Aus dem Lehrstuhl
für Mund-, Kiefer- und Gesichtschirurgie
Prof. Dr. Dr. T.E. Reichert
der Fakultät für Medizin
der Universität Regensburg

Postoperative bleeding after oral surgeries: causes, risk profile of patients and therapy approaches

(Postoperative Blutung nach Operationen in der Mundhöhle: Ursachen, Risikoprofil der Patienten und Behandlungsstrategien)

Inaugural - Dissertation
zur Erlangung des Doktorgrades
der Zahnmedizin

der
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Vorgelegt von
Maria-Eleni Prokopidi

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To my parents for making me who I am
To Luk for loving who I am
To Pappous for inspiring who I am

Table of contents

1 Introduction

1.1 Haemostasis

Haemostasis begins at the site of injury and is accomplished through blood coagulation. When dealing with patients with an increased bleeding tendency, the understanding of this mechanism is of crucial importance. It was Morawitz who first presented a simple two step-four factor model in the early 1900´s, according to which prothrombin is converted to thrombin (activated by FIII and FIV), and then fibrinogen transforms to fibrin, activated by the previously formed thrombin (Morawitz, 1905).

In the years that followed, a number of coagulation factors were discovered by several different groups which coined different terms, thereby causing great misunderstanding. In 1954, with the formation of the ‘‘International Committee on Nomenclature of Blood Clotting Factors’’, however, a common nomenclature was established (Monroe et al, 2007). This allowed short after, in 1964, the developing of the waterfall/cascade model of coagulation (Macfarlane, 1964, Davie, Ratnoff, 1964).

The basic principle of the coagulation waterfall/cascade suggests that the various clotting factors are converted, in succession, to active enzymes until the final substrate, fibrinogen. Thrombin then converts fibrinogen to fibrin (Davie, Ratnoff, 1964). More specifically, the coagulation waterfall/cascade model consists of the extrinsic and intrinsic pathways (Fig. 1), which are clinically assayed using the prothrombin time-international normalised ratio (PT-INR) and the activated partial prothrombin time (aPTT) respectively (Hoffman, Monroe 2007). However, the use of these screening tests to predict clinical bleeding is to be questioned. Deficiencies of factor XII or XI, although they hold a high position in the intrinsic pathway of the cascade, might or might not be associated with significant haemorrhage. On the other side, deficiencies of factors VIII and IX, although lower in the same pathway, are consistently associated with haemorrhage. In spite of the dramatically different risk of haemorrhage, the deficiency of all four factors can equally prolong the aPTT (Hoffman, Monroe, 2007). As the extrinsic and intrinsic pathways are actually interdependent in vivo, the commonly used laboratory screening tests do not accurately reflect the complexity of haemostasis in vivo (Romney, Glick, 2009).

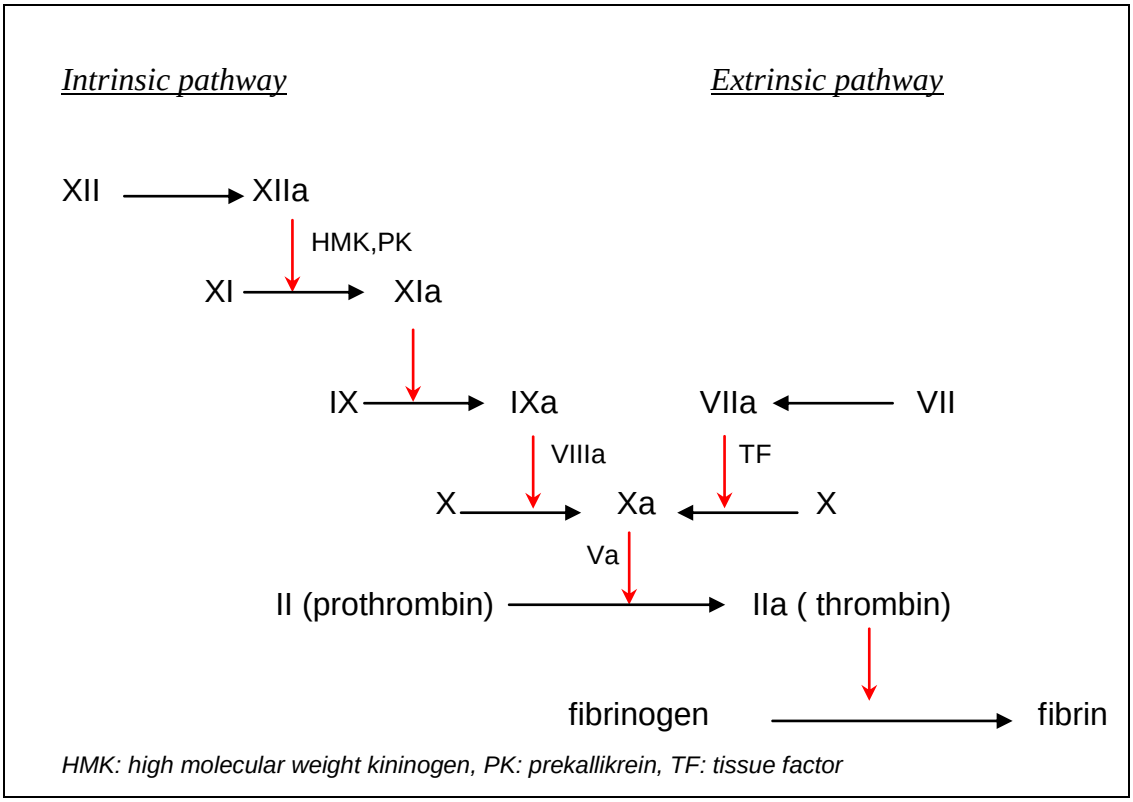
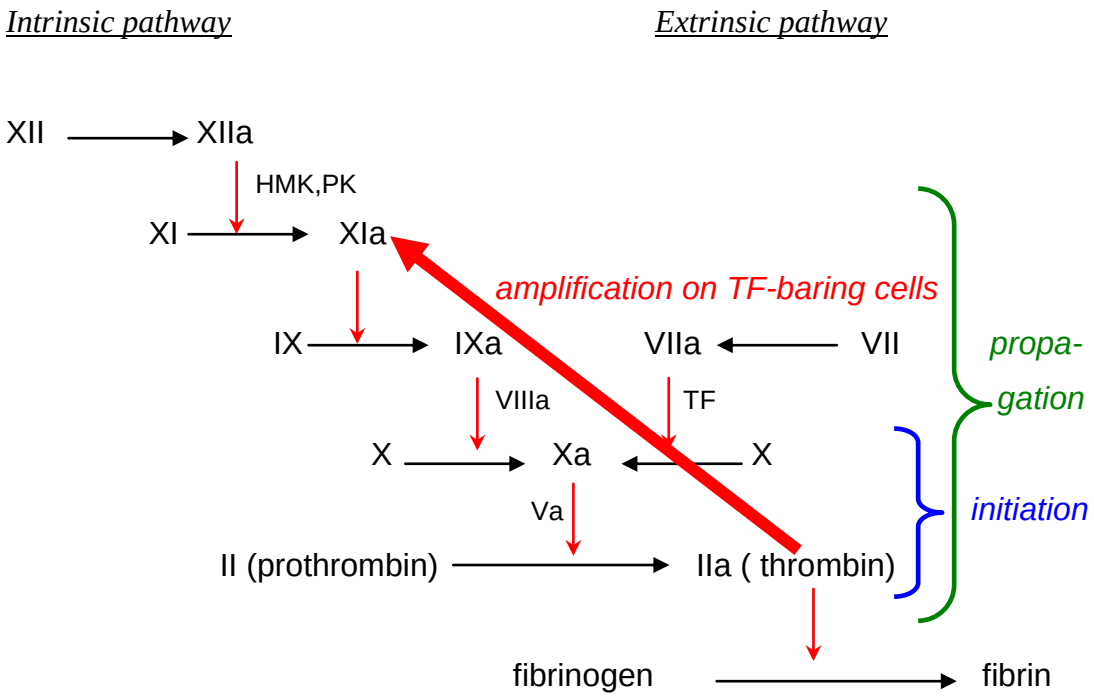


Figure 1. The coagulation waterfall/cascade

Indeed, in 1977 it was observed that the reaction product of tissue factor (TF) and factor VII activates not only factor X of the extrinsic pathway but also factor IX of the intrinsic (Østerud, Rapaport, 1977). In addition, thrombin could activate factor XI on activated platelets in the absence of factor XII, suggesting that factors XII, high molecular weight kininogen (HMK) and prekallikrein (PK) might be of no use for the activation of factor XI and therefore for haemostasis (Oliver et al, 1999). Those two findings led to a concept of haemostasis in which tissue factor (TF) is the primary physiologic activator (cell-based model).

The cell-based model of haemostasis suggests that different cell surfaces have very different properties regarding the coagulation process despite the similar membrane lipid composition. Indeed, the variety of cell features, including protein receptors, is responsible for localising the different components of the coagulation mechanism and, ultimately, for regulating it (Hoffman, Monroe, 2001). Hoffmann and Monroe argue that

haemostasis occurs in three overlapping phases, suggesting initiation, amplification and propagation. According to the cell-based model of coagulation, initiation occurs on the TF bearing cell where activated factor X (Xa) combines with activated factor V (Va) to activate small amounts of thrombin (initiation). This small amount of thrombin amplifies the procoagulant response by activating cofactors, factor XI and platelets (amplification). The large burst of thrombin is formed on the platelet surface (propagation) (Figure 2).



HMK: high molecular weight kininogen, PK: prekallikrein, TF: tissue factor

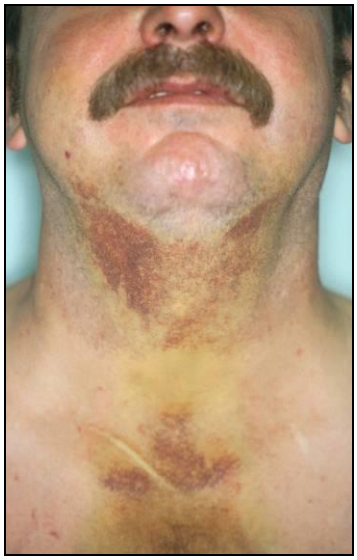
amplification takes place on TF-baring cells, propagation on platelet surface and initiation on TF-bearing cells

Figure 2. The coagulation waterfall/cascade adjusted to the cell-based model

1.1.1 Haemostasis and liver function

Haemostasis is closely related to liver function. Liver parenchymal cells synthesize most coagulation factors. Coagulation factors synthesized by the liver are fibrinogen, factor II, V, VII, VIII, IX, X, XI, XII, XIII, prekallikrein and high molecular weight kininogen. Liver malfunction also affects fibrinolytic system and platelet function as plasminogen and thrombopoietin are also synthesized by the liver (Wada et al, 2008).

Thus, the degree of liver malfunction determines the extent of haemostatic disorders. Acute or chronic hepatocellular diseases may cause decrease in the Vitamin K depending factors while the level of other parameters remain normal. Vitamin K dependent procoagulants and coagulants is factor II, VII, IX, X and protein C and S. A hepatic failure may result in factor deficiency of the entire spectrum and even in disseminated intravascular coagulation (DIC) (Mammen EF, 1992).



Picture 1. Extended haematoma after multiple teeth extractions in patient with severe hepatopathy

1.2 Bleeding disorders

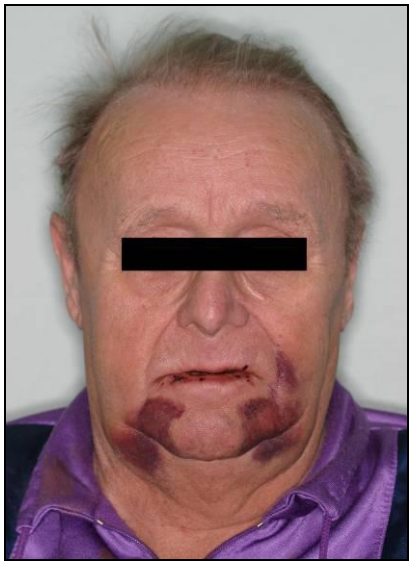
A variety of clinical symptoms, including easy bruising, skin bleeding, mucosal and musculoskeletal bleeding and excessive blood loss after trauma or surgery, can be associated with bleeding disorders, often underlying but undiagnosed. A detailed medical history and physical examination are important when treating a patient. A history of easy or spontaneous bruising, especially the size of more than 2-3 cm or in unusual sites, is a sign of alert. Epistaxis occurring more frequently with age rather than resolving or requiring medical intervention in the absence of a local anatomic abnormality implies an underlying bleeding disorder. In the absence of poor dental hygiene, spontaneous gingival bleeding is seen in primary haemostatic disorders, especially thrombocytopenia. Excessive bleeding at the time of dental extraction, surgery or trauma suggests inherited or acquired bleeding disorder. The patients often experience their first haemostatic challenge after the loss of deciduous teeth and dental extractions. The severity and duration of the bleeding after dental extraction as well as the postoperative measures that were taken should be assessed. The appropriate laboratory investigations will contribute to making the final diagnosis. In the tables that follow congenital and acquired bleeding disorders as well as causes of congenital and acquired thrombocytopenia are listed (White, Ryan, 2005, chap.3) (Tables 1,2).

Congenital bleeding disorders	Acquired bleeding disorders
Autosomal dominant disorders	As a result of anticoagulation therapy
Von Willebrand Disease	Hepatopathy
May-Hegglin anomaly	Disseminated intravascular coagulation
	Vitamin K deficiency
Autosomal recessive disorders	Acute or chronic Leukemia
Bernard-Soulier syndrome	
Glanzmann's thrombasthenia	
Gary platelet syndrome	
Deficiencies of factors V, VII, X, XI, XIII	
Type 3 von Willebrand Disease	
Sex linked recessive disorders	
Factor VIII deficiency	
Factor IX deficiency	
Wiskott-Aldrich syndrome	

Table 1. Congenital and acquired bleeding disorders (White, Ryan, 2005, chap.3)

Congenital thrombocytopenia	Acquired thrombocytopenia
Inherited thrombocytopenia	*Decreased production*
Bernard-Soulier syndrome	Bone marrow failure or infiltration
Wiskott-Aldrich syndrome	Megaloblastic Anaemia
May-Hegglin anomaly	
Von Willebrand´s disease	*Decreased lifespan*
Gray platelet syndrome	Idiopathic autoimmune thrombocytopenia
Alport syndrome	Drug induced thrombocytopenia
	Autoimmune disease, Infections, including HIV
	Post transfusion
	Microangiopathic Anaemia
	Hypersplenism

Table 2. Causes of congenital and acquired thrombocytopenia (White, Ryan, 2005, chap.3)



Picture 2. Excessive haematoma after multiple extractions in patient with thrombocyto-penia

1.3 Deficiency of coagulation factors

1.3.1 Haemophilias

Haemophilias are hereditary bleeding disorders associated with deficiency in a coagulation factor. Haemophilia A involves deficiency of factor VIII (antihaemophilic factor) while Haemophilia B involves deficiency of factor IX (Christmas factor). They are both X-linked recessive diseases recognized almost exclusively in male hemizygotes (Arun, Kessler, 2001). In all ethnic groups, 1 in 10 000 males are affected by haemophilia while the prevalence of Haemophilia B is 20 % that of Haemophilia A (Giangrade, 2005).

The degree of the disease's severity is defined by the levels of factor activity and characterizes the clinical spectrum of bleeding. Factors VIII and IX activity levels are expressed in units per millilitre (U per mL) or as a percentage of the activity determined in normal pooled plasma with 1 U per mL corresponding to 100% of the factor activity found in 1 mL of pooled normal plasma. Normal plasma activity levels range from 0,5 to 1,5 U per mL (50% to 100%). Severe haemophilia is defined by factor activity levels less than 0,01 U per mL (less than 1%), moderately severe haemophilia by 0,02 to 0,05 U per mL (2%-5%) and mild haemophilia by greater than 0,05 U per mL (>5%) (Giangrande, 2005).

Severe haemophilia is characterized by recurrent and intense haemorrhage, occurring after a surgical operation but also after a minor trauma or even spontaneously. In childhood, lip or tongue biting as well as the loss of deciduous teeth are accompanied with intense oral bleeding. Large haematomas may also follow deep intramuscular injections or simple vaccination. In case of moderate haemophilia, bleeding is associated with surgical or minor traumas. Mild haemophilia presents significant bleeding after major trauma or surgery. These patients are more often for the first time diagnosed before elective surgery when routine screening tests reveal prolonged activated partial thromboplastin time (Arun, Kessler, 2001).

Recombinant factor VIII is the therapy of choice for haemophilia A and recombinant factor IX for Haemophilia B (Keeling et al, 2008).

Other therapeutic choices are antifibrinolytic agents, like tranexamic acid and desmopressin (DDACVP). Tranexamic acid inhibits fibrinolysis by reversibly binding both circulating and fibrin-bound plasminogen. It is especially effective in mucosal bleeding where fibrinolytic activity is specially active. Ways of administration are orally, intravenously or as a mouth wash. Its combination with desmopressin provides prophylaxis for dental surgery (Keeling et al, 2008). Desmopressin (1-deamino-8-D-arginine vasopressin, also known as DDAVP) can be the therapy of choice in cases of mild haemophilia A as it boosts the plasma levels of factor VIII after administration (Meili, Brand 2006). Typically FVIII levels will increase 3-5 times above basal levels. It may be administrated as a slow intravenous infusion or as a subcutaneous injection (Keeling at al, 2008). When referring to antifibrinolytic therapy, it should be taken into consideration that factor IX concentrates fall into two classes, pure coagulation FIX products and prothrombin complex concentrates (PCCs). Purified FIX products are largely free of the risk of developing thrombosis or disseminated intravascular coagulation (DIC), which may occur with large doses of intermediate purity PCCs. Thus, antifibrinolytic agents either as primary or adjunctive therapy, are not recommended for treatment of patients with factor IX deficiency already receiving large doses of PCC (World Federation of Hemophilia, 2005).

