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FIBRIN SEALANTS IN MAXILLOFACIAL SURGERY: A INTRODUCTORY REPORT

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The fibrin sealant was first designed as an alternative to surgical suture for the purpose of surface - to - surface union especially in parenchymal organs like the liver, spleen and kidney. The clinical application of currently used fibrin sealant was first introduced in 1972. The fibrin sealant consists of principal two components ; lyophilized human fibrinogen and bovine thrombin. The fibrinogen component also contains coagulation factor XIII. A solution of aprotinin, an inhibitor of fibrinolysis is used to dissolve the fibrinogen and to provide the first component, and a solution of calcium chloride is also used to provide the second component.

From July to December in 1990, during 6 months, we used fibrin sealant in the 28 patients of 33 various cases, in the following ways ; supportive application of fibrin sealant after free autogenouse nerve graft for the repair of inferior alveolar nerve, facial nerve or accessory nerve, treament of hemangioma or lymphangioma to thrombosize and lead to the tumor shrinking, skin grafting to stimulate the adhesion and tissue repair, bone grafting in the patients of cleft alveolus, mandibular reconstruction or orthognathic surgery to facilitate the knitting of bone chips, tissue adhesion after tumor resection, radical neck dissection or flap reconstructions, and supportive adhesion of external auditory cannal after TMJ surgery via postauricular approach. No adverse effects were observed, none of the patients developed hepatitis or other blood transmitted disease, and the wound healing were acceptable.

I. INTRODUCTION

The fibrin sealant was first designed as an alternative to surgical suture for the purpose of surface - to - surface union especially in parenchymal organs like the liver, spleen and kidney. However, early synthetic sealant(cyanoacrylate) were unsuited for this purpose because of their tissue toxicity, poor absorption and stiffness. Limitating the physiologic wound healing process by using the special properties inherent in fibrin appeared to be a logical concept. A tissue adhesive consisting of fibrinogen and thrombin was first tested by Young and Medawar in 1940. However, the poor adhesive effect obtained with fibrinogen - enriched plasma and thrombin prevented the wide spread use of this technique. Improvement in the manufacture of blood products were needed to make tissue sealing with fibrinogen a viable product, as these ensured the production of sufficiantly pure and high concentrated fibrinogen after extensive experimental study. The clinical application of currently used fibrin sealant was first introduced by Helen Matras, in 1972, from Vienna[9,10].

The fibrin sealant consists of principal components : lyophilized human fibrinogen and bovine thrombin. The fibrinogen component also contains coagulation factor XIII, which polymerized soluble fibrin monomers into an insoluble clot. A solution of aprotinin, an inhibitor of fibrinolysis, is used to dissolve the fibrinogen and serves to prolong the life of the

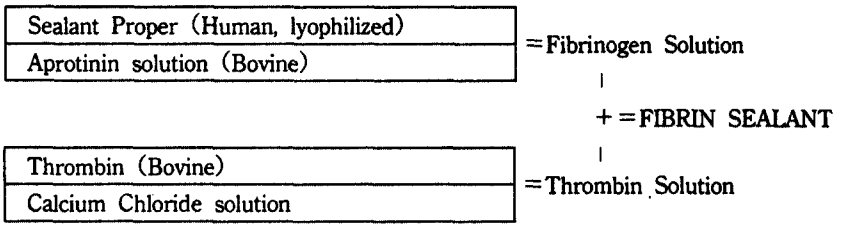

Fig. 1 : The principal components of fibrin sealants

clot. The aprotinin allows the persistence of the clot for 12 to 15 days. The thrombin is dissolved in a solution of calcium chloride to provide the second component. The thrombin concentration may be varied to provide slow(3 min) or fast(30 sec) setting of the adhesive. The main component are listed in figure 1. The action of mechanism are following the normal wound healing process and the degradation of fibrin sealant are following the nomal fibrinolysis mechanism. The glue can be utilized in various way. When immediate gluing is required two syringes containing the components are snapped in a plastic frame, which allows mixing of the solution at the outlet, and through a needle, drops of adhesive are delivered at the desired location. A spray of fibrin glue can be obtained through compressed air delivered at the outlet via sterile tubing attached to the anesthesia machine. The mixture of the two solutions with the compressed air creates an aerosol of fibrin glue[13, 14, 15].

This is a introductory report about the physiologic and biochemical background of fibrin sealant, principles, mode of applications, indications in maxillofacial surgery, and our case presentations.

