had no effect overall on blood coagulation parameters (e.g. platelet counts, activated partial

thromboplastin times and prothrombin times). These observations are expected in the mechanism of action of TXA.[45]
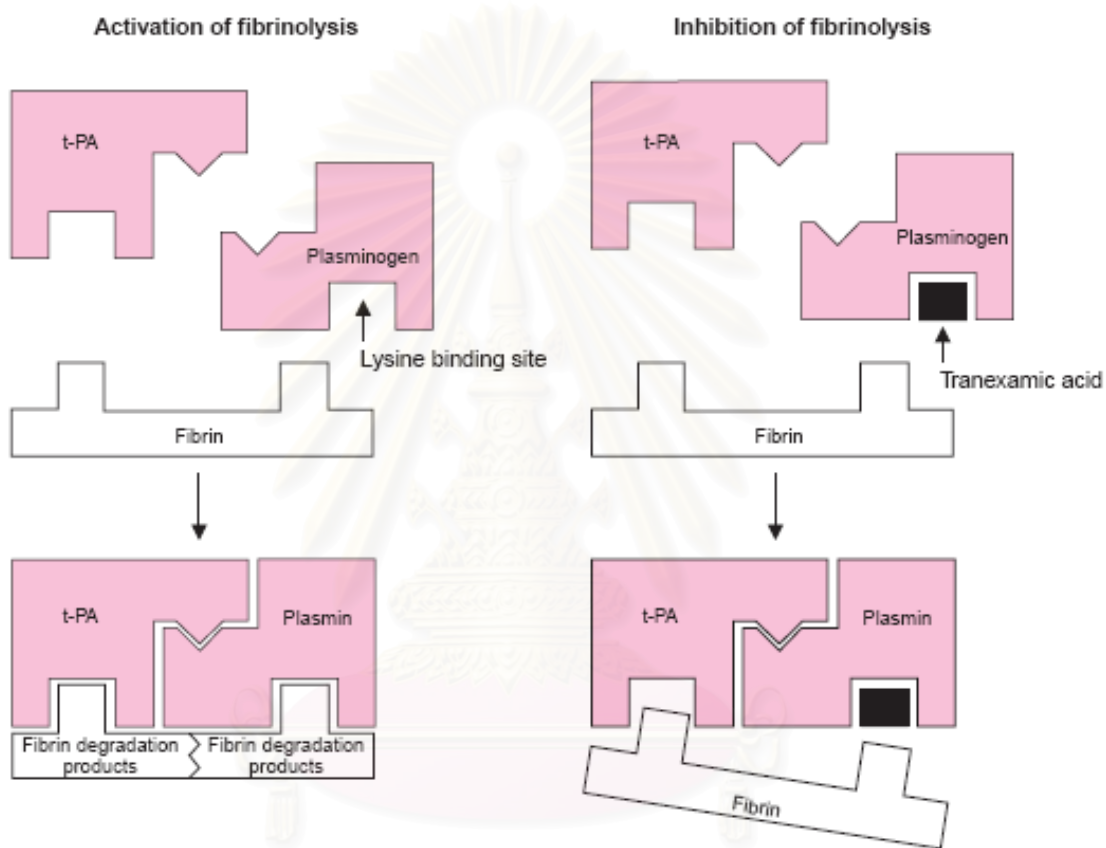
Figure4. Antifibrinolytic action of tranexamic acid.[41]

Pharmacodynamic properties of tranexamic acid in patients. Effects described are relative to those seen in untreated control or placebo groups.

Patients undergoing cardiac surgery with CPB

Suppression of increase in blood D-dimer levels after surgery.

No effect on blood antiplasmin activity.

No effect on blood fibrinogen levels.

Reduction in blood levels of fibrinogen split products.

Reduction in platelet glycoprotein-1b receptor expression after CPB.

Blockade of plasmin-induced partial platelet activation during CPB.

No effect on aPTT, PT or platelet counts.

Women with menorrhagia

Reduced t-PA and plasmin activity in menstrual and peripheral blood.

Patients undergoing total knee arthroplasty

Reduced levels of D-dimer in wound blood.

No effect on α_2-antiplasmin, t-PA or PAI-1 levels in peripheral venous or wound blood.

No effect on levels of prothrombin fragments 1 and 2 or platelet counts in peripheral venous or wound blood.

Patients undergoing orthotopic liver transplantation

No effect on blood levels of fibrinogen or factors V, VII or VIII.

Patients with subarachnoid haemorrhage

Reduced plasminogen activity in blood and CSF.

No effect on levels of fibrin degradation products in CSF.

Noted after initial dose of tranexamic acid before start of CPB.

No significant difference from placebo after CPB.

aPTT = activated partial thromboplastin time; CPB = cardiopulmonary bypass;

PAI-1 = plasminogen activator inhibitor 1; PT = prothrombin time;

t-PA = tissue plasminogen activator

Table 2. Demonstrated the pharmacodynamic effect of tranexamic acid.[41]

2.2.2 Overview of pharmacokinetic properties

A previous study on healthy volunteers demonstrated maximum plasma concentrations of TXA to be reached within 3 hours of oral administration.[46] The presence of food in the gastrointestinal tract has no effect on the pharmacokinetic parameters of the drug (Table 3). After intravenous administration of TXA (single dose of 1 g), elimination followed triexponential phases with over 95% of each dose, is eliminated as inactive drug in the urine. Total clearance (Cl) ranges from 6.6 to 7 L/h(110 to 116 ml/min).[46] Mean total urinary excretion in terms of quantity of drug administered is 959 mg/g.[46] Approximately 30% of an intravenous dose of 10 mg/kg is recovered in the urine during the first hour after administration; the total excretion reached to 45% after 3 hours and to 90% after 24 hours.[40-44]

At therapeutic plasma concentrations (5 to 10 mg/L), TXA weakly (approximately 3%) bounds to plasma protein: this appears to be fully accounted for by binding to plasminogen. The drug crosses the blood-brain barrier and diffuses rapidly into joint fluid and synovial membranes. Excretion through breast milk is minimal. The drug also passes through the placenta. TXA is not detectable in saliva after 1g. of systemic (oral) administration. However very high drug concentrations (mean 200 mg/L) are attained in saliva 30 minutes after mouth rinsing for 2 minutes with a 5% aqueous solution of TXA, this result in plasma drug concentrations remain below 2 mg/L. The topical mouth rinse has been widely studied in patients undergoing oral surgery.

Pharmacokinetics of tranexamic acid. Single oral doses of 2g of tranexamic acid were given to 3 healthy volunteers. Each volunteer received 1 dose while fasting and another after a standard meal.