1.3.2. Von Willebrand disease

Von Willebrand factor (vWF) is a plasma protein that mediates platelet haemostatic function and stabilizes blood coagulation factor VIII. Von Willebrand disease (vWD) is caused by deficiency or dysfunction of vWF (Nichols et al, 2008). Therefore, quantitatively or qualitatively abnormal von Willebrand factor can lead to bleeding by impairing platelet adhesion or by reducing the concentration of FVIII.

The prevalence of the disease ranges from 0,0023-0,1% depending on the case definition that is used (Nichols et al, 2008).

The first patient reported was a five-year-old girl who was examined by Dr. Eric von Willebrand at the Deaconess Hospital of Helsinki in 1924. He first described this disorder as ‘’hereditary pseudohaemophilia’’ (Von Willebrand, 1999).

VWD is classified into three major categories: partial quantitative deficiency (type 1), qualitative deficiency (type 2) and total deficiency (type 3). Type 2 vWD is divided further into four variants (2A, 2B, 2M and 2N) on the basis of details of the phenotype.

Type 1 is inherited as an autosomal dominant trait, its prevalence reaches 1% and the bleeding tendency is mild to moderate.

Type 2A and 2M are inherited as an autosomal dominant or recessive trait while their prevalence is uncommon and their bleeding severity varies leaning to moderate.

Type 2B is likewise uncommon with variable, mostly moderate bleeding tendency but is inherited only as an autosomal dominant trait.

Type 2N is inherited as autosomal recessive trait and presents similarly uncommon prevalence and variable, mostly moderate bleeding propensity.

Type 3 is the severe one with a high bleeding propensity although rare (1: 250 0000- 1: 1 000 000). It is inherited as an autosomal recessive trait (Federici, 2008).

Common bleeding symptoms of patients with von Willebrand disease are epistaxis, menorrhagia, ecchymoses, bleeding after dental extractions or operations, gingival bleeding, bleeding from minor cuts or abrasions, gastrointestinal bleeding, heamarthrosis and postoperative bleeding (Nichols et al, 2008).

Patients with the above mentioned clinical symptoms but with a negative past personal history and family history should be investigated for the presence of acquired von Willebrand disease (AvWD). AvWD may occur spontaneously associated with other diseases, such as monoclonal gammopathies, other plasma cell dyscrasias, lymphoproliferative diseases, myeloproliferative disorders (e.g. essential thrombocythemia), autoimmune disorders, valvular and congenital heart disease, certain tumours and hypothyroidism (Nichols et al, 2008).

Treating vWD aims at correcting the dual defects of haemostasis; abnormal platelet adhesion as a result of low or defective vW factor and abnormal intrinsic coagulation as a

result of low factor VIII (Federici, 2008). This can be done using three therapeutic strategies which are not mutually exclusive and patients can receive one or all of them. The first approach uses desmopressin in order to stimulate endothelial cells to release endogenous vW factor. The second replaces vW factor by using human plasma-derived concentrates. The third approach aims at promoting haemostasis and wound healing without substantially altering the plasma concentration of vW factor. In case of dental surgery tranexamic acid as well as topical thrombin, collagen or fibrin sealant is used at the site of surgery (Nichols et al, 2008).

1.3.3 Other factor deficiencies

Factor XI deficiency is mostly diagnosed in Ashkenazi Jews but is also observed in other ethnic groups. Deficiency of factor XI is often described as Haemophilia C but the bleeding phenotype is much more variable than that of the haemophilias A and B. It is often the case that patients with severe factor XI deficiency have no excessive bleeding and on the contrary, patients with moderate, below the normal levels, factor activity suffer from extreme postoperative bleeding (Gomez et al, 2008). When there is a clear history of abnormal bleeding, FXI concentrate or fresh frozen plasma is the choice of treatment. In case of minor procedures and dental extractions tranexamic acid mouth-wash alone may be adequate (Keeling et al, 2008).

Factor VII deficiency is the most frequent among rare congenital bleeding disorders (1: 500 000). Factor VII deficiency is the only congenital bleeding disorder characterized by isolated prolonged prothrombin time. Thus, its laboratory diagnosis is simple. Clinical manifestations vary from severe life-threatening haemorrhages to miscellaneous minor bleeding (Lapecorella, Mariani 2008). Recombinant VIIa is the treatment of choice (Keeling et al, 2008).

Factor V is the plasma cofactor for the prothrombinase complex. The activation of prothrombin to thrombin is regulated by this complex. The phenotype of patients with factor V deficiency seems to be less severe than the one of patients with haemophilia A or B. Thus, the risk of bleeding has limited correlation with levels of factor V (Huang,

Koerper, 2008). Treatment of bleeding episodes require fresh frozen plasma because no factor V-specific concentrate is available (Keeling et al, 2008). In cases of less severe mucosal bleeding, the use of antifibrinolytic agents alone may be sufficient (Huang, Koerper, 2008).

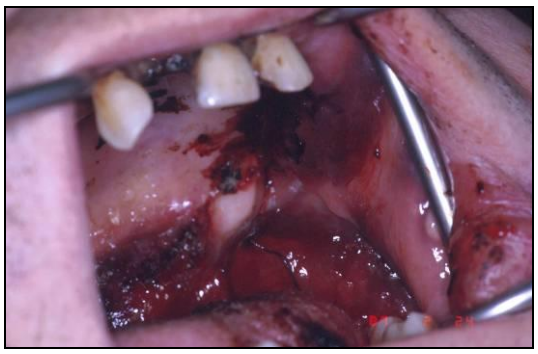
Combined factor V and factor VIII deficiency is extremely rare (1: 1 000 000) and is associated with a mild to moderate bleeding tendency. Treatment requires a source of both factors V and VIII (Spreafico, Peyvandi, 2008).

Factor XIII deficiency is a rare bleeding disorder with a high degree of heterogeneity in molecular basis. Thus it presents different clinical manifestations, severe bleeding, umbilical bleeding during the neonatal period, delayed soft tissue bruising, mucosal bleeding and life-threatening intracranial haemorrhages. Poor wound healing and recurrent spontaneous abortions have been also associated with factor XIII deficiency (Hsieh, Nugent, 2008). The treatment of choice is factor XIII concentrate (Keeling et al, 2008).

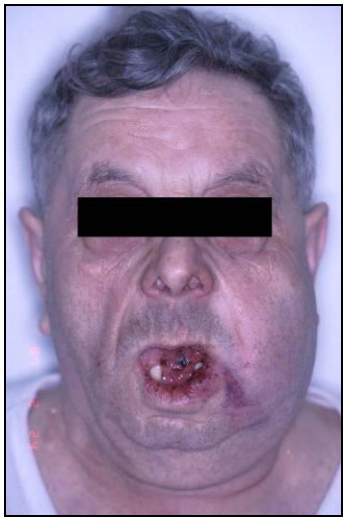
Fibrinogen deficiency can manifest as afibrinogemia and hypofibrinogemia (quantitative defects) or dysfibrinogemia (qualitative defects). The most severe form is afibrinogemia with a prevalence of 1 in 1 000 000. The phenotype of the patient ranges from no clinical manifestations to extreme life-threatening bleeds (Acharya, Dimichele, 2008). Fibrinogen concentrate is the treatment of choice (Keeling et al, 2008).

1.4 Drugs that influence blood circulation

In case of trauma, the mechanism of haemostasis and clotting formation is of crucial importance for the healing of the patient. The formation of an unwanted thrombus that will circulate as an embolous and jeopardise the function of many crucial organs, follows almost the same mechanism. Only in this case the stimulus is a malfunction of the blood circulation. An embolous can block the blood vessels and deprive the tissues of oxygen and nutrients leading to their failure and necrosis. Modern medicine provides a number of medicines that interfere with blood circulation and coagulation in order to prevent or deal with such a malfunction. However, such a therapy is inevitably accompanied by a high risk of unwanted bleeding after a surgery or trauma.



Picture 3. Postoperative bleeding after extracting upper left molars in patient receiving anticoagulation therapy



Picture 4. Extraoral aspect of the same patient

1.4.1 Parenteral anticoagulants

The approved parenteral anticoagulants include indirect and direct. Indirect anticoagulants exert their anticoagulant activity by activating antithrombin. These are unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux and danaparoid. On the other hand, direct anticoagulants target thrombin. They include recombinant hirudins, bivalirudin and argatroban (Hirsh et al, 2008).

Heparin is not absorbed through gastrointestinal mucosa. It must be given by continuous intravenous infusion (immediate onset of action) or subcutaneous injection (onset of action after 1-2 hours) (Majerus, Tollefsen, 2006, chap.54).

One third of the administrated heparin binds to antithrombin and this fraction inactivates a number of coagulation enzymes, including thrombin factor IIa and factors Xa, IXa, XIa and XIIa (shown with pink in Figure 3). Thrombin and factor Xa are most sensitive to the effect of heparin/AT-III (Hirsh, Warketin et al, 2001).

As heparin has rapid onset of action, especially when given intravenously, is used to initiate treatment of venous thrombosis and pulmonary embolism. It is also used to prevent mural thrombosis after myocardial infarction and as treatment for patients with unstable angina and acute myocardial infarction (Hirsh et al, 2001).

The biological limitations of heparin include heparin-induced thrombocytopenia and osteopenia. Osteopenia is caused because osteoclasts are activated by factors that osteoblasts release as heparin binds to them (Hirsh et al, 2001).

Low molecular weight heparin has the advantage of a more predictable pharmacokinetic profile. This allows the use of weight adjusted subcutaneous administrations with no need for continuously laboratory monitoring. It doesn't cross the placenta and hasn't been related to foetal teratogenesis. In comparison to unfractionated heparin the incidence of heparin-induced thrombocytopenia, as well as the possibility of bleeding or osteopenia, is lower (Majerus, Tollefsen, 2006, chap.54).

active ingredient	brand name	manufacturer
LMWH		
Enoxaparin	Clexane	Sanofi-Aventis
Reviparin	Clivarin	Abbott
Dalteparin	Fragmin	Pharmacia
Nadroparin	Fraxiparin	GlaxoSmithKline
	Fraxodi	GlaxoSmithKline
Tinzaparin	Innohep	LEO
Certoparin	Mono-Embolex	Novartis
Fondaparinux	Arixtra	GlaxoSmithKline
Danaparoid	Orgaran	Essex Pharma
Desirudin	Revasc	Canyon Pharma
Bivalidurin	Angiox	The Medicines Company
Argatroban	Argatra	Mitsubishi Ph. Dt.

Table 3. Parenteral anticoagulants commercially available in Germany

1.4.2 Oral anticoagulants

The oral anticoagulants have been synthesized as derivatives of 4-hydroxycoumarin and of the related compound, indan-1,3-dione. Warfarin is widely used in United States of America while in Europe phenprocoumon is the drug of choice. They are antagonists of Vitamin K. Therapeutic doses aim at decreasing the total amount of each vitamin K-dependent coagulation factor synthesized by the liver and diminishing their biological activity. The Vitamin K-dependent factors are II, VII, IX and X (shown in green colour in Figure 3). Some coagulation factors have a long half-life i.e. factor II has 50 hours half-life. This is why the full antithrombotic effect is achieved after several days. However, because of the more rapid reduction of factors with a short half-life, i.e. factor VII has 6 hours half-life, PT may be prolonged soon after administration (Majerus, Tollef-

sen, 2006, chap. 54). Related Vitamin K antagonists also impair the synthesis of anticoagulant factors, protein C and S but this is outweighed by the effect of depressing the above mentioned coagulation factors (Zivellin et al, 1993).

Oral anticoagulants are effective for primary and secondary prevention of venous thromboembolism or pulmonary embolism, for prevention of systemic embolism in patients with atrial fibrillation or prosthetic heart valves, for prevention of acute myocardial infarction in patients with peripheral arterial disease and for prevention of stroke, recurrent infarction or death in patients who survived an acute myocardial infarction (Hirsh et al, 2003).

The safety and effectiveness of anticoagulant therapy critically depends on maintaining the INR within the therapeutic range. Thus, once the INR becomes stable, regular monitoring is necessary every 4 weeks (Hirsch et al, 2003).

It is of great importance that a list of substances can interact with oral anticoagulants increasing or decreasing their effect. More specifically, antiepileptic drugs, antifungal agents, hormones and hormones antagonists, retinoids and high intake of vitamin K can possibly decrease the anticoagulant effect. On the other hand, large amounts of alcohol especially when combined with a liver disease, aspirin and all non-steroidal anti-inflammatory drugs, antibacterial agents, hormone antagonists, lipid lowering drugs, ulcer healing drugs and uricosuric agents can possibly increase the anticoagulant effect (Johnston, 1999, chap. 10). Apart from drugs and agents, a series of food and herbal supplements can also interact with oral anticoagulants. Fish oil, mango, grapefruit, avocado, soy milk and many herbs are included in the list, each one with a different level of potentiation (Ansel et al, 2008).

Contraindication for a therapy with oral anticoagulants are bleeding disorders such as thrombocytopenia, pregnancy, history of a recent surgery to the CNS or eye and any active bleeding site. Severe, uncontrolled hypertension, proliferative retinopathy, recurrent falls, poor compliance and alcoholism are also relative contraindications (Johnston, 1999, chap. 10).

active ingredient	brand name	manufacturer
Phenprocoumon	Falithrom	Hexal
	Marcumar	MEDA Pharma
	Marcuphen-CT	CT Arzneimittel
	Phenpro AbZ	AbZ- Pharma
	Phenprogamma	Wörwag
	Phenpro-ratiopharm	Ratiopharm
Warfarin-natrium	Coumadin	Bristol Myers Squibb

Table 4. Oral anticoagulants commercially available in Germany

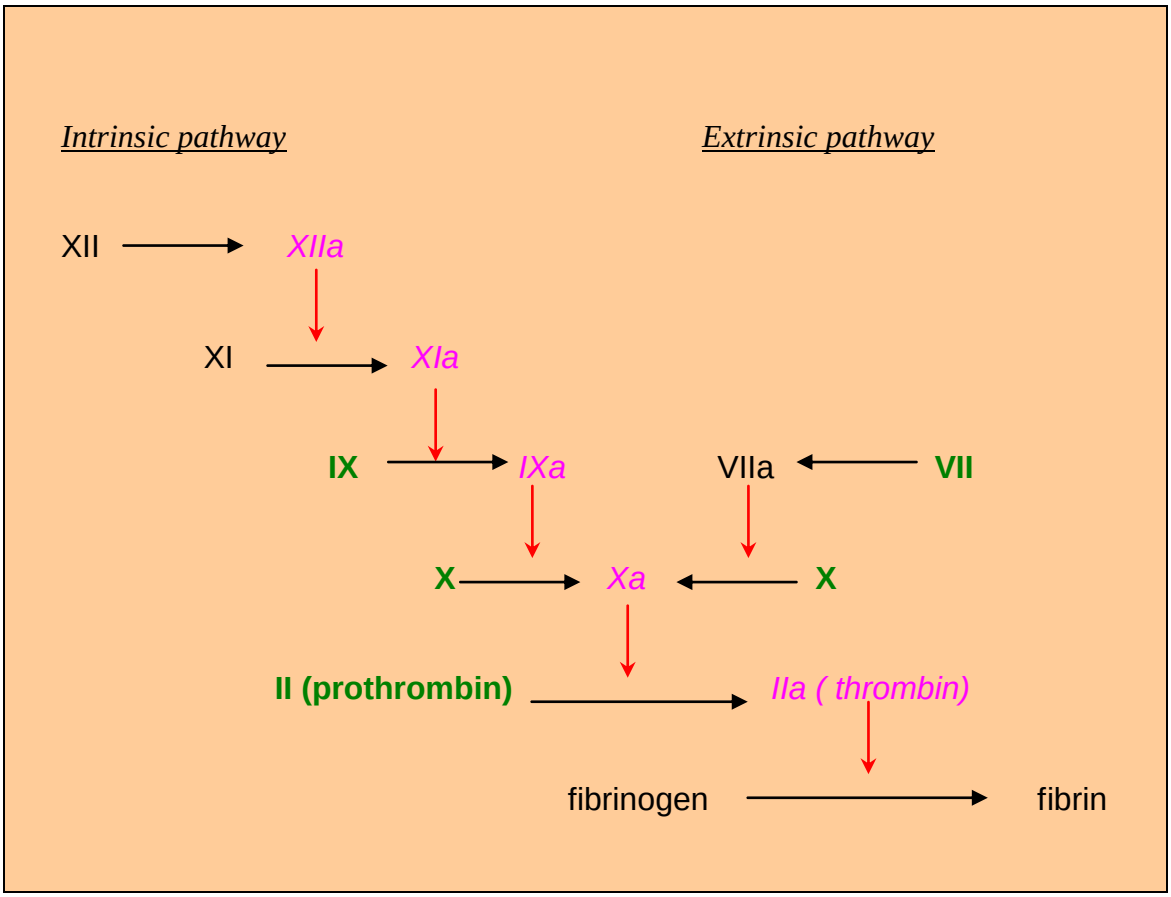


Figure 3. Coagulation factors inactivated by heparin (shown in pink) and oral anticoagulants (shown in green)

1.4.3 Antiplatelet drugs

Approximately 10^{11} platelets are produced every day, a level that can increase up to 10-fold at times of increased need. Platelets provide the initial haemostatic plug at sites of vascular injury. However, they can also participate in pathological thrombosis leading to stroke, myocardial infarction and peripheral vascular thrombosis (Majerus, Tollefsen, 2006, chap.54).

Antiplatelet drugs include aspirin, dipyridamole, thienopyridines (ticlodipine and clopidogrel) and integrin aIIbß3 receptor antagonists (Patrono et al, 2008).

1.4.3.1 Aspirin

Cyclooxygenase enzyme (COX) is needed for prostaglandin and thromboxane synthesis. Aspirin irreversibly inactivates the COX activity of prostaglandin H-synthase-1 and -2. Low-dose aspirin selectively inhibits COX-1, aiming at platelet inhibition, and high-dose aspirin inhibits both COX-1 and COX-2, aiming also at inflammatory cells (Patrono et al, 2008).