II. MATERIALS AND METHODS

From July to December in 1990, during 6 months, we used fibrin sealant in the 28 patients of 33 various cases diagnosed as squamous cell carcinoma, carcinoma in situ, mandibular prognathism, open bite, hemangioma, lymphangioma, neurofibroma, cleft alveolus, traumatic bone cyst, atrophic alveloar ridge, facial trauma and degenerative joint disorders(table 1), and used in the following ways ; supportive application of fibrin sealant after free autogenous nerve graft for the repair of inferior alveolar nerve, facial nerve or accessory nerve, treament of hemangioma or lymphangioma to thrombosize and lead to the tumor shrinking, skin grafting to stimulate the adhesion and tissue repair, bone grafting in the patients of cleft alveolus, mandibular reconstruction or orthognathic surgery to facilitate the knitting of bone chips, tissue adhesion after tumor resection, radical neck dissection or flap reconstructions, and supportive adhesion of external auditory cannal after TMJ surgery via posterior auricular approach (table 2). We use two commercially produced fibrin sealants ; Tisseel^{R} and Beriplast^{R}, the composition are listed in table 3 and 4.

Table 1 : Patients used fibrin sealants

Diagnosis	patients
Squamous Cell Carcinoma	3 cases
Carcinoma in Situ	1 cases
Ameloblastoma	1 cases
Hemangioma	2 cases
Lymphangioma	3 cases
Neurofibroma	1 cases
Cleft Alveolus	4 cases
Traumatic Bone Cyst	1 cases
Atrophic Alveolar Ridge	3 cases
Mandibular Prognathism	5 cases
Open Bite	1 cases
Facial Trauma	2 cases
Degenerative J. Disorder	1 cases
Total	28 patients

Table 2 : Various operations indicated using fibrin sealants

Indications	Cases
Microsurgical nerve anastomosis	3 cases
Hemangioma or lymphangioma	5 cases
Skin grafts or mucosal grafts	7 cases
Bone grafts	10 cases
Myocutaneous or skin flap	5 cases
Adhesion of primary closure wound	3 cases
Total	33 cases

Table 3 : The composition of Tisseel[R*] (1.0ml kit)

Sealant Proper (lyophilized, human plasma)	
Fibrinogen	70 - 110mg
Factor XIII	10 - 50u
Plasmafibronectin	2 - 9mg
Plasminogen	40 - 120ug
Aprotinin Solution (Bovine)	3000 KIU/ml
Thrombin (lyophilized, Bovine)	4IU
	500IU
Calcium Chloride solution	40mmol/L

* Manufactured by Immuno AG, Vienna, Austria

Table 4 : The composition of Beriplast[R**] (1.0ml Kit)

Sealant Proper (lyophilized)	
Fibrinogen (Human Plasma)	65 - 115mg
Factor XIII (Human Placenta)	40 - 80u
Aprotinin Solution (Bovine)	1000 KIU/ml
Thrombin (Bovine)	400 - 600IU
Calcium Chloride solution	40mmol/L

** Manufactured by Behringwerke AG, Marburg/Lahn, Germany

III. RESULTS

Nerve anastomosis were performed in 3 cases, in the first case of facial trauma, 3 branches of facial nerve were completely severed and we performed sural nerve grafting to repair the facial nerves, in the second case of squamous cell carcinoma, we reconstructed the accessory nerve using sural nerve grafting after radical neck dissection, and in the 3rd case, we repaired the inferior alveolar nerve and reconstructed the mandible with bone grafing after resection of amelobastoma. In nerve anastomosis, we reunioned the nerve by group fascicular suture and applied fibrin sealants for the purpose of supporting the nerve approximation.

For the treatment of hemangioma and lymphangioma, we used fibrin sealant in 5 cases for adjunctive measure. Before gross removal of tumor with surgical maneuver, fibrin sealants were injected into the lesion for the effect of quick thrombosis and hemostasis, for the purpose of fibrosis and diminish the size of hemangioma, as the same effect of embolization.

Supportive application of fibrin sealants for skin grafting or mucosal grafting were performed in 7 cases, after maxillectomy(Fig. 2), partial glossectomy by squamous cell carcinoma, or mucosal graft for the vestibuloplasty in atrophic alveolar ridge with deficient vestible.