Parameter (mean value)	Fasting	After food
C_{max} (mg/L)	14.4	14.8
t_{max} (h)	2.8	2.9
AUC_{5h} (mg/L•h)	59.5	61.3
AUC_{∞} (mg/L•h)	147.7[a]	
F (%)	33.4	34.9
CL_R (L/h)	8.2	7.9
Ae_{24h} (mg)	639	669

A   Overall mean result (fasting and non-fasting).

Ae_{24h} = amount excreted in urine in 24 hours; AUC_{6h} = area under the plasma drug concentration versus time curve from zero to 6 hours; AUC_{∞} = area under the plasma drug concentration versus time curve from zero to infinity; C_{max} = peak plasma drug concentration; CL_R = renal clearance; F = systemic bioavailability; t_{max} = time to C_{max}.

Table 3. Demonstrated the pharmacokinetics of tranexamic acid.[41]

2.2.3 Dosage and administration

There are two forms of preparations; a 500 mg tablet and a 50 mg/5 ml ampoule for intravenous injection. TXA is indicated in patients with hemophilia for short term use to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.(Table 4) For intravenous infusion, TXA can be mixed with most solutions for infusion. The mixture should be used shortly after preparation. Heparin may be added to TXA for injection. TXA solution should not be mixed with blood or any solutions containing penicillin.[40-44]

2.2.4 Side effects & drug interactions

Patients may have gastrointestinal discomfort (nausea, vomiting and diarrhea) if they are prescribed with high doses. Giddiness and hypotension have been reported occasionally. Hypotension has been observed when TXA is injected too rapidly. To avoid this side effect, the solution should not be injected faster than 1 ml/minute. This adverse reaction has not been reported with oral administration. Thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, central retinal artery and vein obstruction) have been rarely reported by Worldwide Post marketing in patients who receiving TXA for indications other than hemorrhagic prevention in patients with hemophilia.[40-44]

2.2.5 Precautions & contraindications

In patients with renal insufficiency, the dosage of TXA should be adjusted to reduce the risk of drug accumulation. There were reports of urethral obstruction due to clot formation in patients treated with TXA for urinary tract bleeding. Patients with a previous history of thromboembolic disease may have increased risk of venous or arterial thrombosis. Patients with disseminated intravascular coagulation (DIC), who require treatment with TXA, must be under strict supervision. There were reports of focal areas of retinal degeneration, retinal change in cats, dogs and rats. Post marketing adverse reactions in Sweden reported visual abnormalities in patients who use TXA for a long period. TXA should be discontinued if changes in vision are detected. TXA is

contraindicated in patients with acquired defective color vision, subarachnoid hemorrhage and active intravascular clotting.[40-44]

Serum Creatinine (µmol/L)	Tranexamic acid Dosage	
	IV	Tablets
120 – 250 (1.36-2.83 mg/dl)	10 mg/kg bid	15 mg/kg bid
250 – 500 (2.83-5.66 mg/dl)	10 mg/kg day	15 mg/kg day
> 500 (>5.66 mg/dl)	10 mg/kg every 48 hrs or	15 mg/kg every 48 hrs or
	5 mg/kg every 24 hrs	7.5 mg/kg every 24 hrs

Table 4.demonstrated dosage and administration of tranexamic acid used in hemophiliac patients.[40]

2.3 Review of deep vein thrombosis (DVT) and Pulmonary embolism[45]

DVT is a condition wherein a blood clot (thrombus) forms in deep veins. Thrombophlebitis is a condition in which there are both inflammation and a blood clot in a vein. Thrombophlebitis can occur in either superficial or deep veins. Superficial thrombophlebitis occurs in veins close to the skin surface and usually causes pain, swelling and redness in the area of the vein. This condition is treated with heat, elevation of the affected leg or arm and anti-inflammatory medications. Thrombosis in the deep venous system is a much more serious problem. The reason for this is that a piece of the clot in DVT may break off and travel through the deep veins back to the heart and throw emboli to various vital organs such as lungs, brain, coronary arteries, kidney and etc. Conditions that increase the risk of DVT include the use of certain drugs such as estrogen and contraceptive pills, cancer, inflammatory bowel disease (Crohn's disease or ulcerative colitis), unusual blood conditions (e.g. antiphospholipid syndrome, paroxysmal nocturnal hemoglobinumia), prolonged sitting, bed rest or immobilization such as a long plane or car trips, recent surgery or trauma (especially hip, knee or gynecological surgery), fractures, history of polycythemia vera, malignant tumor, deficiencies of certain blood components (antithrombin III, protein C and protein S), defective blood clotting factors (factor V Leiden) that are necessary for activating the body's system for dissolving blood clots and some enzyme defects caused by certain vitamin deficiencies (B12 or folic acid) that lead to an increase of homocysteine (a compound which increases the tendency for the blood clot).

The most common symptoms of DVT in the legs are edema, pain, tenderness, warmth and changes in skin color (redness) in the affected side. These symptoms are caused by stagnation of clot in the vein and extravasation of intravascular fluid to the adjacent tissue. DVT is difficult to diagnose without specific tests in which the deep vein system can be examined. Furthermore, a number of patients with DVT have no symptoms at all unless the clot dislodges and travels to the lung and causes a pulmonary embolism.[4] The patients may develop a rapid heart rate, shortness of breath, chest pain. If the pulmonary emboli are large and block one or both of the major

pulmonary arteries sending blood to the lungs, the patient may develop a very low blood pressure and possibly die from lung or heart failure.[4]

2.3.1 Investigation for DVT[45]

Several tests, each of which has certain advantages and limitations, can be used to diagnose the presence of a DVT. The oldest of these tests is venography. This test is performed by injecting a radiopaque fluid into a vein on the top of the foot. The dye flows with the blood and fills the veins of the leg, thigh and pelvis. An obstructing blood clot in one of these veins can be seen on an x-ray as a dye-free area within the vein. Venography is the most accurate test to identify a DVT but it is invasive, painful, expensive and occasionally can cause painful inflammation of veins (phlebitis).

Because of these problems, venography has largely been replaced by venous ultrasonography for the diagnosis of DVTs. Venous ultrasonography uses sound waves to examine the veins to determine if a blood clot is present. A recent improvement in venous ultrasonography is the addition of another sound wave technology called Doppler ultrasound. The technique improves the identification of clots in veins by determining the amount of blood flowing the veins. Veins with clots have slow or no flow of blood. The major advantages of venous ultrasonography are non-invasive, painless, easy to perform and capable of diagnosing 96% of patients with DVTs above the knee.

Although rarely used today, another technique for diagnosing DVTs is impedance plethysmography. In this procedure, blood pressure cuffs are placed on the legs to determine the pressures at which the veins are filled or collapsed so that obstructing blood clots can be identified.