The plasma concentration of aspirin reaches its peak 30 to 40 min after ingestion. Inhibition of platelets is evident after 1 hour. The plasma concentration of aspirin has a half-life of 15 to 20 min. However, as aspirin irreversibly inactivates COX-1, the platelet inhibitory effect lasts 8 to 10 days (platelets life span) (Patrono et al, 2008).

Aspirin is used as treatment or prophylaxis in cases of stable or unstable angina, acute myocardial infarction or acute ischemic stroke, transient ischemic attack, severe carotid artery stenosis, men at high cardiovascular risk and polycythemia vera (Patrono et al, 2008).

When used for the platelet-inhibition effect, the most appropriate strategy is the lowest effective dose (50 to 100 mg/d for long term treatment) that maximizes its efficacy and minimizes its toxicity (Patrono et al, 2005).

Aspirin can cause generalised bleeding abnormality when given to patients with underlying bleeding disorder or receiving an anticoagulant therapy. Aspirin can induce gastrointestinal toxicity, especially when gastric mucosal erosions related to use of non steroid anti-inflammatory drugs and Helicobacter pylori infection are underlying. Even

when administrated in low doses it can cause serious gastrointestinal bleeding and enteric-coated or buffered form offer no secure alternative. Aspirin use can also result in major extracranial and intracranial haemorrhage, although the overall risk is difficult to assess (Patrono et al, 2008).

1.4.3.2 Dipyridamole

Dipyridamole is a vasodilator and has little or no benefit as antithrombotic drug (Majerus, Tollefsen, 2006, chap.54). The fixed combination of modified-release dipyridamole and low-dose aspirin has been approved for stroke prevention. It is also used in combination with warfarin to provide primary prophylaxis to patients with a recent history of prosthetic heart valve surgery (Patrono et al, 2008).

1.4.3.3.1 Ticlodipine

Ticlodipine has been associated with hypercholesterolemia and neutropenia as well as with thrombocytopenia, aplastic anaemia and thrombotic thrombocytopenic purpura and therefore its therapeutic use is eliminated in patients with cerebral ischemia when aspirin has failed, cannot be tolerated or is contraindicated (Patrono et al, 2008).

1.4.3.3.2 Clopidogrel

Clopidogrel is a prodrug, inactive in vitro and is metabolically transformed by the liver into a short-lived active platelet inhibitor (Patrono et al, 2008).

The approved indications for Clopidogrel are to reduce the rate of stroke, myocardial infarction and death in patients with recent myocardial infarction or stroke, established peripheral arterial disease or acute coronary syndrome (Majerus, Tollefsen, 2006, chap. 54). Simultaneous treatment with aspirin and Clopidogrel represents the standard care for patients with acute coronary syndrome and following coronary stenting. The combination of these two drugs is also used for the prevention of arterial thrombosis in many other vascular interventions (e.g. carotid or aortic stenting) (Darius, 2010).

On repeated daily administration of low doses, the active metabolite of Clopidogrel has a pharmacodynamic pattern quite similar to that of aspirin in causing cumulative inhibi-

tion of platelet function. Similar to aspirin, when Clopidogrel is administrated platelet function returns to normal 7 days after the last dose. Both the cumulative nature of the inhibitory effects and the slow rate of recovery of platelet function are consistent with acetylsalicylic acid and the active metabolite of Clopidogrel. Thus, they are causing a permanent defect in a platelet protein that cannot be repaired during the 24-hours doses interval and can only be replaced as a function turnover. This explains the effectiveness of the once-daily dose of both drugs (Patrono et al, 2008).

1.4.3.4 Integrin inhibitors

Platelet-integrin aIIbß3 is a dimeric glycoprotein receptor for fibrinogen and von Willebrand factor. By anchoring platelets to foreign surfaces and to each other, it enhances aggregation. Inhibition of this receptor blocks platelet aggregation. Three inhibitors of this receptor have been approved; abciximab, eptifibatide and tirofiban (Majerus, Tollefsen, 2006, chap.54).

active ingredient	brand name	manufacturer
Acetylsalicylic acid	Aspirin	Bayer Vital
	ASS	Hexal, AbZ, ALIUD Pharma, CT-Arzneimittel, ratiopharm, Wörwag, Sandoz, STADApharm, TAD
	Acesal	Nycomed Deutschland
	Godamed	Pfleger
	HerzASS	Ratiopharm
Dipyridamole (+ASS)	Aggrenox	Böhringer Ingelheim
Ticlodipin	Ticlodipin	ALIUD Pharma, CT Arzneimittel, HEXAL, neuraxpharm, ratiopharm Sandoz, STADApharm
	Tiklyd	Sanofi-Aventis
Clopidogrel	Clopidogrel	STADApharm, 1 A Pharma,, AbZ, ALIUD Pharma, CT Arzneimittel, Betapharm, HEXAL, ratiopharm, TAD
	Clopidocor	Sandoz
	Clopigamma	Wörwag
	Iscover	Bristol Myers Squibb
	Plavix	Sanofi-Aventis
Abciximab	ReoPro	Lilly
Eptifibatide	Integrillin	GlaxoSmithKline
Tirofiban	Aggrastat	Iroko/Chiesi

Table 5. Antiplatelet drugs commercially available in Germany

1.5 Laboratory assessment of a possible bleeding patient

The initial laboratory screening tests include complete blood count, prothrombin time, activated partial prothrombin time and thrombin time.

Complete blood count reveals the platelet count. A platelet count less that 150 x 10^9 /L suggests a thrombocytopenic disorder which must be further investigated.

Prothrombin time (PT) evaluates the overall efficiency of the clotting factors of extrinsic and common pathway. An inherited or acquired deficiency of factors V, VII, X, prothrombin and fibrinogen can prolong PT, although the relationship is not linear. The development of an inhibitor against these factors or against a component of the PT reaction can also prolong PT. The test measures the clotting time of plasma after adding tissue factor and calcium to hypocalcemic plasma. Normal rates are between 12 and 15 seconds. However, every laboratory, depending on its methods and reagents, determines its own range of reference. The international normalised ratio (INR) is developed to reduce laboratory variability and to simplify monitoring of anticoagulation with warfarin. It is calculated as a ratio of the patient's PT to the geometric mean of normal control subjects.

Activated partial prothrombin time (aPTT) evaluates the overall efficiency of the clotting factors of the intrinsic and common pathway. Likewise, an inherited or acquired deficiency of factors V, VIII, IX, X, XI, XII, prothrombin, fibrinogen, kallikrein, high molecular weight kinogen, as long as the development of an inhibitor against these factors or against a component of the aPPT reaction can prolong aPPT. The test measures the clotting time of plasma following the activation of contact factors without added tissue factor. Again in this case, the laboratory determines its own range.

As discussed in chapter 1.1, the use of these screening tests to predict clinical bleeding is to be questioned. The commonly used clinical coagulation tests do not really reflect the complexity of haemostasis in vivo as the extrinsic and intrinsic pathways are actually interdependent in vivo. Any laboratory test result is not enough on its own and skilled interpretation and clinical correlation as well as comprehension of the coagula-

tion mechanism are required in order to evaluate the true risk of bleeding (Romney, Glick 2009).

2 Aim of the study

The aim of this study was to investigate the possible relation between postoperative bleeding and age, gender, medical history, medication, type of operation, place of operation, preoperative, intraoperative and postoperative measures against bleeding after minor oral surgeries. This was accomplished by collecting data on all patients who were treated for postoperative bleeding in Oral and Maxillofacial Department of Regensburg Hospital from 2004 until 2009.

3 Materials and Methods

3.1 Patients

The patients selected for this study were obtained through IS-H med SAP program. This is a program module from GSD-Siemens used for healthcare facilities as a complete hospital information system. According to the DRG (Diagnosis-related group) classification, patients classified under one of the following DRG codes were retrieved: T81.0 (bleeding and haematoma as a complication of a surgery), 5-249.0 (other operations and measures in tooth region: arrest of bleeding), 5-279.0 (other operations and measures in oral and maxillofacial region: arrest of bleeding). The time period examined was from 2004 until 2009. The total number of patients retrieved was 134.

All patients classified as above, had undergone a minor surgical procedure in the oral region and then suffered from postoperative bleeding. In the majority of cases, the minor surgical procedure is a single or multiple tooth extraction at the upper or lower jaw. In few cases it can be root amputation, sinus lift augmentation, root scaling or preprosthetic operation. The operation was conducted either ambulant or inpatient in the Oral and Maxillofacial Surgery department of Regensburg University Hospital, or ambulant in a dental office in the region of Regensburg (alio loco). The patients who received ambulant treatment (either in our hospital or in a dental office) and suffered from postoperative bleeding appeared in the emergency department of Regensburg hospital and were treated accordingly.

Treatment of the patient with postoperative bleeding

Once a patient presented himself in the emergency department of our hospital with postoperative bleeding, the first to be checked was the patient's history; special attention was given to the medication list. The history of the operation was also important. The patient was asked about the time and place of operation, the time after the operation until the bleeding occurred and measures taken until then. In cases of patients operated in our hospital, the above information was already known and documented.

In case of a light bleeding, the therapy of choice was the application of a haemostatic agent and sutures, if there were no sutures made. The haemostatic agents included human fibrinogen/human thrombin, collagen and oxidised regenerated cellulose. In case of bleeding that derived from bone, bone wax could also be used. The sutures used were normally absorbable because this allowed multiple, overlapping suturing. In case of arterial bleeding, an arrest of bleeding by using surgical diathermy was applied.

In case that sutures were already done, the surgeon had to decide if over sutures were enough or if there was a need of a flap formation and approximation of wound edges in order to achieve a better haemostasis. In case that a flap had been already made, there was the possibility of removing the sutures, inspecting the wound, adding additional haemostatic agents and re-approximating the wound edges (revision).

If the bleeding could not be brought under control after taking local measures, an inpatient treatment would follow. In this case, the patient was admitted for constant observation of the level of bleeding and monitoring of the blood values. As a measure against bleeding, patients under anticoagulation therapy often received substitution with low molecular weight heparin.

Often the surgeon decided the manufacture and use of a splint. After taking an imprint of the teeth using alginate, a plaster was prepared and thereby a splint was produced. It aimed at pressing the extraction wound in order to stop the bleeding and protecting it from the mechanical load when eating.

Measures taken preoperatively in patients operated in Oral and Maxillofacial Surgery department of Regensburgs University hospital

When the operation took place in the Oral and Maxillofacial Surgery department of Regensburg hospital, many of the above measures were taken in advance in order to prevent a possible bleeding. More specifically, for patients receiving anticoagulation therapy or suffering from a bleeding disorder, special measures were taken before and after the surgery. Antiplatelet drugs, after contacting the internist of the patient and with his permission, were discontinued one week before the surgery. Oral anticoagulants, again after consulting the internist, were substituted by low molecular weight heparin subcutaneous injections or discontinued for one week before the surgery. Haemophilic and

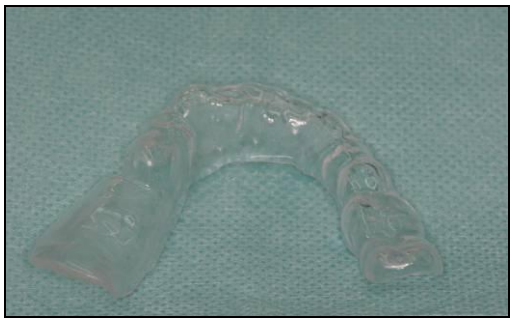
von Willebrand patients received before and after the surgery, after consulting the haematologist and according to factor screening, recombinant factor supplements or antifibrinolytic agents.

As a standard measure for every patient with a higher risk of postoperative bleeding, a splint was prepared before the operation in the laboratory, as described above. More specifically, after taking an imprint of the teeth using alginate, the plaster was prepared and then the teeth that were about to be extracted were removed from the plaster, allowing for the splint to be manufactured.

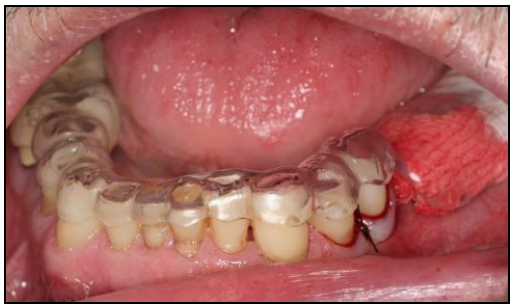
A standardised measure when dealing with high risk patients was to keep them inpatient after the operation. This meant that patients stayed postoperatively under inpatient monitoring and could only be released when they were 24 hours free of bleeding. The need of inpatient treatment depended on various parameters. Patients taking phenprocoumon or other anticoagulants, discontinued, substituted or current were treated inpatient. Alike were treated patients with coagulation disorders and factor deficiencies. Patients with severe hepatopathy were treated inpatient, according to coagulation and blood values. When the patient was under therapy with salicylic acid that could be discontinued, in case of single tooth extractions and minor surgeries, an ambulant treatment was possible. If there were more teeth to be extracted, or the discontinuing of salicylic acid was not allowed, an inpatient treatment was necessary. In case of a double antiplatelet therapy an inpatient treatment was necessary.

Patients receiving a splint after the operation were advised to wear it for four days constantly. After four days the wound was inspected and if there was no bleeding, the splint could be removed and used only when eating to prevent wound injuries. The splint could be totally removed after the suture removal, if the wound healing was complete.

Alike, patients that received a splint after the bleeding had to wear it constantly until the removal of the sutures.



Picture 5. A splint ready to be placed after tooth extractions in left mandible



Picture 6. The splint in intraoral position

A synopsis of the preoperative, intraoperative and measures taken after the bleeding is as followed:

Preoperative measures

1. Detailed medical history, medication list, personal or family history of bleeding
2. Contact with internist if anticoagulation can be discontinued/substituted
3. Imprint in order to manufacture a splint
4. Arrangements for an inpatient operation when:
    a. Coagulation disorders in medical history
    b. Phenprocoumon to be discontinued/substituted/continued
    c. Salicylic acid and other antiplatelets not allowed to be discontinued
    d. Double antiplatelet therapy
    e. Severe hepatopathy affecting blood values and clotting factors

Intraoperative measures

1. Tooth extraction as atraumatic as possible

2. Use of haemostatic agents (collagen tamponade, human fibrinogen/thrombin, oxidised regenerated cellulose, tranexamic acid, bone wax) or diathermy

3. Approximation of wound edges or multiple sutures

4. Placement of the splint. If needed, underlaid with oxidised regenerated cellulose baptised in tranexamic acid

In case of bleeding, postoperative measures

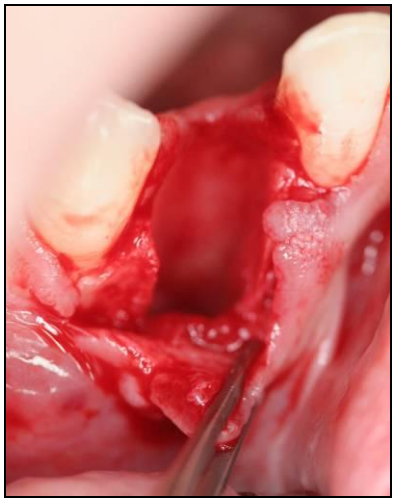
1. Local measures (haemostatic agents, over sutures)

    a. Discharge if bleeding is minimal and stops,

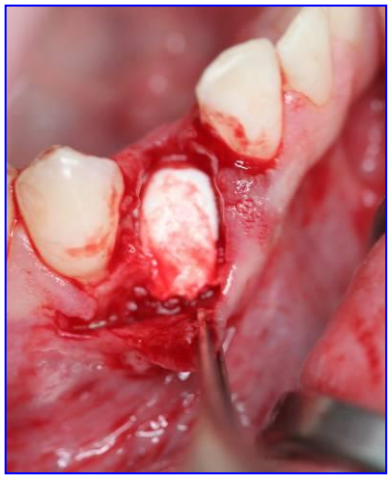
2. Approximation of wound edges, splint manufacture and inpatient admittance
3. Substitution of phenprocoumon with low molecular weight heparin injections if taken currently

4. Administration of antifibrinolytic agents or factor supplements according to medical history

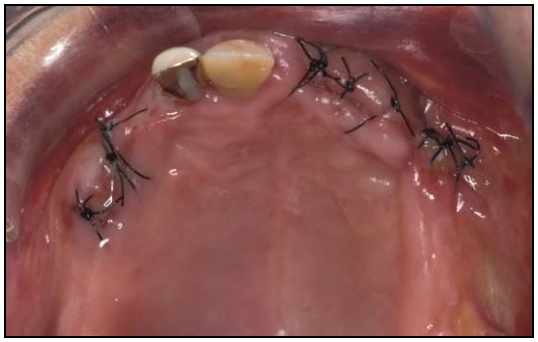
5. Constant monitoring of blood values; transfusion if necessary



Picture 7. Post-extraction alveolus after removal of tooth 43 in patient receiving anticoagulation therapy



Picture 8. Post-extraction alveolus of picture 7 filled with collagen sponge



Picture 9. Approximation of wound edges after multiple extractions in maxilla

An analysis of the data reveals differences between the procedure that was followed when operating a patient in alio loco and in the Oral and Maxillofacial Surgery Department of Regensburg University hospital. Important parameters are the discontinuation of antiplatelet therapy and the discontinuation or substitution with low molecular weight heparin of anticoagulation therapy. The use of haemostyptic measures (splint, haemostyptic agents) is extremely limited in the dental offices. Moreover, in dental offices, concerning the wound care after the operation, simple sutures are used in few cases while the approximation of the wound edges and a primary healing comes almost never in question.

3.2 Statistical methods

The statistical analysis was carried out using the programme Medas (Grund EDV-Systeme, Margetshöchheim, Germany) and the significance tests were conducted using U-test by Mann and Whitney, chi-square test, chi-square test by Fisher and Yates, Kruska- Wallis one-way analysis of variance and exact chi-quadrat test by Mehta and Patel.