For the holding of bone chips and particulated marrow and cancellous bone(PMCB) in bone grafting procedure, we used fibrin sealant in 10 patients, after two - jaw surgery by the cases of maxillary deficiency and mandible prognathism, after alveolorrhaphy, after

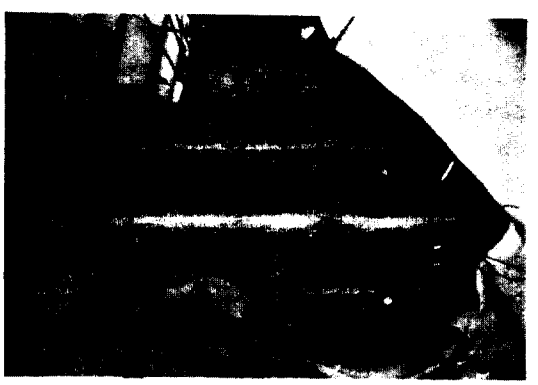

Fig. 2. Application of fibrin sealants for skin grafting after maxillectomy by the case of squamouse cell carcinoma

Fig. 3. Supportive adhesion of suture site on external auditory canal

mandibular sagittal split ramus osteotomy and body osteotomy by mandibular prognathism, and by the cases of mandibular reconstruction. The bone chips and PMCB are ordinarily difficult to hold with other method. In our cases, bone chips and PMCB are packed sufficiently and fibrin sealants are used for the supportive measure of knitting the grafted bone chip.

In the flap reconstruction after radical resection of tumor and after parotidectomy or other major surgical treatment, fibrin sealants were used for intimate adhesion of soft tissue and hemostasis. This improved the results by reduced dead space and hematoma formation, and improved final wound healing were obtained. And in the TMJ surgery via postauricular approach, the fibrin sealants were used for the supportive adhesion of external auditory cannal(Fig 3).

Postoperatively, in all patients of our cases, no adverse effects were observed and none of the patients developed hepatitis or other blood transmitted disease, none of the cases developed wound infection or dehiscence, and the wound healing were acceptable.

Ⅳ. DISCUSSION

The use of sealants for wound healing has been advocated with increasing frequency in the past 10 years. All of these sealants had the disadvantage of being made of an artificial material that could possibly result in significant impairment of wound healing, not to mention the uncertain oncogenic effects. With the introduction of the fibrin sealant, however, a biologic material for wound healing became available. It had the major advantage of complete degradation and consequently full compatibility with the tissue. The fibrin sealant is a homologous material. as a consequence, local and systemic toxicity are absent[9, 10, 17].

The use of fibrin as a biologic adhesive as we know it today began with the studies of Matras, in 1972, who successfully employed a fibrinogen cryoprecipitate for reuniting peripheral nerves in animal experiments. And in 1975, autologous material were used first successfully in human application. The development of a special cryoprecipitation process was needed before the production of a highly concentrated fibrinogen solution with an enhanced factor XIII content become a reality. Additional problems such as the delayed fibrin degradation were solved by including aprotinin, which is an antiprotease isolated from bovine pancreas[9, 10].

The fibrin sealant is available as a freeze-dried powder in a kit together with thrombin, calcium chloride, and aprotinin solution. The substances in the kit are used to prepare two components: sealer and thrombin solution. To obtain the sealer solution, protein concentrate is dissolved in the accompanying stock solution of fibrinolysis inhibitor(aprotinin solution) or a dilution of it[13, 14, 15, 19].

When thrombin is mixed with fibrinogen or with plasma containing fibrinogen, most steps of the mechanism of coagulation can be bypassed and the reactions depicted in figure 4. Thrombin is the active enzyme that splits the fibrinogen molecule. Fibrinogen consists of three double chains, A-α, B-β and γ. The latter two have carbohydrate side chains and all three chains are cross-linked by 29 disulfide bridges. In a fast reaction thrombin splits peptide A from