Recently, studies involving magnetic resonance imaging (MRI), another non-invasive imaging technique, have demonstrated its effectiveness in diagnosing DVTs.

2.3.2 Treatment of DVT

Currently, two types of anticoagulants are used for treatment. The most commonly used is called unfractionated heparin, which usually is given around the clock by infusion in a vein while the patient is in the hospital. A blood test (the activated partial thromboplastin time; aPTT) is checked frequently to assure that the patient's blood is anticoagulated neither too much nor too little. A new type of heparin, called low-molecular - weight heparin, has been gaining in popularity for the initial treatment of DVT. This medication can be given once or twice daily by subcutaneous injection.

2.3.3 Prevention of DVT

Surgery and some medical treatments can increase the risk of having a DVT. It's recommended that pre-operative risk assessment for DVT should be done in patients with high risk and with certain types of surgery. Various measures can then be used to keep the risks as low as possible. These include anticoagulant medication, early ambulation, compression stockings and an intermittent compression pump. This is a mechanical device that automatically squeezes the feet and lower legs in the first few days after surgery.

Thromboprophylaxis included twice daily subcutaneous heparin (dalteparin 5,000 U) started on the day of surgery, anti-stasis stocking and early postoperative mobilization.

2.3.4 General prevention advice

The patients should exercise the legs regularly by taking a brisk of 30 minutes walk every day, maintain a weight that's appropriate for their height and avoid sitting or lying in bed for long periods of time without moving the legs. Most women should consider the risks and benefits before taking the contraceptive pill. All these measures can prevent the incidence of suffering from DVT.

CHAPTER III

LITERATURE REVIEW

Review of related literature

Tranexamic acid (TXA) has been safely used in many different medical treatments. Non surgical uses of TXA include the management of bleeding associated with leukemia, ocular bleeding, recurrent haemoptysis, menorrhagia, hereditary angioneurotic edema and numerous other medical problems. Interest in TXA for orthopedic surgery was rekindled in part by the work of Hiippala et al who explored the use of the drug for total knee arthroplasty.[23] In their prospective double blind study, 75 patients scheduled for 77 total knee arthroplasties were randomized to receive either TXA or saline. A TXA bolus dose of 15 mg/kg was given intravenously before deflation of the tourniquet, followed by two 10 mg/kg additional doses given postoperatively. Blood transfusions were used to keep hemoglobin levels above 10 g/dl. The results from Hiippala et al demonstrated a significant reduction in estimated total blood loss. The use of TXA significantly reduced the number of transfused red cell units in the TXA group compared to the placebo group. Numerous other studies supported the premise that TXA reduced blood loss and more importantly, significantly reduced transfusion rates.[24-26] A meta-analysis of studies using TXA for total knee arthroplasty supported the premise that it reduced total blood loss and reduces both the proportion of patients requiring allogenic blood transfusion and the total number of units of allogenic blood transfused.[27] Husted et al studied the effect of TXA on pre and postoperative blood losses and the number of blood transfusion needed. In their prospective randomized double blind study, 40 patients scheduled for primary total hip arthroplasty were assigned as the experimented group with 10 mg/kg of TXA was given with a bolus intravenous injection, followed by a continuous infusion of 1 mg/kg/hour of TXA for 10 hours and the control group were given 20 ml saline intravenously. The results from this study demonstrated a significant reduction in total blood loss and blood transfusion in TXA group compared to the placebo group. No patients in both groups had prolonged

drainage, infection, clinical deep venous thrombosis or pulmonary embolism.[28] Veien et al studied TXA effect of reducing blood loss after total knee replacement. In their study, 30 consecutive patients scheduled for total knee replacement under spinal anesthesia with the use of a tourniquet, TXA 10 mg/kg was given at the conclusion of surgery and again 3 hour later. The results showed total blood loss was at all times significantly lower in the TXA group. There were no differences in coagulation parameters. No patients in the TXA group had a blood transfusion while 13% in the non-TXA group had blood transfusion. No complications were noted in both groups. This study concluded that TXA significantly reduced blood loss after total knee replacement surgery with no adverse drug effects.[26] Krohn et al studied the effect of locally applied TXA on postoperative blood loss and measured the fibrinolysis in drained blood. In this prospective study, 30 patients underwent spinal surgery for low back pain by screw fixation of the lumbar spine, 16 were given topical TXA. The postoperative blood loss after 18 hours, concentrations of plasmin/alpha2-antiplasmin (PAP) and D-dimer in arterial and drained blood at the time of wound closure and in the drained blood after 1 hour were recorded. The results demonstrated that median blood loss of the TXA group was reduced by half. In the drained blood after one hour there was increased in the concentration of PAP and D-dimer in the TXA group compared with the control group. This study concluded TXA applied in the wound inhibits blood loss by up to a half in major orthopedic surgery probably because it prevents excessive fibrinolysis.[29] Yamasaki et al studied the effects of TXA. In a prospective, randomized study, 40 patients underwent cementless total hip arthroplasty, 20 patients were treated 1000 mg of TXA administered intravenously 5 minutes before the operation. The other 20 patients served as a control group and were operated without TXA. The study compared perioperative and postoperative blood loss in the TXA group and the control group. Postoperative blood loss of the TXA group was significantly less than that of the control group at 2, 4, 6, 8, 10 and 12 hour. Total blood loss was significantly less in the TXA group than in the control group. Regarding time-related changes of postoperative blood loss, significant reduction was observed during the first 2 hours after surgery in the TXA group. After 2

hours, there was no significant difference between the TXA group and the control group. There were no reports of thromboembolic events. [30] Yamasaki et al studied the effects of TXA on blood loss during and following total hip arthroplasty without cement. In 21 patients underwent staged bilateral total hip arthroplasty without cement for the treatment of osteoarthritis of the hip. On one side, 1000 mg of TXA was administered intravenously five minutes before the skin incision. On the other side, TXA was not administered. The volume of postoperative blood loss was recorded at two-hour intervals for the first twelve hours and then again at twenty-four hours. The results demonstrated the total intraoperative blood loss and the postoperative blood loss in the TXA group was significantly lower than that in control group at all time-points during the first twenty-four hours. The greatest reduction in blood loss was observed during the first four hours after surgery in the TXA group. This study concluded that total blood loss was reduced in patients underwent total hip arthroplasty without cement during the first 24 hours, especially during the first four hours after surgery. [31] Hynes et al studied the reduction in hemoglobin following unilateral total knee arthroplasty with TXA administration, 60 consecutive patients underwent unilateral primary total knee arthroplasty. 30 received TXA 10 mg/kg on induction and another dose shortly before the release of the tourniquet. Surgery was performed by the senior author in a standardized fashion using the Freeman Samuelson cemented total knee replacement. Hb levels were measured 2 weeks at pre and 3 days post operatively. Any complications arise were noted. A control group was matched using the Bone and Joint Research Unit database for age, sex, disease and pre-operative hemoglobin level. 30 patients with no TXA had been monitored in the same way. The results demonstrated that the group receiving no TXA, the mean fall in Hb was 2.8 g/dl while in the group treated with TXA was 1.7 g/dl. There were no complications in either group. This study concluded that the administration of TXA is an effective method of minimizing the post operative reduction of Hb level following knee arthroplasty. [25] Hynes et al studied the reduction of Hb level following total hip arthroplasty was reduced by TXA administration. 64 patients underwent total hip arthroplasty. 32 received TXA 20 mg/kg on induction