More specifically:

In order to describe the relationship between two classified variables, the chi-square test of maximum likelihood was generally calculated. When the expected values were low, the exact chi-square test by Fisher and Yates was computed in 4 field tables and in larger tables the exact chi-square test by Mehta and Patel.

The U-test by Mann and Whitney was used to compare measured values between two groups when a Gaussian distribution of measured values could not be attained. For a limited number of patients, under 20, the exact U-test was used.

The Kruskal-Wallis one-way analysis of variance replaced the U-test when three or more groups were compared.

In order to compare the test results quantitatively, p-values were calculated. A p value below 0.05 was considered significant and the result was interpreted as significant. The p-values were indicated with star-symbols:

$p < 0.05$ with *, $p < 0.01$ with ** and $p < 0.001$ ***.

4 Results

4.1 Demographic data

The 134 patients of this survey were 16 to 90 years old, with a mean age of 59.9 ± 17.1 years. The median was 65 years with a 68%-CI from 40.3 to 75 years. 71 patients (53%) were male and 63 patients (47%) were female (Figure 4).

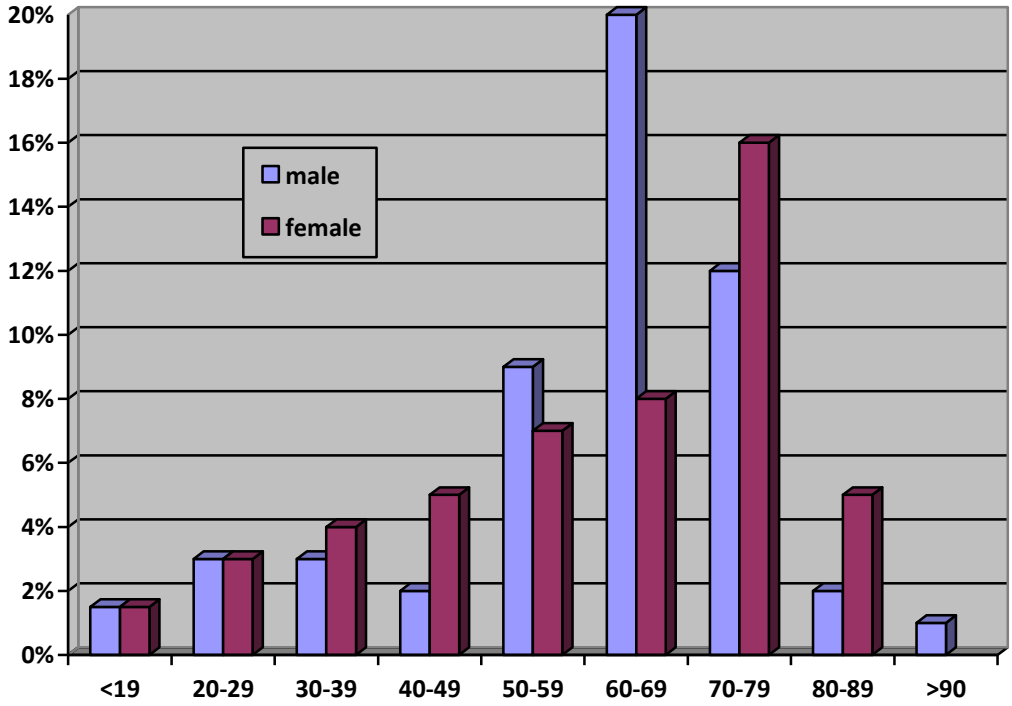


Figure 4. Age and gender. The columns represent the percentage of patients according to age group and gender (n=134)

4.2 Medical history

The vast majority of the patients suffered from hypertension and heart diseases. 14 patients (10,3%) suffered from coagulation disorders (including 4 haemophilic patients) while 8 patients (5,9%) suffered from liver failure. 10 patients (7,4%) had in their medical history a stent operation, 5 patients (3,7%) a bypass operation, 17 patients (12,6%) a stroke, 10 patients (7,4%) a myocardial infarction, 9 patients (6,7%) a heart pacemaker, 11 patients (8,2%) a thrombosis and 2 patients (1,5%) a lung infarction (Table 6).

Disease	n	%	95%-CI	
Hypertension	41	30.5970%	23.0889%	39.2375%
Coronary heart disease	30	22.3881%	15.8339%	30.5609%
Heart failure	7	5.2239%	2.1258%	10.8664%
Heart rhythm disorder	26	19.4030%	13.2834%	27.3209%
Cardiac pacemaker	9	6.7164%	3.1169%	12.7337%
Heart valve disease	9	6.7164%	3.1169%	12.7337%
Myocardial infarction	10	7.4627%	3.6365%	13.6484%
Stent	10	7.4627%	3.6365%	13.6484%
Bypass	5	3.7313%	1.2225%	8.9339%
Stroke	17	12.6866%	7.7786%	19.8078%
Thrombosis	11	8.2090%	4.1692%	14.5527%
Lung infarction	2	1.4925%	0.1813%	5.2875%
Peripheral Arterial Disease	5	3.7313%	1.2225%	8.9339%
Coagulation disorders	10	7.4627%	3.6365%	13.6484%
Haemophilia	4	2.9851%	0.8192%	7.9344%
Diabetes mellitus	13	9.7015%	5.2674%	16.3338%
Nephropathy	8	5.9701%	2.6124%	11.8069%
Hepatopathy	8	5.9701%	2.6124%	11.8069%

Table 6. Diseases in medical history, number and percentage of the 134 patients. CI = Confidence Interval

4.2.1 Demography and medical history

The mean age of the patients that suffered from hypertension was 67 years, from coronary heart disease 68 years, from heart failure 71 years, from heart rhythm disorder 69 years, from thrombosis 69 years and with a heart pacemaker 71 years. The patients suf-

fering from haemophilia had a mean age of 22 years and from hepatopathy 46 years. All results were statistically significant (Table 7).

Disease		Age [Years] n	MW	ST	p
Hypertension	yes	41	66.610	10.908	0.014*
	no	93	57.011	18.571	
Coronary heart disease	yes	30	67.767	8.573	0.018*
	no	104	57.692	18.332	
Heart failure	yes	7	71.429	10.533	0.040*
	no	127	59.315	17.245	
Heart rhythm disorder	yes	26	69.577	8.448	0.0012**
	no	108	57.630	17.913	
Heart pacemaker	yes	9	71.000	6.062	0.029*
	no	125	59.152	17.422	
Thrombosis	yes	11	69.182	14.176	0.038*
	no	123	59.122	17.197	
Haemophilia	yes	4	22.000	8.165	0.00015***
	no	130	61.115	15.988	
Diabetes Mellitus	yes	13	70.538	10.852	0.0092**
	no	121	58.810	17.340	
Nephropathy	yes	8	71.750	6.409	0.028*
	no	126	59.198	17.352	
Hepatopathy	yes	8	46.500	8.767	0.0025**
	no	126	60.802	17.213	

Table 7. Age and diseases in medical history. MW = Mean, ST = Standard Deviation, p according to U-Test by Mann and Whitney

The male patients presented more often a coronary heart disease, a history of myocardial infarction or have had a Stent operation. These results were statistically significant (Table 8).

Disease		Gender				
		male		female		
		n	%	n	%	p
Coronary heart disease	yes	21	29.58%	9	14.29%	0.032 *
	no	50	70.42%	54	85.71%	
Myocardial infarction	yes	9	12.68%	1	1.59%	0.019*$_{fy}$
	no	62	87.32%	62	98.41%	
Stent	yes	9	12.68%	1	1.59%	0.019*$_{fy}$
	no	62	87.32%	62	98.41%	

Table 8. Gender and diseases in medical history. Number and percentage of the patients. The percentages refer to the columns, i.e. to gender. p according to Chi-Square-Test or (fy) to exact Chi-Quadrat-Test by Fisher and Yates

4.3 Anticoagulation/antiplatelet therapy

40 patients (30%) were under no anticoagulation therapy. 15 patients (11%) were taking phenprocoumon, 23 patients (17%) acetylsalicylic acid, 5 patients (4%) Clopidogrel and one patient was under continuous heparin infusion therapy. 32 patients (24%) were under low molecular weight heparin (LMWH) therapy. 27 patients (20%) had phenprocoumon with LMWH substituted, 19 patients (14%) had discontinued phenprocoumon therapy and 6 patients (4%) had discontinued therapy with acetylsalicylic acid (Table 9, Figure 5).

Medication		**Number**	%
Phenprocoumon	no	73	54.48 %
	discontinued	46	34.33 %
	yes	15	11.19 %
Aspirin	no	105	78.36 %
	discontinued	6	4.48 %
	yes	23	17.16 %
Clopidogrel	no	125	93.28 %
	discontinued	4	2.99 %
	yes	5	3.73 %
LMWH	no	102	76.12 %
	yes	32	23.88 %
Heparin	no	133	99.25 %
	yes	1	0.75 %

Table 9. Anticoagulation/antiplatelet therapy, in case of phenprocoumon discontinued includes also substituted. Number and percentage of patients. n = 134. LMWH= Low Molecular Weight Heparin

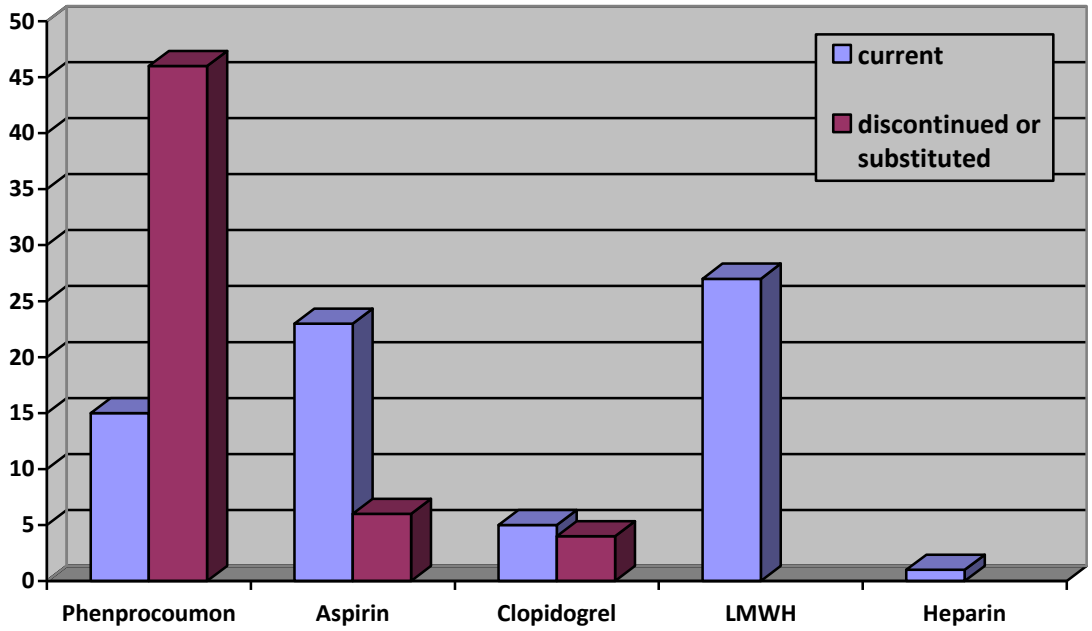


Figure 5. Anticoagulation therapy discontinued, substituted or current taken at the day of operation. The columns represent the number of patients (n=134). LMWH=Low Molecular Weight Heparin

4.3.1 Demography and medication

The mean age, statistical significant, of the patients receiving phenprocoumon is 68,2 years old and of the ones receiving acetylsalicylic acid 67,7 years. The mean age of patients under low molecular weight heparin therapy is 66,9 years (Table 10).

Medication		n	Age MW	ST	
Phenprocoumon	yes	15	68.267	8.137	
	stopped/substituted	46	66.544	9.697	0.00085***
	no	73	54.082	19.861	
Aspirin	yes	23	67.783	14.722	
	stopped/substituted	6	60.500	7.714	0.031*
	no	105	58.200	17.626	
LMWH	no	102	57.745	18.413	0.016^{*}_{U}
	yes	32	66.969	9.499	

Table 10. Age and anticoagulants/antiplatelets. LMWH=Low Molecular Weight Heparin, MW = Mean, ST = Standard Deviation, p according to Kruska-Wallis analysis of variance or (U) to U-Test by Mann and Whitney

Among the 7 medication groups presented in table 10 there were no differences concerning the gender (p = 0.44 in exact Chi-Quadrat-Test by Mehta and Patel). The patients receiving anticoagulants or antiplatelets -discontinued/substituted or not- had a mean age of 66.8 ± 10.7 years. The patients with no such a medication, however, were only 44.4 ± 19.3 years old (p < 0.000005*** in U-Test by Mann und Whitney).

4.3.2 Medical history and medication

92,68% of the patients suffering from hypertension were under anticoagulation or antiplatelet therapy. Under anticoagulation or antiplatelet therapy were also 90% of the patients suffering from coronary heart disease, 96,15% of the patients with heart rhythm disorder, 100% of the patients after a myocardial infarction, 94,12% of the patients after a stroke, 100% of the patients with thrombosis and 12,5% of the patients with hepatopathy. No patient suffering from haemophilia received anticoagulation therapy. All the above mentioned results were statistically significant (Table 11).

Disease		Anticoagulation/antiplatelet therapy: yes n	yes %	no n	no %	p
Hypertension	yes	38	92.68%	3	7.32%	0.000034***
	no	55	59.78%	37	40.22%	
Coronary heart disease	yes	27	90.00%	3	10.00%	0.0033**
	no	66	64.08%	37	35.92%	
Heart failure	yes	7	100.00%	0	0.00%	0.10_{fy}
	no	86	68.25%	40	31.75%	
Heart rhythm disorder	yes	25	96.15%	1	3.85%	0.00020^{***}_{fy}
	no	68	63.55%	39	36.45%	
Heart pacemaker	yes	9	100.00%	0	0.00%	0.057_{fy}
	no	84	67.74%	40	32.26%	
Heart valve failure	yes	7	77.78%	2	22.22%	0.72_{fy}
	no	86	69.35%	38	30.65%	
Myocardial infarction	yes	10	100.00%	0	0.00%	0.032^{*}_{fy}
	no	83	67.48%	40	32.52%	
Stent	yes	9	90.00%	1	10.00%	0.28_{fy}
	no	84	68.29%	39	31.71%	
Bypass	yes	5	100.00%	0	0.00%	0.32_{fy}
	no	88	68.75%	40	31.25%	
Stroke	yes	16	94.12%	1	5.88%	0.0085**
	no	77	66.38%	39	33.62%	
Thrombosis	yes	11	100.00%	0	0.00%	0.034^{*}_{fy}
	no	82	67.21%	40	32.79%	
Lung infarction	yes	1	100.00%	0	0.00%	1.0_{fy}
	no	92	69.70%	40	30.30%	
Periph. arterial disease	yes	5	100.00%	0	0.00%	0.32_{fy}
	no	88	68.75%	40	31.25%	
Coagulation disorder	yes	3	30.00%	7	70.00%	0.0082^{**}_{fy}
	no	90	73.17%	33	26.83%	
Haemophilia	yes	0	0.00%	4	100.00%	0.0073^{**}_{fy}
	no	93	72.09%	36	27.91%	
Diabetes mellitus	yes	12	92.31%	1	7.69%	0.11_{fy}
	no	81	67.50%	39	32.50%	
Nephropathy	yes	6	75.00%	2	25.00%	1.0_{fy}
	no	87	69.60%	38	30.40%	
Hepatopathy	yes	1	12.50%	7	87.50%	0.00092^{***}_{fy}
	no	92	73.60%	33	26.40%	

Table 11. Diseases in medical history and anticoagulation/antiplatelet therapy. Number and percentage of the patients. The percentages refer to the rows, i.e. to the diseases. p according to Chi-Quadrat-Test or (fy) to exact Chi-Quadrat-Test by Fisher and Yates

4.4 Primary operation

42 % of the patients were operated in Regensburg hospital and 58% in alio loco; documentation about one patient is missing (Figure 6).

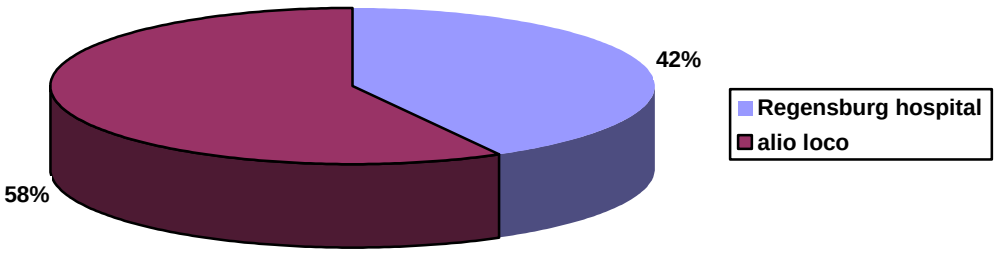


Figure 6. Place of operation. Percentages of patients according to place of operation (n=134)

88,81% of the patients bled after a simple tooth extraction, 2,99% after a surgical extraction, 2,99% after an apicectomy, 2,24% after an augmentation of the sinus, 2,24% after a root scaling and 0,75% underwent no operation and bled spontaneously (Figure 7).