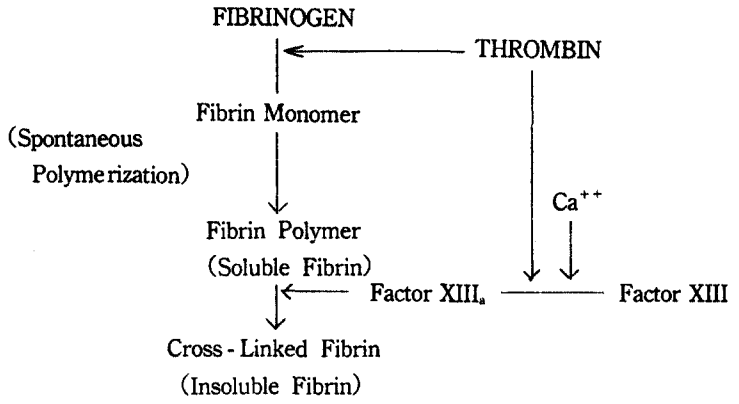

Fig. 4. Final steps of coagulation

the A-α-chain and in a somewhat slower reaction, peptide B is split from the B-β-chain. Fibrinogen is thereby transformed into fibrin monomer. Soon after the loss of peptide A the molecules begin to form longitudinal polymers between α-chains. This results in macroscopically visible fibrin strands which still have a very low rigidity, however. The structure of the fibrin clot is called Des-A-polymer. Splitting off of the B-chain from the remaining molecule results in further cross-linking. Polymerization then goes on between the C-terminal ends of the fibrin monomers and between the N-terminal ends of the exposed α and β chains. The result is a side-to-side polymerization in addition to the longitudinal polymerization. This product is called soluble fibrin because it can be depolymerized by 5 mol/L urea[15, 19].

A further increase of cross-linking, and therby rigidity, is achieved by the action of faxtoir XIII. This protein consists of two pairs of polypeptide chains called a-and b-chain. In the presence of Ca^{++}, thrombin splits a peptide from the N-terminal end of the a-chain, thereby activating factor XIII to factor $XIII_a$. In the presence of Ca^{++} the chains disassociate to form an active a_2-dimer and an inactive b_2-dimer. The a_2-dimer forms peptide bonds between a glutamic acid side chain of an α-chain of the fibrin polymer and a lysine side chain of another α-chain by splitting off ammonia. By this reaction the fibrin clot is considerably strengthened. It is now insoluble in urea and is the end product of coagulation[15, 19].

Factor $XIII_a$ carried out another important function. By its action a high-molecular-weight glycoprotein, known as cold-insoluble protein or fibronectin, is bound to the α-chain of the fibrin polymer as well as to collagen. Since collagen is present in subendothelial structures of blood vessels as well as in most tissues there is a firm attachment of the fibrin clot to the wound[13, 14, 15, 19].

The proenzyme of fibrinolysis, plasminogen, is present in plasma and is absorbed onto the fibrin clot. Plasminogen can be activated into the enzyme plasmin in several different ways. Endogenous activation is brought about by factor XII_a which is formed from factor XII in an early stage of activation of blood coagulation. Exogenous fibrinolysis is activated by a tissue activator present in the vascular endothelium. The resulting plasmin is capable of splitting fibrin into soluble fibrin degradation products. This process is controlled by plasmin inhibitors in plasma. Such inhibition, however, cannot completely prevent a slow fibrinolytic action inhibition, however, cannot completely prevent a slow fibrinolytic action by activation of plasminogen attached to the fibrin clot. This can be prevented by synthetic or natural inhibitors in sufficiently high concentration. The mechanism of fibrinolysis is shown in figure 5[15, 19].

The fibrin sealant consists of two composition. The first component consists of lyophilized human fibrino-

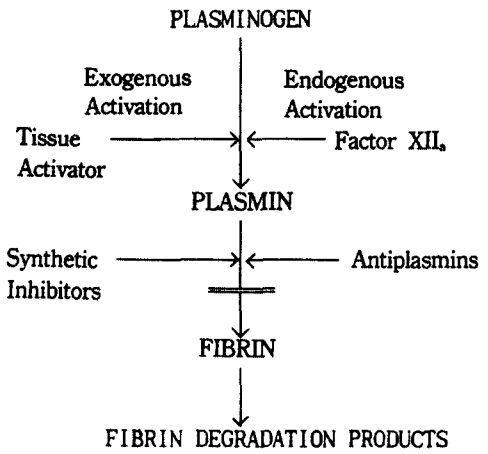

Fig. 5. Mechanism of fibrinolysis

gen, factor XIII, and fibronectin. Variable amounts of aprotinin, a plasmin inhibitor, can be added. The second component is lyophilized thrombin, which is reconstituted with calcium chloride solution. The velocity of the primary reaction depends on the concentration of thrombin. When equal amounts of thrombin and fibrinogen are mixed at 37°C a fibrin clot results in about 30 seconds when the concentration of thrombin is 2 IU/ml. At a concentration of 50 IU/ml fibrin is formed within less than 10 seconds. The secondary reaction, a cross-linking of α-chains by factor XIII$_a$, depends on the final concentration of calcium chloride and on the final ionic strength[15, 19].