while 32 had no TXA served as the control group. Surgery was performed by the senior author in a standardized fashion. A control group was matched using the Bone and Joint Research database for age, sex, procedure, disease and pre-operative hemoglobin level. The study demonstrated the group receiving no TXA the mean fall in hemoglobin was 3.8 g/dl and the group treated with TXA the fall was 2.8 g/dl. There was one non-fatal pulmonary embolus in the TXA group. This study concluded that the administration of TXA is an effective method of prevention of Hb reduction following hip arthroplasty.[32] Good et al studied the overall effect of TXA in decreasing the external blood loss in total knee replacement. In a double-blind fashion, 51 patients with osteoarthrosis had unilateral cemented total knee arthroplasty using spinal anesthesia. They received either placebo (n=24) or TXA 10 mg/kg (n=27) intravenously just before tourniquet release and another dose 3 hours later. Two patients in each group developed DVT.[33] The use of TXA does not increase the risk of thromboembolic complications such as DVT, pulmonary embolism, thrombotic cerebral vascular accident or myocardial infarction.[27,31] Intravenous TXA is a safe and effective in reducing allogenic blood transfusion and blood loss in total knee arthroplasty. The major concern regarding the use of TXA and other antifibrinolytics is the potential for an increase risk of thrombotic events. No thrombo-embotic events occurred in their studies. The studies on the use of TXA in patients undergoing total knee arthroplasty also did not experience an increased incidence of DVT.[23-24,27] Reports of thrombo-embolic events attributed to TXA are uncommon, occur in the non-operative setting and are primarily anecdotal in nature. A common misconception is that these drugs are procoagulants and they will increase blood clotting. The drugs do not alter blood clotting but instead slow the process of dissolution of blood clots. Sites where clots have formed will therefore remain or enlarge but spontaneous formation of clots should not occur.[24] Benoni et al suggested that TXA was not associated with thrombo-embolic events because the effects of TXA were more pronounced in operative wounds than in the peripheral venous blood.[24] The beneficial effects were probably due to the inhibition of local fibrinolytic activity in the surgical field. TXA had no significant effects on peripheral fibrinolysis or other coagulation variables [24]

There have been very few studies regarding the use of TXA to control bleeding in oral & maxillofacial surgery especially in orthognathic surgery. Zellin et al studied the addition of hemorrhage depressors during orthognathic surgery would reduce the blood loss. A retrospective study, 30 patients consecutively operated with Lefort I osteotomies in 1998 (n=15, control group) and 1999 (n=15, treatment group), were included in the study. Both groups received hypotensive anesthesia during surgery and the treatment group received additional hemorrhage depressors: TXA and desmopressin. The results showed the mean blood loss was 740±410 ml (11.3 ml/kg) in the control group and 400±210 ml (5.7 ml/kg) in the treatment group. The results showed a statistically significant reduction of blood loss in the treatment group (p < 0.01). This study concluded that blood loss during orthognathic surgery under hypotensive anesthesia could be significantly reduced when a combination of TXA and desmopressin administered preoperatively. [46]

CHAPTER IV
RESEARCH METHODOLOGY

4.1 Patients and methods

Nineteen patients, ages ranged between 18 to 40 years, planned for bilateral sagittal split ramus osteotomies (BSSRO) to correct the dentofacial deformities along with orthodontic treatment at the department of Oral & Maxillofacial Surgery and the department of Orthodontics, Faculty of Dentistry, Chulalongkorn University from February 2006 to October 2006 were selected to participate in this study. The patients were fit and healthy and no medical history of hematopoitic disorder, deep vein thrombosis, previous exposure to TXA, currently taking the oral contraceptive pills or anticoagulants, ischemic heart disease, renal disease, liver cirrhosis, acquired defective color vision and allergy to TXA. Patients who had injury of major blood vessels during operation and bad splits were also excluded from this study. The patients were randomly divided into two groups; a study group and a control group. This study was approved by the medical ethics committee for human research of the faculty of Dentistry. The patients were informed and consents were obtained from all patients participated in this study.

4.2 Preoperative Protocol

Samples of blood for each patient were collected for evaluation of hematological parameters (CBC; Hb, Hct, platelet count, BUN, Creatinine) and were recorded before and after operation. Patients were starved at least 6 hours before operation and strictly prepared under standard preanesthetic and care.

4.3 Anesthesia and Monitoring

All surgical interventions were performed under general anesthesia administered by only one anesthesiologist using the standard general anesthetic technique. Anesthesia was induced with thiopental and then neuromuscular blockage was achieved with succinyl-choline. After endotracheal intubation, the anesthesia was

maintained with non-depolarize muscle relaxants and isoflurane, nitrous oxide and oxygen were delivered by mechanical intermittent positive ventilation. Narcotic analgesic was given intravenously as required. At the end of the procedure prostigmine and atropine were used to reverse the neuromuscular blockage. Throughout the operation, the patients were given intravenous fluid or blood transfusion regarding the anesthesiologist. After operative, intravenous fluid was maintained until the patients were able to take oral diet.

4.4 Protocol for giving TXA or placebo

Patients and drugs were randomized. The drugs; Tranexamic acid (Transamin®. Daiichi Pharmaceutical Co. Ltd., Thailand) 250 mg/5ml 2 ampoules or saline 20 ml 2 ampoules were prepared in a syringe with labeled by a person who was not involving with the surgical procedure and administered by the anesthesiologist. In the TXA group, 10 mg/kg of TXA was administered intravenously five minutes before the incision. In the control group, 10 ml/kg of NSS was administered intravenously five minutes before the incision.