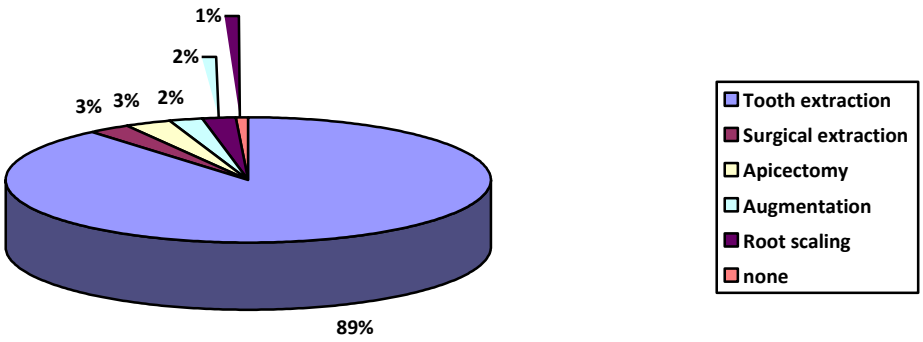


Figure 7. Type of operation. Percentages of the patients according to type of operation (n=134)

74,44% of the patients underwent an operation in maxilla and 37,59% in mandible. 10% of the patients were operated in anterior maxilla, 58,18% in posterior maxilla and one patient both in posterior and anterior maxilla. 2,52% of the patients were operated in anterior mandible and 27,73% in posterior mandible. No one was operated in both regions of the mandible. More specifically in maxilla, 8,96 % of the patients were operated in lateral incisor region, 5,97% in canines, 14,92% in pre-molars, 49,35% in molars and 20,9% in wisdom teeth region. In mandible, no patients were operated in incisors and canine region, 16,66% were operated in pre-molars, 43,34% in molars and 40% in wisdom teeth region (Table 12).

		Maxilla		**Mandible**	
		Number	%	Number	%
Operation	yes	99	74.44	50	37.59
	no	34	25.56	83	62.41
	unknown	*1*	–	*1*	–
Localization	no	34	30.91	83	69.75
	anterior	11	10.00	3	2.52
	posterior	64	58.18	33	27.73
	both	1	0.91	0	0.00
	unknown	*24*	–	*15*	–
Tooth	1	0		0	
	2	6	8.96	0	
	3	4	5.97	0	
	4	9	13.43	1	3.33
	5	1	1.49	4	13.33
	6	20	29.85	5	16.67
	7	13	19.40	8	26.67
	8	14	20.90	12	40.00
	unknown	*67*	–	*104*	–

Table 12. Localization of the primary operation according to mandible or maxillary localization. Number and percentage of the 134 patients

83 patients (62%) were operated only in maxilla, 34 patients (25%) only in mandible while 16 patients (12%) in both. In one patient localization was not documented.

4.4.1 Demography and Operation

The patients operated in maxilla were significantly older, with a mean age of 62.3 ± 20.6 years, in comparison to patients operated in mandible which had a mean age of 53.1 ± 20.6 years (p = 0.034* in U-Test by Mann and Whitney).

3 patients operated in anterior mandible had a mean age of 73.7 ± 8.5 years, 33 patients operated in posterior mandible had a mean age of 51.2 ± 20.6 years while 83 patients that were not operated in mandible had a mean age of 62.6 ± 15.2 years (p = 0.0088 in Kruskal-Wallis analysis of variance).

The lower wisdom teeth were extracted in 12 patients which were significantly younger, with a mean age of 33.5 ± 17.9 years.

There were also differences in age concerning the type of operation. 4 patients that underwent a surgical extraction had a mean age of 24.8 ± 16.4 years. Between the other 5 groups, there were no statistical significant differences, with a mean age of 61.0 ± 16.3 years (p = 0.75 in Kruskal-Wallis analysis of variance).

4.4.2 Medication and type of operation

77,55% of the patients operated in maxilla were under anticoagulation therapy while only 58% of the patients operated in mandible were under the same therapy. 59,21% of patients operated in maxilla were under therapy with phenprocoumon –discontinued, substituted or not- and 40,78% under therapy with aspirin or Clopidogrel. All results are statistically significant (Table 13).

		Maxilla				
		yes		no		
		n	%	n	%	p
Anticogulation/antiplatelet therapy	yes	76	77.55%	16	47.06%	0.0012 **
	no	22	22.45%	18	52.94%	
phenprocoumon		11	14.47%	3	18.75%	
Aspirin/Clopidogrel		25	32.89%	0	0.00%	
phenprocoumon substituted		20	26.32%	7	43.75%	0.018 *
phenprocoumon stopped		14	18.42%	5	31.25%	
Asp./Clopid. substituted/stopped		6	7.89%	1	6.25%	
		Mandible				
		yes		no		
		n	%	n	%	p
Anticoagulation/antiplatelet therapy	yes	29	58.00%	63	76.83%	0.023 *
	no	21	42.00%	19	23.17%	

Table 13. Anticoagulation/antiplatelet therapy and localization of the operation. Number and percentages of patients, percentages refer to the columns, i.e. to the localization. n = 133 patients

4.5 Primary wound care measures

In 87,31% of patients (117) were wound care measures taken. Among them, 3 (3%) were ambulant operated and 114 (97%) inpatient (p = 0.028* in exact Chi-Quadrat-Test by Mehta and Patel).

Among the 117 patients who received wound care measures, 14,17% received a splint. In 56,71% of the patients sutures were made, in 30,59% of the cases a flap was used in order to approximate the wound edges, 2,23% of the patients received collagen, in 1,49% of the patients desmopressin was administrated and in 0,7% of the cases tranexamic acid was used. 25,3% of the patients stayed inpatient after the operation (Table 14).

Wound care measures	n	%	95%-CI	
Measures after operation	117	87.3134%	80.1922%	92.2214%
Splint	19	14.1791%	8.9682%	21.5092%
Suture	76	56.7164%	47.8851%	65.1570%
Approximation of wound edges-Flap	41	30.5970%	23.0889%	39.2375%
Collagen	3	2.2388%	0.4641%	6.4033%
Desmopressin	2	1.4925%	0.1813%	5.2875%
Tranexamic acid	1	0.7463%	0.0189%	4.0877%
Inpatient stay	34	25.3731%	18.4345%	33.7526%

Table 14. Wound care after operation. Number and percentage of n=134 patients. CI = Confidence Interval

4.5.1 Demography and wound care measures

The two patients that received desmopressin as part of the therapy against bleeding were significant younger than the rest of the patients, 27.0 ± 9.9 years old, in comparison to the rest of the patients who received no desmopressin, 60.4 ± 16.8 years (p = 0.023* in U-Test by Mann and Whitney).

The patients that were inpatient operated had a mean age of 66.5 ± 8.5 years, not significant older than the ones treated outpatient which were 57.7 ± 18.7 years old (p = 0.055 in U-Test by Mann and Whitney).

4.5.2 Anticoagulation therapy and wound care measures

Wound care measures were taken in 66,67% of the patients under current phenprocoumon therapy. In 95,65% of the patients who had phenprocoumon therapy substituted, there were also wound care measures taken. These results are statistically significant. 39,13% of the patients taking aspirin were operated inpatient while 50% of the patients who had aspirin discontinued, were also inpatient operated. However, these results are not statistically significant. In 40% of the patients who received therapy with Clopidogrel, an approximation of the wound edges was used while the same measure was taken in all patients who had Clopidogrel discontinued. These results are statistically significant (Table 15).

		n	%	n	%	n	%	p
		Phenprocoumon						
		no		stopped		yes		
Wound care measures	yes	63	86.30%	44	95.65%	10	66.67%	0.018 *
	no	10	13.70%	2	4.35%	5	33.33%	
Splint	yes	7	9.59%	11	23.91%	1	6.67%	0.070
	no	66	90.41%	35	76.09%	14	93.33%	
		Aspirin						
		no		stopped		yes		
Inpatient stay	yes	22	20.95%	3	50.00%	9	39.13%	0.087
	no	83	79.05%	3	50.00%	14	60.87%	
		Clopidogrel						
		no		stopped		yes		
Flap	yes	35	28.00%	4	100.00%	2	40.00%	0.0065 **
	no	90	72.00%	0	0.00%	3	60.00%	
Inpatient stay	yes	29	23.20%	3	75.00%	2	40.00%	0.076
	no	96	76.80%	1	25.00%	3	60.00%	

Table 15. Anticoagulation/antiplatelet therapy and wound care measures. Number and percentage of the patients, percentage refers to the columns, i.e. to the medication. p according to Chi-Quadrat-Test. n = 134 patients

73,33 % of patients who received phenprocoumon were operated ambulant, in Regensburg hospital or in alio loco, while 26,27% were operated inpatient. 59,26 % of patients who had phenprocoumon substituted were operated ambulant and 40,74% inpatient. 73,68% of patients who had phenprocoumon discontinued were operated ambulant and

26,32% inpatient. 64 % of the patients under Aspirin or Clopidogrel therapy were operated ambulant and 36% inpatient. 57,14% of patients who had aspirin or Clopidogrel discontinued were operated ambulant and 42,86% inpatient. The results are statistically significant (Table 16).

		Operation				
		inpatient		ambulant		
		n	%	n	%	p
Group	Phenprocoumon	4	26.67%	11	73.33%	
	Aspirin/Clopidogrel	9	36.00%	16	64.00%	
	Phenprocoumon substituted	11	40.74%	16	59.26%	
	Phenprocoumon stopped	5	26.32%	14	73.68%	0.0043**
	Aspirin/Clopid. stopped	3	42.86%	4	57.14%	
	no anticoagulation therapy	2	5.00%	38	95.00%	

Table 16. Inpatient or ambulant operation and anticoagulation/antiplatelet therapy. Number and percentage of the patients, percentage refers to the rows, i.e. to the medication. p according to exact Chi-Quadrat-Test by Mehta and Patel. n = 134 patients

4.5.3 Operation and wound care measures

100% of the patients operated in Regensburg hospital received wound care measures after the operation in comparison to 79,22% of the patients treated in alio loco. In 71,43% of the patients operated in Regensburg hospital a flap was used and simple sutures were made only in 28,57% of the patients. In alio loco, 77,92% of the patients received simple sutures and only 1,30% a flap. In 28,57% of the patients operated in Regensburg hospital and in 3,90% of the patients operated in alio loco a splint was used. All above results are statistically significant. Although not statistically significant, collagen tamponade, desmopressin and tranexamic acid were not at all used when the operation took place in alio loco. 60,71% of the patients operated in Regensburg hospital received an inpatient treatment after the operation. All patients operated in alio loco were ambulant patients. (Table 17, Figure 8).

		Place of operation				
		Regensburg hospital		alio loco		
		n	%	n	%	p
Wound care measures	yes	56	100.00%	61	79.22%	0.000013***
	no	0	0.00%	16	20.78%	
Suture	yes	16	28.57%	60	77.92%	<0.00000005***
	no	40	71.43%	17	22.08%	
Flap	yes	40	71.43%	1	1.30%	<0.00000005***
	no	16	28.57%	76	98.70%	
Splint	yes	16	28.57%	3	3.90%	0.000044***
	no	40	71.43%	74	96.10%	
Collagen tamponade	yes	3	5.36%	0	0.00%	0.072_{fy}
	no	53	94.64%	77	100.00%	
Desmopressin	yes	2	3.57%	0	0.00%	0.18_{fy}
	no	54	96.43%	77	100.00%	
Tranexamic acid	yes	1	1.79%	0	0.00%	0.42_{fy}
	no	55	98.21%	77	100.00%	
inpatient stay	yes	34	60.71%	0	0.00%	<0.00000005***
	no	22	39.29%	77	100.00%	

Table 17. Place of operation and type of wound care measures taken. Number and percentage of patients, the percentage refers to the rows, i.e. the measures taken. p according to exact Chi-Quadrat-Test by Mehta and Patel. n = 134 patients

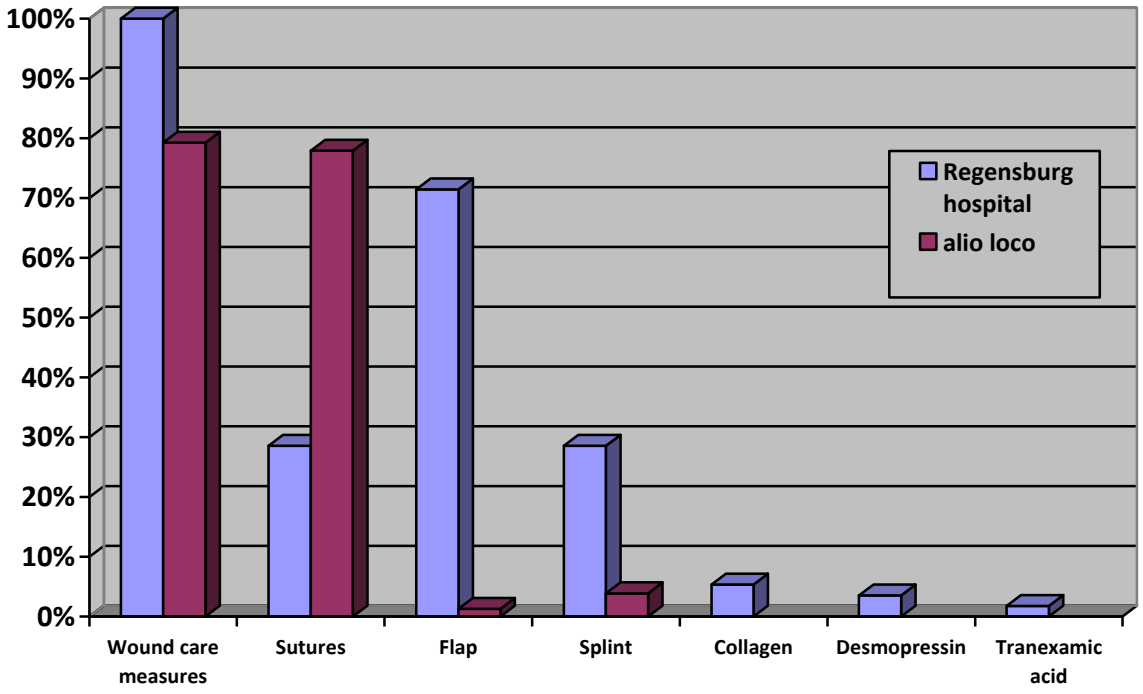


Figure 8. Type of wound care measures taken in Regensburg hospital and in alio loco. The columns represent the percentage of patients (n=134).

44,54% of tooth extractions took place in Regensburg hospital and 55,46% in alio loco. 75% of surgical extractions took place in Regensburg hospital and 25% in alio loco, while all apicectomies, sinus augmentations and root scaling took place in alio loco. The results are statistically significant.

Wound care measures were taken in 89,92% of tooth extractions, 100% of surgical extractions, 100% of apicectomies and 100% of sinus augmentations. No wound care measures were taken in 10,08% of the tooth extractions and in 100% of root scaling (Table 18).

Type of operation	n	%	n	%	p
	Place of operation				
	Regensburg hospital		alio loco		
Tooth extraction	53	44.54%	66	55.46%	
Surgical extraction	3	75.00%	1	25.00%	
Apicectomy	0	0.00%	4	100.00%	0.047*$_{mp}$
Augmentation	0	0.00%	3	100.00%	
Root scaling	0	0.00%	3	100.00%	
	Wound care measures				
	yes		no		
Tooth extraction	107	89.92%	12	10.08%	
Surgical extraction	4	100.00%	0	0.00%	
Apicectomy	4	100.00%	0	0.00%	
Augmentation	2	100.00%	0	0.00%	0.0011**$_{mp}$
Root scaling	0	0.00%	3	100.00%	
keine	0	0.00%	1	100.00%	

Table 18. Type of operation and place of operation, wound care measures. Number and percentage of patients, percentage refers to the rows, i.e. type of operation. p according to exact Chi-Quadrat-Test by Mehta and Patel. n = 134 patients.

In Regensburg hospital 47/56 Patienten (84%) were in maxilla operated while alio loco only 52/77 (68%, p = 0.029* in Chi-Quadrat-Test). In maxilla, a flap was made in 35/99 patients (35%) otherwise in mandible only in 6/34 patients (18%, p = 0.045* in Chi-Quadrat-Test).

Patients operated in maxilla were treated more often inpatient (31/99 = 31%), in comparison to patients operated only in mandible (3/34 = 9%, p = 0.0051** in Chi-Quadrat-Test).

A splint was used only in 4 patients operated in maxilla (4/46 = 8%), while in mandible a splint was used in 15 patients (15/83 18%, p = 0.095 in Chi-Quadrat-Test).

4.6 Therapy against bleeding

In 26,87% of the patients simple sutures were made in order to deal with the postoperative bleeding. Over sutures were used in 45,52% of the patients. A flap was made in 11,94% of the cases, while in 5,22% of the patients the flap was once again approximated and sutured. 29,85% of the patients received a splint after they bled while in 3 cases the splint which was already placed, was fixated. In 25,37% of the patients oxidised regenerated cellulose was used, in 4,48% collagen, in 2,24% bone wax, in 1,49% human fibrinogen/thrombin, in 22,39% tranexamic acid and in 7,46% diathermy was used. 4,48% of the patients required a transfusion, in 2,98% was phytomenadione administrated, one patient was given FIII/VWF complex and in 2,24% of the patients phenprocoumon had to be substituted with low molecular weight heparin (Table 19).

Therapy against bleeding		Number	%
Suture	yes	36	26.87 %
	new suture	2	1.49 %
	no	96	71.64 %
Over sutures	yes	61	45.52 %
	no	73	54.48 %
Flap	yes	16	11.94 %
	once again approximated	7	5.22 %
	no	111	82.84 %
Splint	yes	40	29.85 %
	fixation	3	2.24 %
	no	91	67.91 %
Oxid. regen. cellulose	yes	34	25.37 %
	no	100	74.63 %
Collagen	yes	6	4.48 %
	no	128	95.52 %
Bone wax	yes	3	2.24 %
	no	131	97.76 %
Revision	yes	9	6.72 %
	no	125	93.28 %
Transfusion	yes	6	4.48 %
	no	128	95.52 %
Diathermy	yes	10	7.46 %
	no	124	92.54 %
Tranexamic acid	yes	30	22.39 %
	no	104	77.61 %
Human fibrinogen/thrombin	yes	2	1.49 %
	no	132	98.51 %
Phytomenadione	yes	4	2.98 %
	no	130	97.02 %
FVIII/VWF complex	yes	1	0.75 %
	no	133	99.25 %
Phenprocoumon substitution	yes	3	2.24 %
	no	130	97.76%

Table 19. Measures against bleeding. Number and percentage of n = 134 patients

4.6.1 Demography and therapy against bleeding

The mean age of patients receiving a splint was 65 years; the patients requiring a transfusion had an average age of 72 years. All results statistically significant (Table 20).