There are different ways of mixing the components when a fibrin seal is applied. Application of thrombin in a high concentration of more than 50 IU/ml results in rapid clotting of fibrinogen at the interface of the two components. In consequence there is insufficient mixing of thrombin and fibrinogen, resulting in poor rigidity of the clot. When a low concentration of thrombin of 4 IU/ml is used, premixing of the components is possible without immediate clotting. By this slowing down of the process the components are thoroughly mixed. This method resulted in a considerably higher rigidity of the clot. The final degree of fibrin cross-linking was therefore higher when this method was applied[13, 14, 15, 19].

Fibrin and factor XIII both stimulate the growth of fibroblasts, and fibronectin plays an important role in the regulation of cell growth and thereby also are completely absorbed. This is partly due to degradation by fibrinolysis but probably also a consequence of phagocytosis. A lysis time of between 7 and 10 days was sufficient since the fibrin sealant should yield to wound healing and should eventually be completely absorbed[12, 13].

The development of the fibrin sealant system resulted in a new, safe tool that could be applied for topical hemostasis, for support of wound healing, for the sealing and coating, for glueing of different tissues, and for suture support. The side effect of fibrin sealant and the interactions with other drugs were not known[13, 14, 19]. Neither hepatitis virus nor HIV transmition are detected[3, 19]. The advantages of this system include its physiologic components, the strength of the sealant's cohesion and adhesion, and its complete absorption during the process of wound healing[12]. The indications in the maxillofacial surgery are nerve anastomosis[1], treatment of hemangioma[8,20], skin graft [5, 6, 7, 18], bone chip or PMCB holding in bone graft[2, 9] and tissue adhesion in flap reconstruction[4, 11] or all other surgery at the final stages of replacing the soft tissue and in the periodontal flap surgery in dental practice[16, 17].

V. SUMMARY

We used fibrin sealants in the 28 patients of 33 various cases as following ways : in the cases of microsurgical nerve anastomosis for suppportive approximation of suture site, in the cases of hemangioma or lymphangioma to thrombosize and reduce the tumor and hemostasis, for securing the adhesion and stimulating the tissue repair of skin or mucosal grafts, for knitting the grafted bone chips and PMCB, for support of skin or myocutaneous flap surgery, and to secure the primary suture support. No adverse effects were observed, none of the patients developed hepatitis or other blood transmitted disease, no wound infection, and the wound healing were acceptable.

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국문초록

악안면 외과 영역에서의 FIBRIN SEALANTS의 이용

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Fibrin Sealants는 과거 간, 비장, 신장등의 일반외과 수술에서 단순한 외과적 봉합으로는 해결하지 못하는 넓은 면적의 조직의 유착을 위하여 1940년경 부터 개발되기 시작한 것으로 악안면 영역에서는 1970년대 중반부터 미세신경접합술과 피부이식을 위하여 사용되기 시작한 후, 현재, 골이식후의 골세편의 고정, 혈관봉합술, 연조직에서 조직들의 유착과 지혈, 그리고 혈관종의 치유등을 목적으로도 광범위하게 연구되고 사용되고 있다. 이것은 인체에서 채취한 혈액응고인자 XIII을 포함하는 Fibrinogen성분과, 소에서 추출한 Thrombin의 두가지 주요 성분으로 구성되며, Fibrinogen 용해제인 Aprotinin액과 Thrombin 용해제인 염화칼슘액과 함께 네부분으로 구성된다. 각제품에 따라 그리고 사용된 농도에 따라 차이는 있으나, 대개 수분후에 조직이 응고되어 달라붙기 시작하고, 수시간후에 최대접착효과에 도달하며, 응고된 접착효과는 12일에서 15일간 유지되고 그후 정상적인 섬유소분해작용과 식세포활동에 의하여 분해된다.

저자는최근 6개월간 서울대학교병원 구강악안면외과에서 28명의 각종 질환 및 기형 환자에서 미세신경봉합술, 피부이식, 악교정성형술과 구개파열 또는 하악골 재건을 요하는 환자의 골이식후의 골세편의 고정, 경부곽청술이나 종양제거술후 각종 피부판 또는 근피판을 이용한 연조직의 적합, 혈관종의 처치, 후이개접근 법에 의한 악관절수술후의 외이도의 접합등 다양한 목적을 위하여 적용된 Fibrin Sealants를 사용하여 양호한 결과를 얻었기에 보고하는 바이다.