4.5 Surgical technique

Each surgical site was infiltrated with 3.6 ml of 2% lidocaine HCl with epinephrine 1:100,000 solution 5 minutes before making incisions. Then, standard BSSRO procedures were performed. The mandibles were set back or advanced as presurgical planned. Each osteotomy site was fixed with a four hole titanium miniplate and four 2.0 mm titanium screws 7 or 5.5 mm in length. The vacuum drain was applied at each osteotomy site before wound closing. The surgical wound was sutured with resorbable suture and maxillo-mandibular fixation applied for one week. Patients were given 1.2 g amoxicillin-clavulanate intravenously before surgery and a single dose of 1.2 g amoxicillin-clavulanate at 8 hour postoperatively and then continued with oral regimen of 625 mg amoxicillin-clavulanate every 8 hours for five days. Any patients who were allergic to penicillin, 600 mg of clindamycin was administered intravenously before operation and every 8 hours during operation and a single dose of 600 mg clindamycin

at 8 hours postoperatively and then continued with oral regimen of 300 mg of clindamycin every 8 hours for five days. Intravenous Dexamethasone 8 mg was given preoperatively and then every 12 hours for 3 days. Postoperative nausea and vomiting were controlled by 10 mg metoclopramide given intramuscularly as required. Early post operative pain was control with 40 mg Parecoxib and 200 mg Ibuprofen syrup once the patients were able to take oral fluid. Patients were fed with liquid diet until the maxillo-mandibular fixation removed. Any postoperative complications detected were recorded and treated. Patients were kept in the hospital for 3 days then discharged once the condition was fit for discharge.

4.6 Assessment of perioperative and postoperative blood loss

The perioperative blood loss was assessed from the blood in the suction container and the blood soaked surgical sponges, gauzes and swabs. Postoperative blood loss was measured from vacuum drains which were retained until the 2nd postoperative days or until postoperative blood loss was less than 20 ml/day for each side. Total blood loss was calculated by the combination of intraoperative blood loss and postoperative blood loss. Postoperative Hb level was measured at the first and third postoperative day. Any patients where Hct reduced more than 25%[47] of the baseline or Hb was below 7 g/dl[8] on the second postoperative day or developed clinical symptoms of anemia, a blood transfusion would be considered.[47] The volume of blood transfused would be recorded if there was any blood transfusion. The patients were evaluated for postoperative thrombosis during hospitalization and at the out patient clinic on the 1st, 2nd and 4th week postoperatively. All wounds were inspected daily during hospitalization and patients were reviewed at the 1st, 2nd and 4th week postoperatively. Any signs of prolonged drainage or infection would be noted and treated.

4.7 Assessment of DVT

All patients underwent medical reviewed and full physical examination with no signs of DVT detected. We observed the Homan's sign (calf pain with forcible dorsiflexion of the feet) and edema, pain, tenderness, increased warmth, changes in

skin color (redness) in legs for as long as four weeks postoperatively. Any abnormal findings would be noted.

4.8 Data collection

1. Total blood loss was measured from all blood in the suction container in the theatre, the blood in the suction drains from the wound sites and the blood soaked all swabs and gauzes used during operation.

2. Hemoglobin level was recorded at preoperative, the first and the third postoperative day.

4.9 Data analysis

The One Sample Kolmogorov-Smirnov test was used to test the normality of the distribution of the continuous variables. Nonparametric as well as non-normally distributed data was reported as median and 25th to 75th percentiles and evaluated by the Mann-Whitney U-test. Normally distributed data were analyzed by the parametric Independent T-test and were reported as means±SD. P values less than 0.05 were considered statistically significant.

Data were analyzed using the statistical package for social sciences (SPSS) version 11.5.

CHAPTER V

RESULTS

Results

Nineteen patients underwent BSSRO. Ten patients were in experimental group and nine patients were in control group. Mean age of the experimental group was 25.4±5.15 years and the control group was 25.22±4.09 years. Mean weight of the experimental group was 58.86±11.31 kg and in the control group was 57.50±15.58 kg. There were 4 males (40%) and 6 females (60%) in the experimental group and there were 3 males (33.33%) and 6 females (66.67%) in the control group. All patients were in ASA I catagory and no contraindication for TXA.

The mean intraoperative blood loss of the experimental group was 198.96±227.07 ml and the control group was 315.43±294.99 ml. The mean postoperative blood loss of the experimental group was 115.35±43.54 ml and the control group was 117.33±32.89 ml. The mean total blood loss in the experimental group was 314.31±233.49 ml and the control group was 432.76±318.31 ml. The intraoperative, postoperative and total blood loss in the experimental group was not statistically significantly different from the control group. (p > 0.05) (Table 6)

The operation time of the experimental group was 128.1±47.34 minutes and the control group was 163.22±31.02 minutes. (Table 5) The operating time in the experimental group was not significantly different from the control group (p = 0.076).

The intraoperative blood loss was normally distributed in the experimental group (P = 0.103) and in the control group (P = 0.919). The postoperative blood loss was normally distributed in the experimental group (P = 0.926) and in the control group (P = 0.894). The total blood loss was normally distributed both in the experimental group (P = 0.178) and in the control group (P = 0.871). The intraoperative, postoperative and total blood loss in the experimental group was not significantly different from the control group (p > 0.05). Test variance in the intraoperative blood loss was P = 0.257, the postoperative blood loss was P = 0.357 and the total blood loss was P = 0.180

respectively. The intraoperative blood loss of both groups using the equal variance assumed (P = 0.346), the postoperative blood loss was P = 0.913 and the total blood loss was P = 0.364 respectively. Therefore, the intraoperative, postoperative and total blood loss in the experimental group was not significant different from the control group (P > 0.05).

The mean preoperative Hb was 12.53±1.12 g/dl in the experimental group and 12.92±1.74 g/dl in the control group. The mean Hb on the 1st postoperative day was 11.57±1.22 g/dl in the experimental group and 11.15±1.0 g/dl in the control group. The mean Hb on the 3rd postoperative day was 10.68±1.88 g/dl in the experimental group and 11.22±1.16 g/dl in the control group. (Table 7)