Therapy against bleeding		Age			
		n	MW	ST	p
Splint	yes	43	65.116	14.026	0.032*
	no	91	57.505	17.999	
Transfusion	yes	6	72.333	5.391	0.036*
	no	128	59.367	17.298	

Table 20. Age and measures against bleeding. MW = Mean, ST = Standard Deviation, p according to U-Test by Mann and Whitney. Splint yes includes also fixation of a splint already in use.

4.6.2 Medical history and therapy against bleeding

30% of the patients that suffered from bleeding disorders needed a transfusion. This result is statistically significant (Table 21).

		Bleeding disorders				
		yes		no		
		n	%	n	%	p
Transfusion	yes	3	30.00%	3	2.42%	0.0054**$_{fy}$
	no	7	70.00%	121	97.58%	

Table 21. Bleeding disorders and therapy against bleeding. Number and percentage of the patients, percentage refers to the column, i.e. to disease. p according to exact Chi-Quadrat-Test by Fisher and Yates

4.6.3 Anticoagulation therapy and therapy against bleeding

As part of the measures against bleeding, transfusion was needed in 21,05% of the patients who had phenprocoumon discontinued and in 5% of the patients who received no anticoagulation therapy (Table 22).

	Transfusion				
	yes		no		
Medikations-Cluster	n	%	n	%	p
1 Phenprocoumon	0	0.00%	15	100.00%	
2 Aspirin/Clopidogrel	0	0.00%	25	100.00%	
3 Phenprocoumon substituted	0	0.00%	27	100.00%	
4 Phenprocoumon stopped	4	21.05%	15	78.95%	0.048^{*}_{mp}
5 Aspirin/Clopid. stopped	0	0.00%	7	100.00%	
6 no medication	2	5.00%	38	95.00%	
7 Heparin	0	0.00%	1	100.00%	

Table 22. Medication-clusters and transfusion to deal against the bleeding. Number and percentage of the patients, percentage refers to the rows, i.e. to clusters. p according to exact Chi-Quadrat-Test by Mehta and Patel

4.6.4 Primary wound care measures and therapy against bleeding

When primary wound care measures were taken, there was a need of approximation of the wound edges after the bleeding in only 6,84% of the patients and 52,14% of the patients required only over sutures. On the contrary, when there were no wound care measures taken, 47,06% of the patients needed after the bleeding approximation of wound edges (p=0.0000026*** according to Chi-Quadrat-Test, p= 0.00017*** according to exact Chi-Quadrat-Test by Mehta and Patel).

When a splint was already placed as part of the wound care measures, in 15,79% of the patients it had to be fixated. When there was no splint initially used, in 34,78% of the patients there was one after the bleeding produced and placed (Table 23).

Therapy against bleeding		primary use of splint: yes n	yes %	no n	no %	p
Splint	yes	0	0.00%	40	34.78%	
	fixation	3	15.79%	0	0.00%	0.000014***$_{mp}$
	no	16	84.21%	75	65.22%	

Table 23. Primary use of splint and therapy against bleeding. Number and percentage of the patients, percentage refers to the columns, i.e. to primary measures taken. p according to exact Chi-Quadrat-Test by Mehta and Patel

4.7 Time and duration of bleeding

After the bleeding, 91,79% of the patients (123) were treated inpatient. 90 out of the 123 patients were admitted after the bleeding occurred while the rest 33 were already inpatient. 4,48% of the patients (6) were treated only ambulant. 3,73% of the patients (5) were already inpatient in another clinic for other medical reasons (Figure 9).

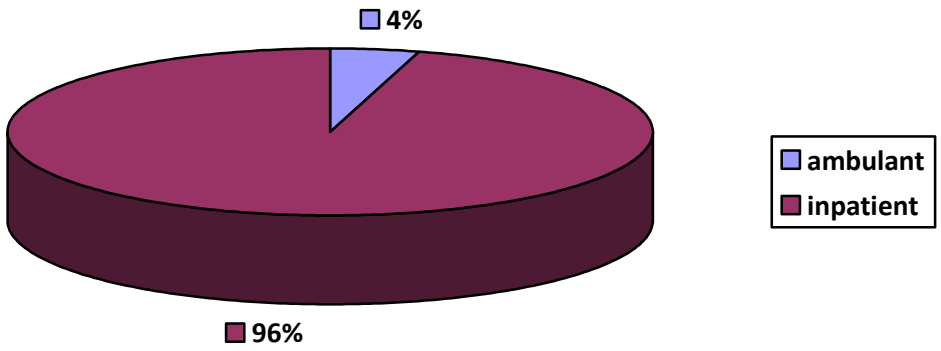


Figure 9. Percentage of patients treated ambulant or inpatient after the bleeding (n=134).

The time of appearance of the bleeding varied between 1 and 28 days, on average 2.88 ± 4.22 days (median one day with 68%-CI from 1 until 5 days). 5% of the patients bled after the 10th postoperative day (Figure 10). More specifically, 3 patients bled on the 12th postoperative day, one on the 13th, one on the 20th, one on the 24th and one patient bled on the 28th postoperative day (Figure 10).

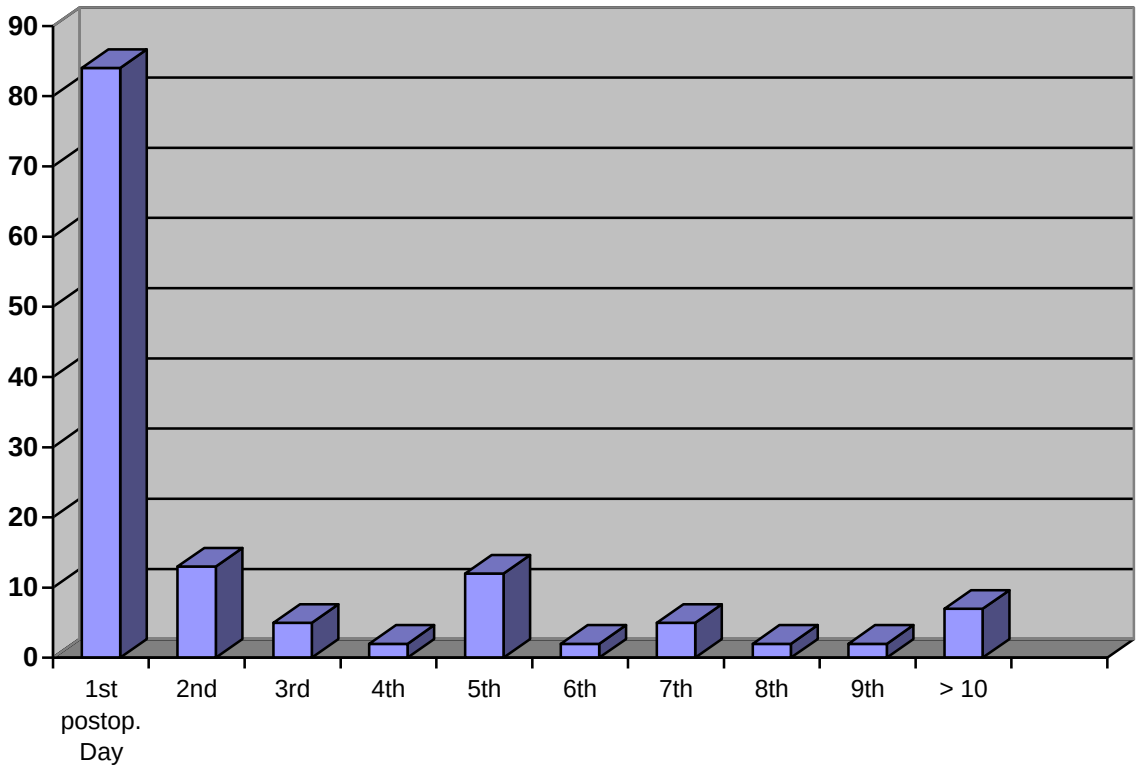


Figure 10. Postoperative day when bleeding occurred. The columns represent number of patients (n=134).

The duration of the inpatient stay varied between 1 and 24 days. Ambulant treatment is considered of 0 days duration (Figure 11).

On average the inpatient treatment lasted 5.37 ± 5.38 days (median 3 days with 68%-CI from 2 until 9.7 days).

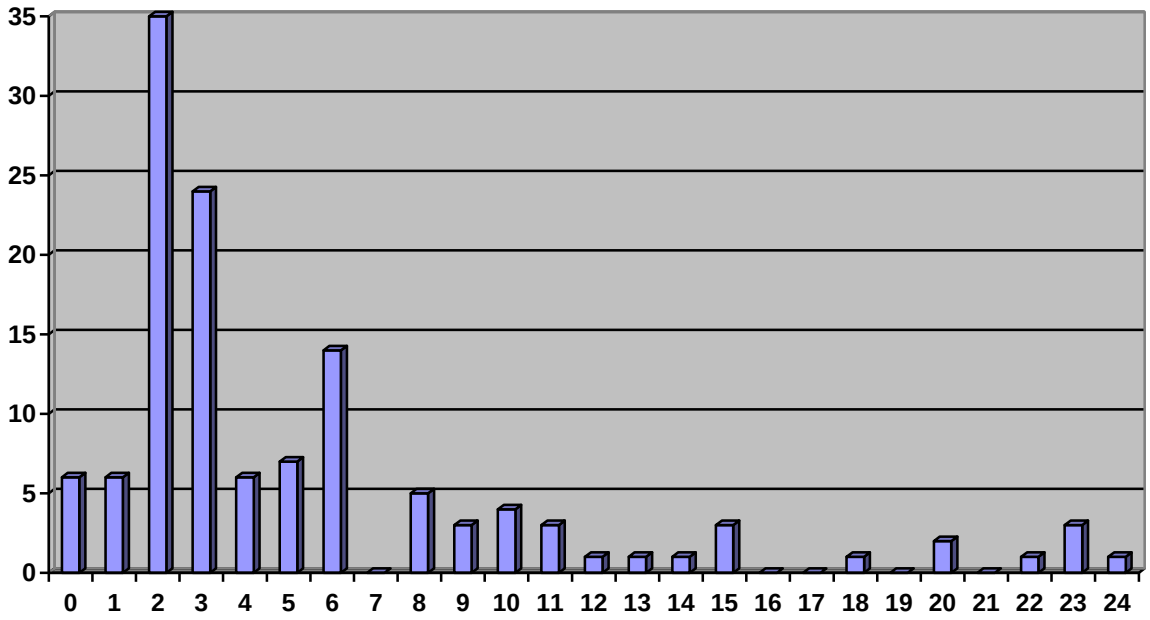


Figure 11. Duration of inpatient treatment after bleeding in days. 0 days stands for ambulant treatment of the bleeding. The columns represent the number of patients (n=129, excluding the ones inpatient in another department).

The later the bleeding occurred, the longer lasted the inpatient treatment of the patient. (tau = 0.29, p < 0.000005*** according to Kendall rank correlation).

In case of bleeding at the first or second day, 15/95 (16%) of the patients required an inpatient treatment for 7 or more days. If the bleeding occurred after the third day, then 12/30 (40%) of the patients had to stay more than 6 days inpatient. (p = 0.0073** in Chi-Quadrat-Test).

4.7.1 Demography and time until bleeding

The older the patient, the more lasted his inpatient treatment (tau = 0.15, p = 0.014*) while the time period between the operation and the time of bleeding shows no correlation with age (tau = 0.09, p = 0.12, both according to Kendall rank correlation).

The duration of the inpatient treatment as well as the time of bleeding shows no correlation with gender.

4.7.2 Medical history and time until bleeding

Patients with a coagulation disorder bled, on average, the fifth postoperative day, patients with haemophilia on the eleventh postoperative day while patients with liver disease on the sixth postoperative day. All results are statistically significant (Table 24).

		n	MW	ST	p(U)
Disease			**Day of bleeding**		
Coagulation disorders	yes	10	5.500	4.301	0.00055***
	no	120	2.667	4.159	
Haemophilia	yes	4	11.250	11.673	0.012*
	no	126	2.619	3.580	
Hepatopathy	yes	8	6.250	4.496	0.0018**
	no	122	2.664	4.127	

Table 24. Time in days until bleeding. MW = Mean, ST = Standard deviation, p according to U-Test by Mann and Whitney

4.7.3 Anticoagulation therapy and duration of inpatient stay

30 patients receiving LMWH stayed inpatient after the postoperative bleeding significant more days (7.2 ± 5.7) than patients receiving no LMWH or other anticoagulants (4.8 ± 5.2) (p = 0.0045** in U-Test by Mann and Whitney).

Patients under phenprocoumon therapy had to stay for an inpatient treatment, on average, 4,46 ± 3,46 days, while patients who had phenprocoumon discontinued or substituted required an inpatient treatment of 7,95 ± 6,29 days. These results are statistically significant. Patients under therapy with aspirin had to stay inpatient 3,09 ± 2,09 days and patients who had aspirin discontinued stayed 3 ± 2,19 days. These results are scarcely not significant.

More specifically, statistically significant results are as followed: Patients under Aspirin or Clopidogrel therapy stayed inpatient 3,08 ± 2,02 days, patients who had phenprocoumon substituted 7,08 ± 5,1 days, patients who had phenprocoumon discontinued 9,10 ± 7,52 days, patients who had aspirin or Clopidogrel discontinued or substituted 5,57 ± 7,72 days, patients receiving no medication 4,17 ± 4,87 days and one patient under heparin therapy had to stay inpatient 3 days (Table 25).

		Duration of inpatient stay [d]			
Medication		n	MW	ST	p
Phenprocoumon	yes	15	4.46667	3.46135	
	discontinued/substituted	44	7.95455	6.29490	0.00005 ***
	no	70	3.94286	4.48471	
Aspirin	yes	21	3.09524	2.09535	
	discontinued	6	3.00000	2.19089	0.052
	no	102	5.98039	5.81562	
Group	Phenprocoumon	15	4.46667	3.46135	
	Aspirin/Clopidogrel	23	3.08696	2.02064	
	Phenprocoumon substituted	25	7.08000	5.16333	
	Phenprocoumon discontin.	19	9.10526	7.52695	0.0011 **
	Aspirin/Clopid. discontin.	7	5.57143	7.72134	
	no medication	39	4.17949	4.87135	
	Heparin	1	3.00000	-	

Table 25. Duration of inpatient stay after bleeding under anticoagulation therapy. MW = Mean, ST = Standard Deviation, p according to Kruskal-Wallis analysis of variance

4.7.4 Operation and duration of inpatient stay, time until bleeding

Inpatient stay after the bleeding of 54 patients, operated in Regensburg hospital, lasted 7.0 ± 6.5 days, while patients initially operated in alio loco, had to stay only 4.3 ± 4.2 days (p = 0.0049** in U-Test by Mann and Whitney).

When the operation took place in Regensburg hospital, the bleeding occurred after 3,51 ± 4,71 days. When the patient was operated in alio loco, the bleeding occurred after 2,43 ± 3,80 days. The bleeding in cases of tooth extraction occurred 3,07 ± 4,40 days

after the operation, while in all other cases the bleeding occurred the next day (1,15 ± 0,37). These results, however, are not statistically significant (Table 26).

primary operation		postoperative bleeding [d] n	MW	ST	p(U)
Place	Regensburg hospital	54	3.519	4.713	0.061
	alio loco	76	2.434	3.803	
Type	Tooth extraction	117	3.077	4.408	0.066
	other	13	1.154	0.376	
Type	Tooth extraction	117	3.077	4.408	
	Surgical extraction	4	1.000	0.000	
	Apicectomy	4	1.000	0.000	0.22 $_{kw}$
	Augmentation	2	1.000	0.000	
	root scaling	3	1.667	0.577	

Table 26. Time until bleeding in days according place and type of operation. MW = Mean, ST = Standard Deviation, p according to U-Test by Mann and Whitney or (kw) according to Kruskal-Wallis analysis of variance

4.7.5 Wound care measures and duration of inpatient stay, time until bleeding

When there were sutures made after the operation, the bleeding occurred after 2,71 ± 4,45 days (statistically significant), while when approximation of the wound edges was performed, the bleeding occurred after 3,4 ± 4,43 days (statistically not significant) (Table 27).

Wound care measures		n	MW	ST	p(U)
		Day of bleeding			
Suture	yes	74	2.716	4.458	0.046*
	no	56	3.107	3.916	
Flap	yes	40	3.400	4.431	0.069
	no	90	2.656	4.130	

Table 27. Wound care measures and time until bleeding. MW = Mean, ST = Standard deviation, p according to U-Test by Mann and Whitney

4.7.6 Therapy against bleeding and duration of inpatient stay

When there was a flap made, in order to deal with the bleeding, the inpatient stay lasted 3,66 ± 3,22 days, in comparison to 5,42 ± 5,6 days when there was no flap made. All above results are statistically significant (Table 28).

		n	MW	ST	p
		Duration of inpatient stay [d]			
Flap	yes	15	3.66667	3.22195	
	once again	7	8.14286	4.81070	0.040 *$_{kw}$
	no	107	5.42991	5.60174	

Table 28. Therapy against bleeding and duration of inpatient stay. MW = Mean, ST = Standard deviation, p according to Kruskal and Wallis analysis of variance

4.8 Changes over the years

In the year 2004, 9 patients (6,72%) were treated, in 2005 20 patients (14,93%), in 2006 21 patients (15,67%), in 2007 33 patients (24,63%), in 2008 27 patients (20,15%) and in 2009 24 patients (17,91%) (Figure 12).

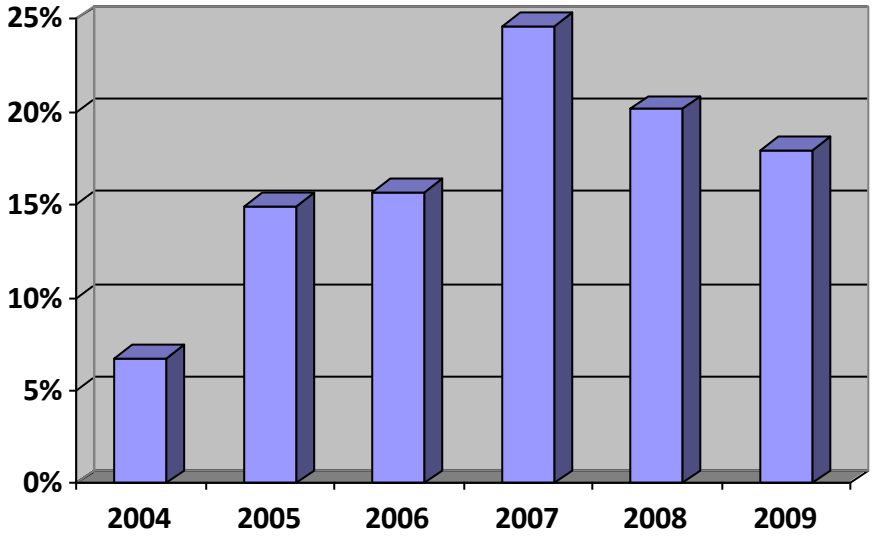


Figure 12. Percentage of patients with postoperative bleeding according to year of operation (n=134).

4.8.1 Demography and year of operation

Among the years, no change was noticed in age or gender .

4.8.2 Anticoagulation therapy and year of operation

Among the years, there was no change noticed in the number of patients receiving anticoagulants.

4.8.3 Type of operation and year of operation

Among the years, there was no change noticed in the number of patients who were operated in Regensburg hospital and in alio loco. There was also no change noticed in the number of operations in upper and lower jaw.

4.8.4 Wound care measures and year of operation

In the last years, wound care measures are less taken. Sutures were made mostly earlier; the approximation of wound edges is more common in the last years. Inpatient operation is more common in the last years. A splint has been already in use since 2004. The results are statistically significant (Figure 13).

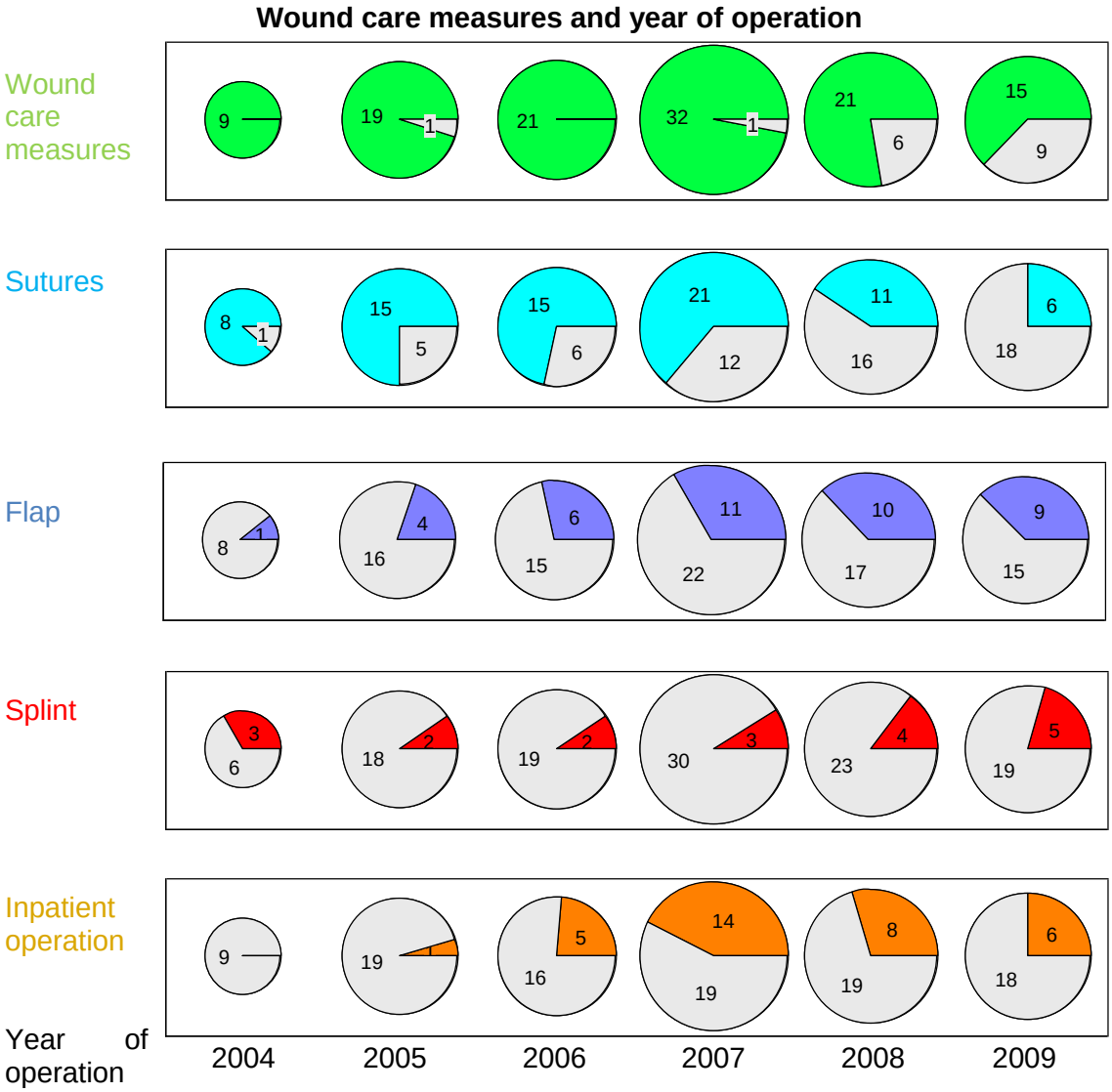


Figure 13. Wound care measures according to year of operation. Each area of the circle represents the number of patients. ■ = *Wound care measures,* ■ = *Sutures,* ■ = *Approximation of wound edges-Flap,* ■ = *Splint,* ■ = *inpatient operation,* □ =*no.*

4.8.5 Therapy against bleeding and year of operation

In order to deal with the postoperative bleeding, over sutures were mostly used earlier and have been lately replaced by approximation of wound edges. Revision is also most common in the last years while haemostatic agents are more popular in the last years. Human fibrinogen was not used until 2009. All results are statistically significant (Figure 14).

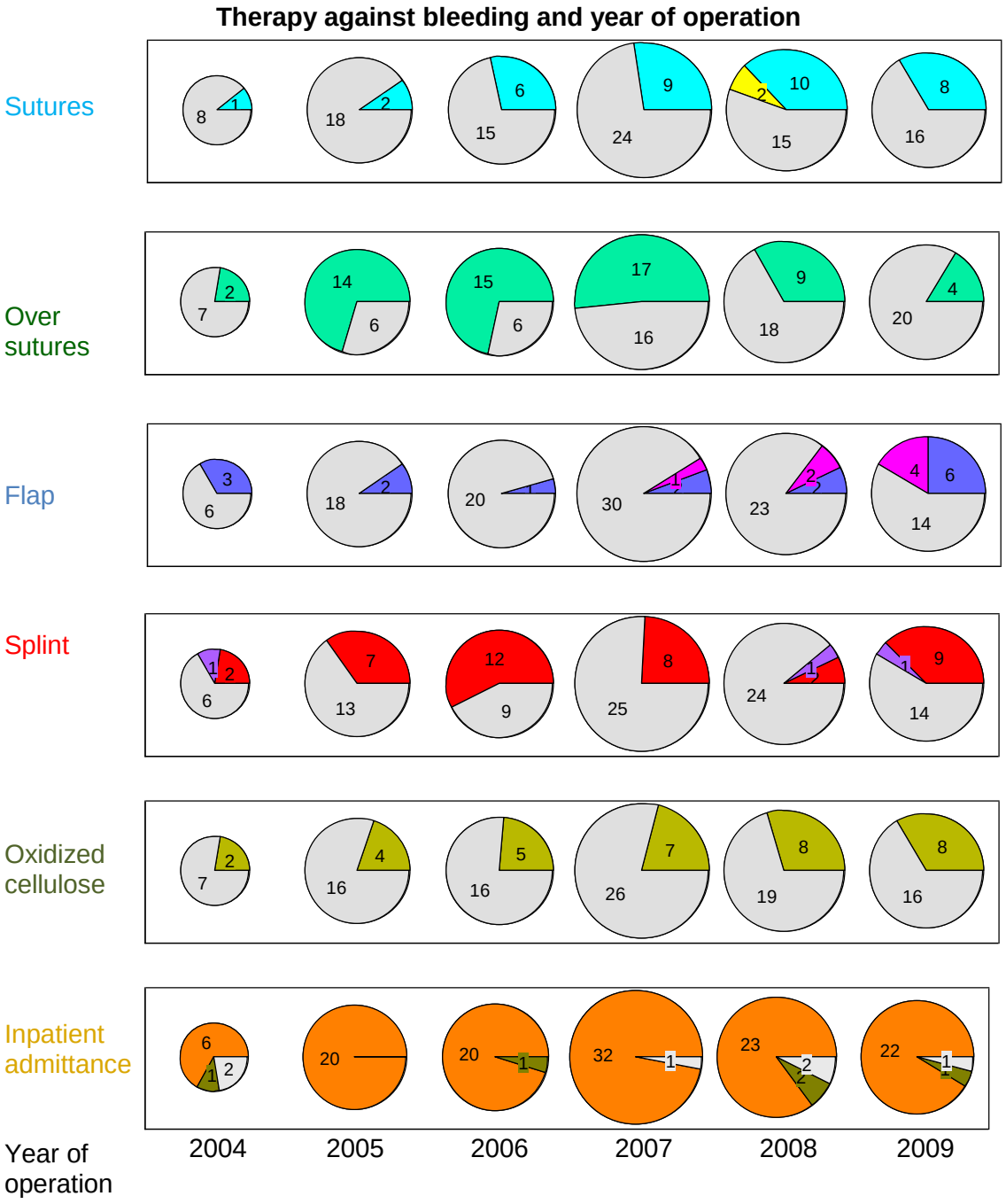


Figure 14. Therapy against bleeding according to year of operation. Each area of the circle represents the number of patients. ■ *= Suture,* ■ *= New sutures (revision),* ■ *= Over sutures,* ■ *= Flap,* ■ *= Flap revision,* ■ *= Splint,* ■ *= Splint fixated,* ■ *= Oxidized cellulose,* ■ *=Inpatient admittance,* ■ *= already inpatient,* □ *= no.*

4.8.6 Time until bleeding, duration of inpatient stay and year of operation

The duration of the inpatient stay because of the postoperative bleeding decreased over the years (tau = -0.20, p = 0.00062***) while the time after the operation until bleeding remained unchanged (tau = -0.04, p = 0.50, both according to Kendall Rank correlation).

5 Discussion

After noticing an increase in the number of patients coming to our clinic with a postoperative bleeding after minor oral surgery, we decided to study a possible relation between postoperative bleeding and age, gender, medical history, medication, type of operation, place of operation, preoperative, intraoperative and postoperative measures.

5.1 Demographic data and medical history

In our study, 68% of the patients were between 40,3 and 75 years old. The above results were expected because at this age group patients suffer from disorders that require anticoagulation therapy. According to the statistical fact sheet of American Heart Association, 71,3 % of general male population and 75,1% of general female population aged from 60 until 79 years present cardiovascular diseases. For ages between 40 and 59 years old the percentage is 39,1% for males and 39,5% for females. The percentages climb to 83% and 92% for males and females, respectively, in the age of 80+, while at the age of 20 until 39 years old, cardiovascular disorders are present only in 14,8% of male and 9,4% of female population (American Heart Association, 2007). In our study group, less than 2% of the patients are between 16 and 39 years old. A small number of patients in that age takes anticoagulation therapy.

In general population of white people aged 20 years and older, 8,5% have coronary heart disease (American Heart association, 2011). In our study group the percentage of patients with coronary heart disease ranges between 15,83% und 30,56. Haemophilia in general population is present in 0,0053- 0,020% (Venkateswaran L, 1998). The high percentage of patients suffering from haemophilia in our results is expected because these patients are more likely to present postoperative bleeding than the general population.

5.2 Anticoagulation therapy

Among the patients who presented postoperative bleeding, 34,33% were patients under phenprocoumon therapy which was discontinued or substituted on the day of the operation. This fact raises the question whether the substitution or discontinuation of phenprocoumon therapy is necessary or effective before minor surgery in oral and maxillofacial area. Of course, we did not have information concerning the nutrition or alternative drugs used by the patients that could effect the normalization of haemostasis and the INR values of the patients on the day of surgery. In the study of Schulman et al, although warfarin had been discontinued five days before the operation, 7% of the patients did not normalize their prothrombin at the desired levels for surgery (Schulman et al, 2008).

Indeed, several publications strongly disagree with discontinuing anticoagulation therapy before dental procedures. Devani et al suggest that there is no justification in discontinuing warfarin before dental procedures, provided that INR is between 2.0 and 4.0 and local haemostatic measures are used (Devani et al, 1998). Wahl considers a myth that patients receiving anticoagulation therapy experience more postoperative bleeding complications than patients with normal coagulation when undergoing a dental procedure. He concludes that when anticoagulation therapy is interrupted, serious embolic complications, including death, are three times more likely to occur. He also points out that consulting the patients' physician is not the answer to the problem as many physicians do not understand dental procedures and "simply following a physician's order is unlikely to be an effective legal defence if the dentist is charged with failure to exercise reasonable professional judgement" (Wahl, 2000). Jeske and Suchko conclude that the literature does not support routine discontinuation of anticoagulation therapy in patients undergoing dental procedures and suggest effective haemostatic measures and high level of awareness intra and postoperatively (Jeske, Suchko, 2003).

Van Diermen et al, after assessing different guidelines on the management of patients using antithrombotic drugs in dental surgery according to Appraisal of Guidelines for Research and Evaluation (AGREE), strongly recommend the guidelines of Perry et al, as well as those of Aframian et al with certain alterations (van Diermen et al, 2009). Perry et al suggest that in the majority of patients undergoing dental extraction, oral

anticoagulation should not be discontinued (Perry et al, 2007). Aframian et al suggest that only when INR exceeds 3,5 and invasive or complicated procedures are planned, discontinuing warfarin should be discussed with the physician. Moreover, low-dose (until 100 mg) aspirin therapy should not be interrupted for outpatient dental procedures (Aframian et al, 2007).

5.3 Primary operation

The vast majority of the patients suffered from postoperative bleeding after having a tooth extracted. It comes as a surprise that only 2,99% of the operations was a surgical extraction. Taking into consideration that a surgical extraction means cutting gingival tissue and bone, one could have expected more patients suffering from bleeding after a surgical extraction. Indeed, blood flow in alveolar mucosa is significantly higher than in free gingiva (Kerdvongbundit et al, 2002). The only possible explanation is that after cutting tissue the surgeon has to make sutures providing subsequently a more effective haemostasis than that after removing a tooth where the alveolus is left open. We also have to take into account the possibility that the surgeons who confronted with the bleeding in Regensburg hospital inaccurately documented surgical extractions as simple extractions.

Surprisingly, almost 75% of the postoperative bleedings came from maxilla and mostly from its posterior region. Posterior mandible, anterior maxilla and anterior mandible follow in this order.

A comparison of maxillary and mandibular mineral densities has proven that the mean bone mineral density of the mandible was twice that of the anterior maxilla and both were significantly greater that the bone mineral density of the posterior maxilla (Devlin et al, 1998). However, there was no correlation found between mineralization density and cortical proportion of vascular space (Kingsmill et al, 2007).

The majority of the patients receiving anticoagulation therapy suffer from cardiological disease. Evidence for a link between periodontal disease and several systemic diseases, mostly cardiological, is growing rapidly (Williams et al, 2008). The most probable teeth to be extracted because of the periodontal disease are the teeth of maxilla and mainly the molars (Chambrone et al, 2010, Hirschfeld, Wasserman, 1978, McFall 1982). So a

possible explanation for the high prevalence of bleeding in upper molars is the high prevalence of upper molars being extracted.

Patients that bled after a wisdom tooth extraction were significantly younger. This result comes as no surprise taking into consideration that wisdom teeth are more often extracted in young people.

The number of patients operated in all dental offices of Regensburg region is much greater than the ones operated in Regensburg Oral and Maxillofacial Surgery Department. Subsequently, one could expect that the great majority of the patients suffering from a postoperative bleeding would have been operated in alio loco. However, 42% of the patients who presented postoperative bleeding were operated in Regensburg hospital and bled despite all the wound care measures. Of course, Oral and Maxillofacial Surgery Department of Regensburg hospital treats mostly patients at high risk for bleeding and therefore, the prevalence of bleeding is greater.

One patient who was under anticoagulation therapy bled spontaneously without any history of trauma. Anticoagulation therapy can consist of 'double-edged sword' between thrombosis prevention and bleeding (May et al, 2008). Periodontitis is a chronic inflammation characterized by lymphocytic (T and B cell) and monocytic infiltrate, connective tissue destruction, and bone resorption while clinically it is characterised by gum bleeding (Moutsopoulos, Madianos, 2006). Patients under anticoagulation are prone to spontaneous bleeding and concerning oral and maxillofacial area this can occur in the presence of periodontitis. Moreover, awareness is necessary after root scaling in patients under anticoagulation therapy.