The preoperative Hb in the TXA group (P = 0.919) and in the control group (P = 0.916) was normally distributed. The Hb on the 1st postoperative day was normally distributed in the TXA group (P = 0.903) and in the control group (0.906). The Hb on the 3rd postoperative day was normally distributed in the TXA group (P = 0.843) and in the control group (0.829). The difference between the preoperative Hb and the Hb on the 1st postoperative day was normally distributed in the TXA group (P = 0.997) and in the control group (0.773). The difference between the preoperative Hb and the Hb on the 3rd postoperative day was normally distributed in the TXA group (P = 0.672) and in the control group (0.999). The preoperative Hb and the Hb on the 1st and 3rd postoperative day in the TXA group was not significantly different from the control group (p>0.05). Test variance in the preoperative Hb was P = 0.124, Hb on the 1st postoperative day was P = 0.212, Hb on the 3rd postoperative day was P = 0.251. The difference between the preoperative Hb and the Hb on the 1st postoperative day was P = 0.770 and between the preoperative Hb and Hb on the 3rd postoperative day was P = 0.273. The difference between the preoperative Hb and in Hb on the 1st postoperative day and the difference between the preoperative Hb and the Hb on the 3rd postoperative day of both groups were compared using the equal variance assumed. Preoperative Hb was P = 0.563, Hb on the 1st postoperative day was P = 0.432 and Hb on the 3rd postoperative day was P = 0.471, the difference between preoperative Hb and the Hb on the 1st postoperative day

was P = 0.188 and the difference between preoperative Hb and the Hb on the 3rd postoperative day was P = 0.823. The preoperative Hb, the Hb on the 1st and 3rd postoperative day, the difference between the preoperative Hb and the Hb on the 1st postoperative day and the difference between preoperative Hb and the Hb on the 3rd postoperative day in the TXA group were not significantly different from those in the control group (P > 0.05).

No patients in both groups required blood transfusion. There were no problems of thromboembolic events and infection in all patients during 4 weeks postoperative review.

Id	number	operator	case	Age (yrs.)	sex	Weight (kg)	operation	Time (min.)
1	10	1	1	19	2	44.5	Set back	90
2	8	4	1	29	1	74.5	Set back	160
3	5	4	1	25	1	71	Set back	188
4	9	1	1	33	2	53	Set back	90
5	12	2	1	27	2	54.3	Set back	161
6	6	1	1	30	1	56	Set back	105
7	13	1	1	20	2	47.3	Set back	113
8	11	1	1	19	2	63	Set back	90
9	14	1	1	22	2	50	Set back	75
10	7	3	1	30	1	75	Set back	209
mean	10 pts.		Exp.	25.4		58.86		128.1
SD.				5.15		11.31		47.34
11	15	4	2	25	2	60.3	Set back	115
12	16	1	2	25	2	45.5	Set back	140
13	17	3	2	29	2	52.5	Set back	180
14	2	2	2	30	2	40	Set back	187
15	18	4	2	19	2	43.7	Set back	145
16	1	1	2	31	2	51	Advance	210
17	3	4	2	24	1	62	Set back	195
18	19	1	2	21	1	87.5	Set back	152
19	4	3	2	23	1	75	Set back	145
mean	9 pts.		Ctrl.	25.22		57.5		163.22
SD.				4.09		15.58		31.02

Table 5. demonstrates demographic data of experimental group and control group.

Case1 = Experimental group; Case 2 = Control group

id	number	Intra-bleed (cc)	Post-bleed (cc)	Total-bleed (cc)
1	10	50.0	77.0	127.0
2	8	73.2	165.0	238.2
3	5	88.34	165.0	253.34
4	9	100.0	115.0	215.0
5	12	131.57	119.0	250.57
6	6	135.0	165.0	300.0
7	13	150.0	65.0	215.0
8	11	150.0	90.0	240.0
9	14	295.0	50.0	345.0
10	7	816.49	142.5	958.99
mean	10 pts.	198.96	115.35	314.31
SD.		227.07	43.54	233.49
11	15	20.27	80.0	100.27
12	16	35.97	80.0	115.97
13	17	81.16	82.0	163.16
14	2	188.39	160.0	348.39
15	18	218.21	114.0	332.21
16	1	302.56	105.0	407.56
17	3	513.42	158.0	671.42
18	19	578.86	132.0	710.86
19	4	900.0	145.0	1045.0
mean	9 pts.	315.43	117.33	432.76
SD.		294.99	32.89	318.31

Table 6. demonstrates intraoperative, postoperative, total blood loss data of experimental group and control group.

Case1 = Experimental group; Case 2 = Control group

id	number	Hb2 (g/dl)	Hb3 (g/dl)	Diff.Hb2	Diff.Hb3
1	10	10	.	2.1	.
2	8	13.1	11.4	-1.7	0.0
3	5	13	12	1.3	2.3
4	9	12.8	12.1	-0.2	0.5
5	12	12.0	9.4	0.2	2.8
6	6	11.0	11.5	1.4	0.9
7	13	10.2	9.8	0.7	1.1
8	11	12.4	12.9	0.6	0.1
9	14	10.4	10.3	1.6	1.7
10	7	10.8	6.7	3.6	7.7
mean	10 pts.	11.57	10.68		
SD.		1.22	1.88		
11	15	12.2	12.4	1.4	1.2
12	16	10.9	10.1	0.7	1.5
13	17	12.6	13.3	2.6	1.9
14	2	10	10.2	2.8	2.6
15	18	9.9	10.2	0.8	0.5
16	1	10.1	10.6	0.1	-0.4
17	3	11.9	10.8	1.6	2.7
18	19	11.4	12.3	2.8	1.9
19	4	11.4	11.1	3.1	3.4
mean	9 pts.	11.15	11.22		
SD.		1.0	1.16		

Table 7. demonstrates data of preoperative Hb, the Hb of the 1st postoperative day, the Hb of 3rd postoperative day, the difference between preoperative Hb and the Hb of 1st postoperative day and the difference between preoperative Hb and the Hb of 3rd postoperative day in the experimental group and control group.

Case1 = Experimental group; Case 2 = Control group

Diff. Hb2 = Preoperative Hb baseline – Hb of the first postoperative day

Diff. Hb3 = Preoperative Hb baseline – Hb of the third postoperative day

CHAPTER VI

DISCUSSION

6. Discussion

In an attempt to reduce blood loss and the need for blood transfusion in orthognathic surgery, several methods have been employed to reduce blood loss. In the management of hemorrhage from mandibular osteotomies, many of the previously discussed techniques in the management of hemorrhage following maxillary surgeries are also valid, particularly with regard to specific vessel ligation and embolization. Most cases of blood loss from the mandibular osteotomies are intraoperative bleeding. The most common initial modality that can be used to treat bleeding is pressure packing. Pressure packing is used initially because the bleeding is usually coming from relatively inaccessible areas that make it difficult for direct approach to the source of hemorrhage. Prophylactic use of drugs to reduce bleeding has recently emerged as another approach. The antifibrinolytic drugs such as TXA have been administered in association with a variety of surgical procedures. TXA is an inhibitor of fibrinolysis that blocks the lysine-binding site of plasminogen to fibrin and inhibits the activation of plasminogen by plasminogen activators. The reduction of blood loss is now recognized to be a priority in all surgeries. In this study there was no statistically significant difference in the demographic data on both groups of patients. Luz *et al* reported that blood loss during BSSRO is considered minimal.[49] Moenning *et al* found that the average blood loss for BSSRO group was 176.61 ml (range from 50 to 750 ml).[8] Mohorn et al found that patients underwent BSSRO lost about 191 ml of blood.[53] Panula et al found that the average blood loss for patients who underwent BSSRO was about 341 ml in the mandibular advancement group and about 349 ml in the mandibular setback.[1]