5.4 Primary wound care measures

All patients operated in Regensburg hospital received precaution wound care measures. It is important to note that when no wound care measures were taken, the patients were always operated in alio loco. This means that in many cases, patients receiving anticoagulation therapy or having bleeding disorders were operated ambulant in dental offices and the dentists did not take any haemostatic measures. What is of great importance is whether the dentists had been aware of the patients' medical history and chose not to

take any measures or if they failed taking an accurate medical history. In almost 80% of the cases operated by dentists in alio loco, the wound care measure taken was a simple suture and in only 1,30% of the cases was an approximation of the wound edges the choice of wound treatment. On the other hand, 71% of the patients operated in Regensburg hospital received an approximation of the wound edges. A more limited familiarization of the general dentists with surgical techniques is to be expected and therefore, a simple suture is often their treatment of choice. The question that rises is the need of acquaintance of the dentists with surgical skills as part of their basic education or at least more extended referral to hospitals or oral surgeons. The use of a splint postoperatively is more common in Regensburg hospital. Only 3,90% of the patients operated in alio loco received a splint from their dentist after the surgery. Although not statistically significant it has to be pointed out that collagen tamponade was never used by a dentist as a precursory measure. In case of operation in Regensburg hospital it was used in 2,23% of the cases. Again, there is a need of familiarization of the general dentist with the haemostatic agents available.

Aframian et al suggest the use of fibrin glue, gelatine sponges, oxidised cellulose or tranexamic mouthwash after dental procedures in patients receiving anticoagulants (Aframian et al, 2007).

Surprisingly, almost 74% of the patients receiving phenprocoumon on the day of the operation were operated ambulant. Once again, it is unclear whether this was due to lack of information with regard to the patients' medication or, instead, whether the dentist was aware of their history and decided to operate them without inpatient treatment. However, one can conclude that in cases of minimal surgeries, i.e. one tooth extraction, there is always the possibility of an ambulant operation with a known risk of postoperative bleeding. In all cases, the patient should be informed of the possible bleeding risk and a high level of awareness in case of a bleeding is necessary. Indeed, Perry et al suggest the referral of patients receiving anticoagulants to a hospital-based oral and maxillofacial surgeon, when INR is unstable and patients suffer simultaneously from liver or renal disease, thrombocytopenia or are under antiplatelet therapy (Perry et al, 2007).

5.5 Therapy against bleeding

Therapy against bleeding includes suturing or approximation of wound edges in almost all cases. However, when a flap was made, the bleeding stopped earlier and patients were earlier discharged in comparison to patients who received only sutures after the bleeding.

The surgeons in Regensburg hospital seem to be familiar with haemostatic agents and the use of a splint. Despite all local measures, three patient receiving phenprocoumon continued to bleed during their inpatient treatment and therefore phenprocoumon therapy was substituted.

A complete schema in order to confront bleeding involves inpatient treatment with constant monitoring. An inpatient treatment assures constant control of the amount of bleeding, of the blood values and immediate intervention if necessary. A soft food diet which will protect the wound from mechanical trauma is also guaranteed.

A blood transfusion was necessary in 5% of the patients. More specifically, erythrocyte concentrates were transfused in six patients in order to prevent or correct the symptoms and signs of a lack of oxygen in tissues. Among the six patients, two were under discontinued phenprocoumon therapy, one suffered from leukaemia, one suffered from thrombocytopenia and two patients suffered from anaemia and received phenprocoumon which was at that time discontinued. Surprisingly, it was these patients who had discontinued phenprocoumon before the surgery who needed postoperatively transfusion.

In 2,24% of the cases, the splint, which was already in use, had to be fixated. Often, especially in case of edentulous jaws, the splint needs to be fixated with a screw in order to be stable and effective.

One can observe that when there where wound care measures taken after the extraction, postoperatively over sutures were enough to stop the bleeding. When there were no wound care measures taken, the approximation of wound edges is the therapy of choice for stopping the bleeding.

5.6 Time and duration of bleeding

Only 4,48% of the patients who presented postoperative bleeding were allowed to return home after treatment. Excluding the patients who were already inpatient as part of the precaution measures, 73,17% (90/123) of the patients who presented with a bleeding at the emergency room were treated inpatient. This implies a severe degree of bleeding. One should, however, take into consideration that all patients were not treated by the same surgeon and inevitably, the admittance criteria were subjective.

The vast majority of the patients, 86 patients, bled on the first postoperative day while 116 patients bled until the fifth day. One can assess the results assuming that the patients came immediately after the bleeding occurred and had not wasted a day or more waiting for the bleeding to stop automatically or trying to find a way to reach the hospital.

When the bleeding occurred after the 10^{th} postoperative day, and assuming that there was no wound trauma during chewing, the existence of a disorder in the healing process would be most probable which, in combination with the underlying disease or medication intake, led to the bleeding. Patients with a coagulation disorder, haemophilia or liver disease bled much later than the ones taking anticoagulation therapy while patients with haemophilia bled later than all patients. Subsequently, especially for patients with coagulation disorders, one should be highly aware of bleeding several days after the operation. On the day that the sutures are removed and later on, there is a high possibility of postoperative bleeding. Patients should be advised to protect the wound, especially when chewing, for several days after the suture removal. Furthermore, the use of resorbable sutures in order to avoid the minimal trauma of suture removal is suggested.

The duration of the inpatient stay depended on medical history. All patients with coronary heart diseases had to be treated inpatient.

An average of 68% of the patients had to stay from 2 until 9,7 days inpatient after the bleeding occurred. Surprisingly, in some cases the duration of the inpatient treatment lasted for more than 20 days. However, we have to notice that Figure 5 also includes patients who were admitted before the bleeding occurred. For this group of patients the duration of the inpatient stay begins on the operation day which is not always the day of bleeding.

The older the patient, the longer is his inpatient treatment. Presumably, this has to do with the condition of his general health and the severity of the underlying diseases.

What can be of great importance is that patients taking phenprocoumon, had to stay inpatient significantly less than patients who had phenprocoumon discontinued or with low molecular weight heparin substituted. Although scarcely statistically significant, patients taking aspirin and patients who had discontinued their aspirin therapy before the operation, had to stay inpatient the same amount of days. This questions the efficacy and need of substituting or discontinuing anticoagulation/antiplatelet therapy before oral surgeries.

Although the results are not statistically significant, it could be of importance that the bleeding after a tooth extraction occurred on average on the second day after the operation, whereas in the cases of sinus augmentation, apicectomy, root scaling or surgical extraction the bleeding is to be expected on the first postoperative day.

5.7 Changes over the years

An increase in the number of patients treated with postoperative bleeding is noticed after the year 2007. It is impossible to know if this is due to the increase of the number of teeth being extracted. Possibly, as years go by, patients suffering from heart diseases are increasing in number and hypertension is becoming ‘a rising tide’ (Fields et al, 2004). As a result, the number of patients in anticoagulation/antiplatelet therapy is also increasing and the risk of postoperative bleeding after tooth extraction in the general population is greater. However, no change was noticed over the years in the number of patients receiving anticoagulants. As there was no change noticed in the number of patients operated in Regensburg hospital and patients operated in other dental clinics, a possible explanation would be that in the last years, dentists having to deal with a postoperative bleeding tend to send the patients to hospital, instead of confronting with the bleeding themselves.

Concerning the wound care measures taken after the operation, lately there is an increase in the number of patients in which no suture or other method of haemostasis was used. Taking into consideration that there was no change noticed in the number of pa-

tients operated in Regensburg hospital and patients operated in other dental clinics, one can assume that dentists have taken earlier more often wound care measures after the operation than they did in the last years. And when measures were taken, assuming mostly in patients operated in Regensburg hospital, then, in the last years, simple sutures are being replaced by approximation of wound edges. The use of tranexamic acid is more common in the last years; the inpatient admittance of high risk patients after the operation is also more common in the last years.

Over the years, the duration of the inpatient treatment after the bleeding has decreased. A possible explanation would be that lately the means to confront bleeding are more effective. Human fibrinogen was used for the first time in 2009 and approximation of the wound edges has been established in the last years. Tranexamic acid has been more often in use after 2007. It seems that haemostatic agents have been established in the daily surgical routine over the past years when confronting with postoperative bleeding.

6 Summary and conclusion

The aim of this study was to investigate the possible relation between postoperative bleeding and age, gender, medical history, medication, type of operation, place of operation, preoperative, intraoperative and postoperative measures against bleeding after minor oral surgeries. This was accomplished by collecting data on all patients who were treated for postoperative bleeding in Oral and Maxillofacial Department of Regensburg Hospital from 2004 until 2009. In the majority of cases, the minor surgical procedure was single or multiple tooth extraction at the upper or lower jaw (88,81%) and in few cases it was root amputation (2,99%), sinus lift augmentation (2,24%), root scaling (2,24%) or spontaneously (0,75%). The operation was conducted in Oral and Maxillofacial department of Regensburg hospital or in alio loco. A number of patients suffered from coagulation or liver disorders (16,2%) and the majority was under anticoagulation/antiplatelet therapy (70%). Wound care measures, such as the approximation of wound edges (11,94%) and the use of haemostatic agents (53,73%) or a splint (29,85%), were used in many patients. Many patients were operated inpatient (24,62%) while others were admitted inpatient after the bleeding (67,16%).

The patients selected as material for this study, 134 in total, were obtained through IS-H med SAP program (GSD-Siemens). The patients classified under one of the following DRG codes (Diagnosis-related group classification) were retrieved: T81.0 (bleeding and haematoma as a complication of a surgery), 5-249.0 (other operations and measures in tooth region: arrest of bleeding), 5-279.0 (other operations and measures in oral and maxillofacial region: arrest of bleeding).

The statistical analysis was carried out with the programme Medas (Grund EDV-Systeme, Margetshöchheim, Germany) and the significance tests were made using U-Test by Mann and Whitney, Chi-Square Test, Chi-Square Test by Fisher and Yates, Kruska- Wallis analysis of variance and exact Chi-Quadrat Test by Mehta and Patel. The results were significant at $p<0,05$.

- Patients with heart or arterial diseases are more likely to present postoperative bleeding because of the anticoagulation therapy they are receiving. Dentists should take accurate medical history placing emphasis on medication list.
- When deciding to discontinue anticoagulation, one should take seriously into consideration the possible embolic complications. The final decision should be taken in correspondence with the physician. The physician must be adequately informed about the nature of the operation. However, the dentist is also obliged to "exercise reasonable professional judgement" (Wahl, 2000).
- We suggest no discontinuation of aspirin before single extractions and in case of multiple extractions or more invasive procedures, additional inpatient surveillance. In case of phenprocoumon, we suggest no discontinuation, and substitution only in case of more invasive procedures. In all cases of phenprocoumon therapy we consider an inpatient treatment necessary.
- Haemophilia patients should always be treated in hospital environment and a haematologist should always be consulted in case of a need to administrate replacement factors.
- In patients with liver disease, the severity of hepatopathy will determine the precautious measures and the need of ambulant or inpatient treatment.
- The most expected site to bleed is posterior maxilla. High awareness is needed especially when extracting upper molars.
- The bleeding is more likely to occur on the first or second postoperative day. However, the risk of bleeding remains for several days after the operation and potentially after the suture removal as well.
- There is a need for dentists to be familiar with the haemostatic agents available which together with several tight sutures can provide, in many cases, adequate haemostasis.
- The use of splint is highly recommended especially after ambulant surgeries.
- Patients receiving anticoagulants and suffering from periodontitis can potentially bleed after root scaling or spontaneously.

- Lege artis treatment of postoperative bleeding includes often inpatient treatment where blood values are constantly monitored and transfusion of erythrocyte concentrate is anytime possible.

7 Zusammenfassung und Schlussfolgerung

Das Ziel dieser Studie war, mögliche Korrelationen zwischen einer postoperativen Nachblutung in der Mundhöhle und Parametern wie Alter, Geschlecht, Vorerkrankung, Medikation, Art der Operation, Ort der Operation, prä-, intra- und postoperative blutstillende Maßnahmen darzustellen.

Dazu wurden die Daten von insgesamt 134 Patienten, die mit einer postoperativen Nachblutung im Bereich der Mundhöhle in der Klinik und Poliklinik der Mund- Kiefer- und Gesichtschirurgie in den Jahren 2004 bis 2009 vorstellig wurden, gesammelt und analysiert. Generiert wurden die Patienten anhand der DRG Kodierung des SAP-Betriebssystems (GSD-Siemens). Folgenden Kodierung wurden untersucht: T81.0 (Blutung und Hämatom als Komplikation einer Operation), 5-249.0 (andere Operationen und Maßnahmen im Zahnbereich: Blutstillung, 5-279.0 (andere Operationen und Maßnahmen im Mund-Kiefer-Bereich: Blutstillung).

Die statistische Auswertung erfolgte mit dem Programm Medas (Grund EDV-System, Margetshöchheim, Deutschland). Zur Auswertung der Ergebnisse dieser Studie wurden folgende Tests herangezogen: U-Test nach Mann und Whitney, Chi-Quadrat-Test, Chi-Quadrat-Test nach Fisher und Yates, Kruska - Wallis Varianzanalyse und exakter Chi-Quadrat-Test nach Mehta und Patel. Als Signifikanzniveau der Testergebnisse wurde ein p-Wert kleiner als 0,05 festgesetzt.

Die chirurgischen Eingriffe wurden in der eigenen Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie sowie durch niedergelassene Zahnärzte, Oral- oder MKG-Chirurgen durchgeführt. In den meisten Fällen (88,81%) traten die Nachblutungen nach Extraktion einzelner oder mehrerer Zähne des Ober- und Unterkiefers auf. Seltener führten Wurzelspitzeresektion (2,99%), sinus lift augmentationen (2,24%), parodontale Kürettagen (2,24%) oder spontan (0,75%) zu einer verstärkten postoperativen Blutung.

Als kausale Ursache der Nachblutung lag bei den meisten Patienten (16,2%) eine Störung der Blutgerinnung vor. Hierbei handelte es sich um Patienten mit eingeschränkter Leberfunktion (5,97%) oder mit einer hereditären Gerinnungsstörung wie einem Von-

Willebrand-Jürgens-Syndrom (7,46%) oder einer Hämophilie A (2,98%). Den größten Teil (70%) stellten jedoch Patienten mit einer antikoagulatorischen Therapie dar.

Als therapeutische Maßnahme wurde zumeist ein primärer Wundverschluss (11,94%) durchgeführt. In meisten Fällen (53,73%) wurden zusätzliche Hämostyptika wie Gelatin oder Kollagen appliziert, bei ausgeprägten Nachblutungen nach Zahnextraktionen wurden Verbandsplatten (29,85%) angefertigt. Bei einem Großteil der Patienten (91,79%) wurde aufgrund einer intraoralen Nachblutung eine stationäre Aufnahme notwendig.

Schlussfolgerungen:

- Postoperative Nachblutung treten häufiger bei Patienten mit Herz- oder Gefäßerkrankungen aufgrund ihrer antikoagulatorischen Therapie auf. Zahnärzte sind zu einer detaillierten allgemeinen Anamnese mit Dokumentation der Medikation angehalten.
- Bei der Entscheidung, antikoagulatorische Medikamente ab- oder umzusetzen, muss eine durch den Entzug der Medikation bedingte erhöhte Morbidität des Patienten (z.B. Embolie, Koronarstenose) mitberücksichtigt werden. Eine Rücksprache mit dem behandelnden Hausarzt ist diesbezüglich zu empfehlen.
- Ein Absetzen der Medikation mit ASS ist vor Einzelzahnextraktionen nicht zwingend notwendig. Im Falle von Reihenextraktionen oder ausgedehnteren invasiven Verfahren ist eine postoperative stationäre Überwachung sinnvoll. Eine Marcumartherapie (Phenprocoumon) kann bei Einzelzahnextraktionen fortgeführt werden. Bei größeren Eingriffen mit erhöhtem Blutungsrisiko ist die Umstellung auf niedermolekulare Heparine indiziert. In allen Fällen ist eine stationäre Überwachung des Patienten zu empfehlen.
- Patienten mit einer Hämophilie sollten unter stationären Bedingungen operiert werden. Vor Verabreichung eines Gerinnungsfaktors ist die Rücksprache mit dem behandelnden Hämatologen erforderlich.
- Bei Patienten mit Lebererkrankung muss vor dem operativen Eingriff das Ausmaß der Hepatopathie durch Rücksprache mit dem behandelnden Internisten bzw. Chirurgen sowie durch ein aktuelles Labor abgeklärt werden.

- Bezüglich der Lokalisation treten Nachblutungen nach Zahnextraktionen am häufigsten im Bereich des posterioren Oberkiefers, der Molarenregion auf.
- Bezüglich des Zeitpunkts kommt es zumeist am ersten oder zweiten postoperativen Tag zu Nachblutungen. Jedoch bleibt das Risiko einer postoperativen Nachblutung auch mehrere Tage nach der Operation bis zum Tag der Nahtentfernung bestehen.
- Der dichte Wundverschluss der Alveole, gegebenenfalls durch eine plastische Deckung und der zusätzlichen Applikation eines Hämostyptikums, ist die sicherste Form der Blutstillung nach einer Zahnextraktion bei Patienten mit einer Gerinnungsstörung. Die Anfertigung einer Verbandsplatte ist besonderes bei rezidivierenden Blutungen oder ambulanten Operationen sinnvoll.
- Patienten mit einer Parodontitis können unter laufender Antikoagulation nach einer professionellen Zahnreinigung und Kürettage bluten. In seltenen Fällen treten Blutungen bei diesen Patienten auch spontan auf.
- Die Behandlung von Patienten mit Nachblutungen bedingt häufig eine stationäre Überwachung. Dabei können die Wundverhältnisse sowie die Laborparameter (Hämoglobin, Gerinnung, Elektrolyte) kontinuierlich kontrolliert werden, zudem sind notwendige Transfusion von Erythrozytenkonzentraten gewährleistet.

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9 Lebenslauf

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Eidesstattliche Erklärung

“Ich erkläre hiermit, dass ich, Maria-Eleni Prokopidi, die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet. Insbesondere habe ich nicht die entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten (Promotionsberater oder andere Personen) in Anspruch genommen. Niemand hat von mir unmittelbar oder mittelbar geldwerte Leistungen für Arbeit erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen. Die Arbeit wurde bisher weder im Innoch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt".

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