In this study, with the administration of 10 mg/kg TXA intravenously 5 minutes before operation, the intraoperative blood loss in the TXA group (198.96±227.07 ml) was lower than that in the control group (315.43±294.99 ml). The intraoperative blood loss was reduced by 36.92%, but this was not a significant reduction (P > 0.05). Similar to

several previous studies, the surgeons were familiar with the procedure and operation time was short. There was only a small amount of blood loss in the BSSRO procedure, so it was difficult to demonstrate the significant hemostatic effect of TXA of patients in the study group. Some studies in orthopedic surgery demonstrated a significant reduction during the first 2 hours after surgery in the TXA group ($p < 0.001$).[30,31] There were some limitation in this study because the amount of blood collected in the vacuum drains in our patients was also too small and it was not practical to measure the blood in the drain every hours. So our study measured only the total blood in vacuum drains before removal. Estimations of operative blood loss using the methods used in most of hospital operating rooms are not exactly accurate. Inaccuracy of the weight of sponges and gauzes used, the volume of fluid used for irrigation, the blood that was collected in the tissue space, the blood on the surgical drapes and surgeon gowns and gloves are factors that made the measurement of true blood loss far from accuracy. However, we tried to avoid these factors and made our measurement as accurate as possible.

In this study, the operating time was not correlated to the intraoperative blood loss but depended on individual patient's anatomy and surgeons. Hemoglobin level was used instead of Hct to evaluate blood loss as an indicator for the consideration of giving blood transfusion. The Hct, as a measure of the cellular content of the blood, is dependent on the dilution state of the intravascular compartment and is greatly influenced by the dynamics of plasma volume equilibrium as described, so the Hct is not a reliable parameter of either the pre or postoperative blood volume status.[52]

In this study, there was not significant reduction of Hb on the 1st and 3rd postoperative day and no signs of anemia, so there were no patients in both groups requiring blood transfusion. The Hb level on the 1st and 3rd postoperative day, the difference between the preoperative Hb and the Hb on the 1st postoperative day and the difference between the preoperative Hb and the Hb on the 3rd postoperative day in the experiment group were not significantly different from those in the control group. There were very few changes in Hb in the experiment group which corresponded to the changes in blood loss.

There was no marked bleeding in the operation of BSSRO in this study because it was operated by experienced surgeons and the operation was not complicate. Luz et al reported that no patients in the single-jaw surgery had blood transfusion during or after the operation.[49] Samman et al also found the transfusion was not necessary for single-jaw surgery, although 27% of their bimaxillary osteotomy patients required transfusion.[48] Gong et al found that the amount of blood loss in bimaxillary osteotomy procedures was 899 ml (range 200 to 1,800 ml).[7] There was more blood loss in other procedures in orthognathic surgery. So it was difficult to predict the hemostatic effect of TXA to prevent intraoperative and postoperative bleeding. It would have been better if we could have done the same experiment on bimaxillary surgery or other more extensive orthognathic surgery than the BSSRO. This might show a different outcome between the study and control group. However, we do not have a sample size large enough for the bimaxillary osteotomy or other more extensive orthognathic cases in such a short period of time. Nevertheless, this study demonstrated some degree of hemostatic effect of the TXA in the study group though it was not statistically significant.

CHAPTER VII
SUGGESTIONS FOR FURTHER STUDIES

7. Suggestions for further studies

Further studies are suggested:

The other orthognathic operations such as bimaxillary osteotomies and other more advanced orthognathic surgery which cause more extensive bleeding will be more preferable to evaluate the hemostatic effects of TXA. Because this surgery caused extensive perioperative bleeding, the study might show more significant reduction of blood loss. The study in larger sample size might be performed for more reliable result.
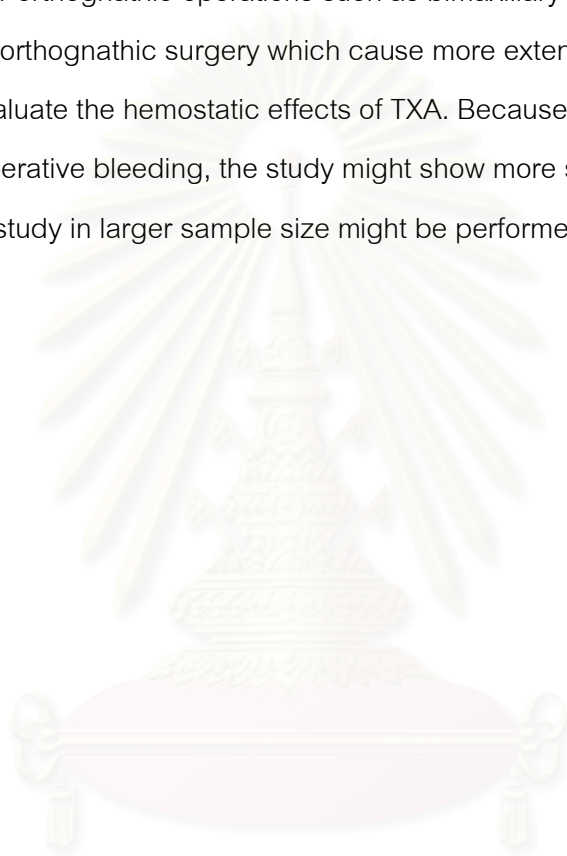
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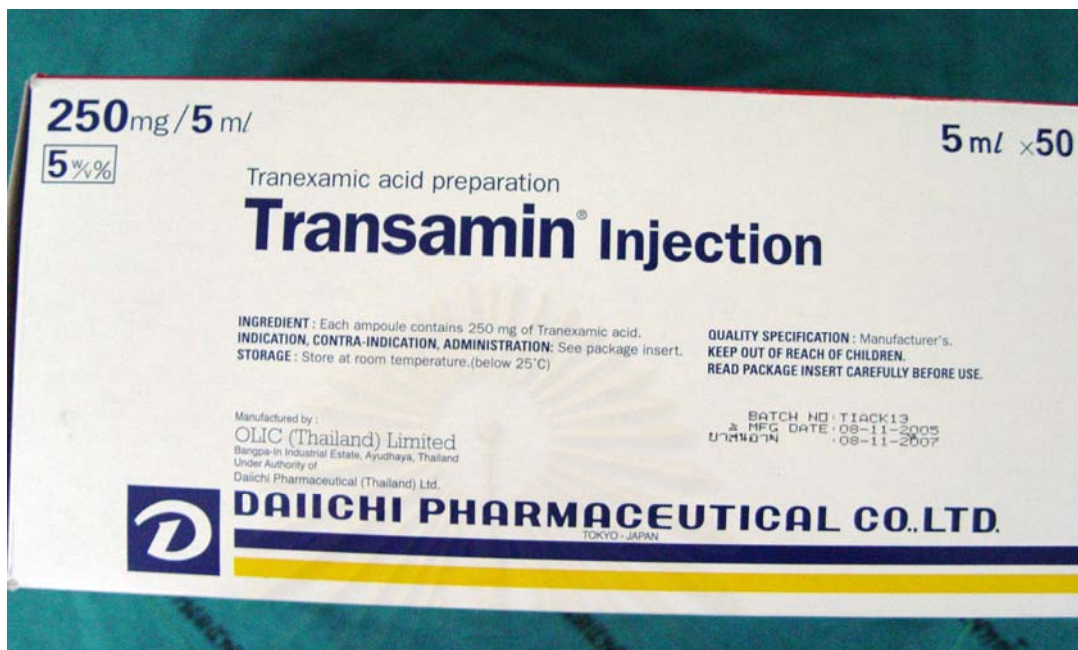
APPENDICES
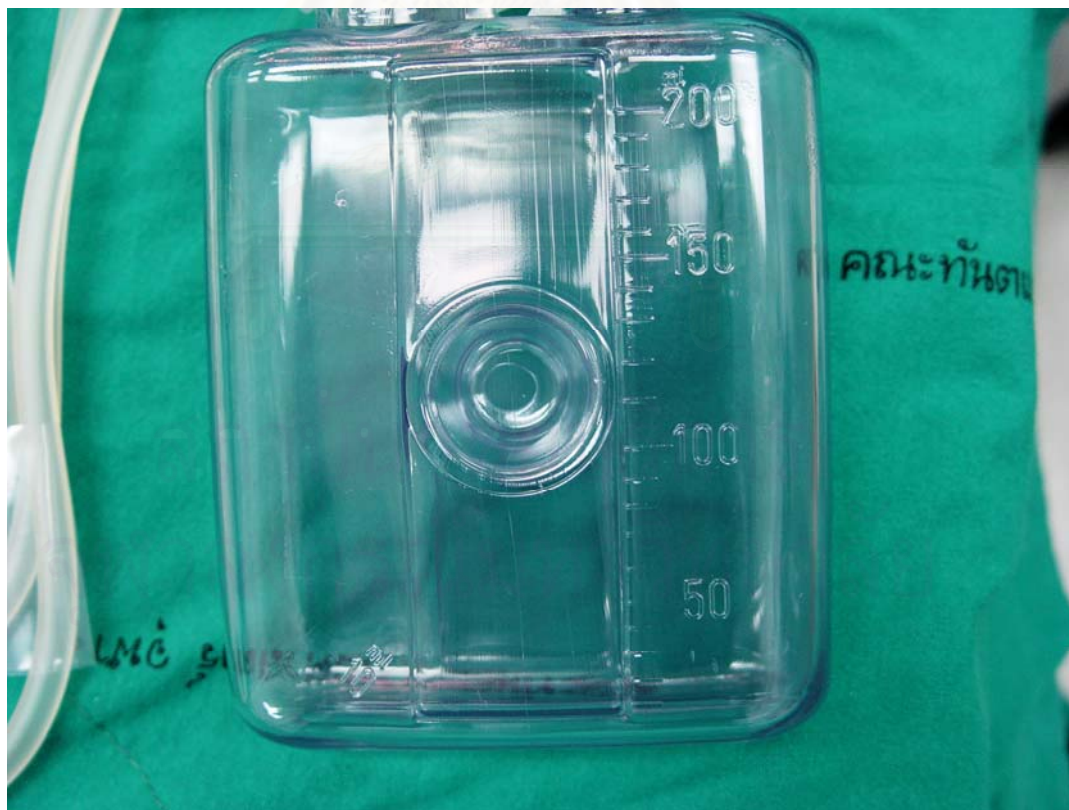
Vacuum drain (Radivac®)

TRANEXAMIC ACID (TRANXAMIN®)

Normal saline (NSS)
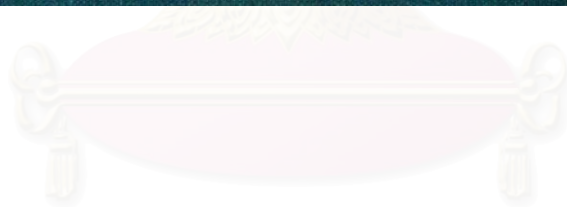
Syringe and needle

Suction container
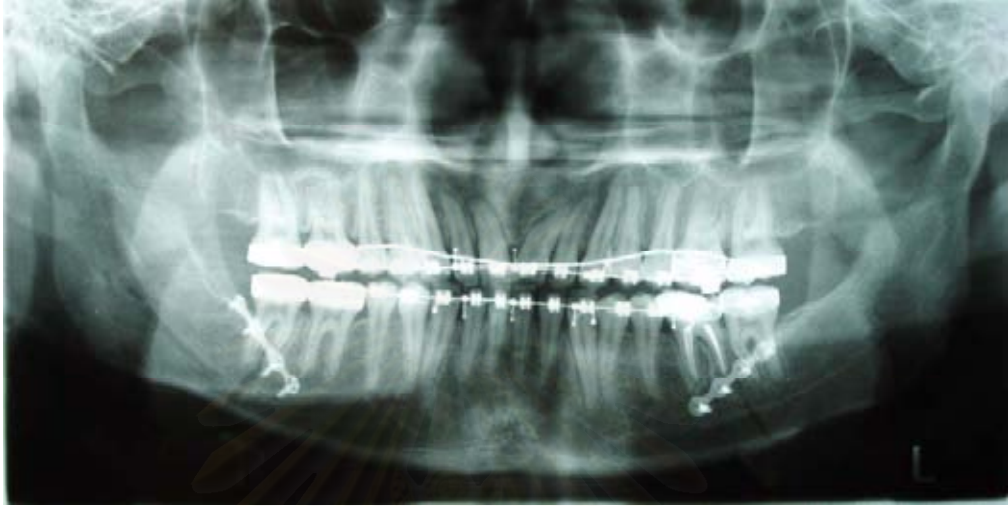
Bottle for measuring the volume of blood loss

Extraoral and radiograph showed vacuum drain at the osteotomied sites

Postoperative radiograph showed plates and screws at the osteotomied sites.

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