SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

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PROJECT REPORT

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Programme : M.Ch. NEUROSURGERY

Month and Year of Submission : NOVEMBER - 2000

PROJECT REPORT

TITLE OF THE PROJECT:

CLINICAL TRIAL OF CHITRA FIBRIN GLUE IN NEUROSURGICAL PROCEDURES

Name	:	**RAKESH KUMAR GOYAL**
Programme	:	**M.Ch. NEUROSURGERY**
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CERTIFICATE

I, Dr. **Rakesh Kumar Goyal** hereby declare that I have actually performed all the procedures listed/carried out the project under report.

Signature:

Place: Thiruvananthapuram

Name in capital letters:

Date : 1st November -2000 **(RAKESH KUMAR GOYAL)**

Forwarded. He has carried out the minimum requirement of procedures / etc.

3.11.2000

Signature

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I am grateful to my parents , my wife Monica and my child Tanmay who were always there for my endeavors.

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RAKESH KUMAR GOYAL

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Preface

PREFACE

Cerebrospinal fluid (CSF) leak is the single most dreaded complication of any intracranial procedure. CSF leak may manifest as fulminant meningitis in an unfortunate patient whereas in others it may manifest as CSF rhinorrhoea, otorrhoea, pseudomeningocele, and persisting CSF fistula. CSF leakage through dura increases the risk of complication such as persisting CSF fistula, meningitis and subcutaneous, bone graft or epidural infection. Sealing all routes of CSF drainage to outside of the intracranial content, is thus an essential part of any neurosurgical procedure as the consequences may at times be fatal.

Various techniques have been tried and various materials used to prevent postoperative CSF leak. This is usually achieved by muscle and fat plugs, homograft dura, fascia and sutures. Fibrin glue has been a recent addition to the above group of surgical adhesives. The use of fibrin glue might affect and lessen the likelihood of CSF leak. The use of autologous fibrin glue, as an adjunct to dural closure, is an effective means of preventing CSF leak following various neurosurgical procedures.

The high cost of the glue and the lack of availability of the currently available fibrin glue have been a serious handicap. It was to overcome this problem that the biomedical research wing of Sree Chitra Tirunal Institute for medical sciences and technology developed an indigenously devised version of fibrin glue. The production methods and material characteristics are briefly described in this study. This version is comparable in strength to other formulations, yet is simpler and more convenient to produce. This study was conducted to evaluate the efficacy of the Fibrin Glue when used as an adjunct to dural closure along with primary dural closure alone, sutures with graft and packing with fat and fascia in human being in various neurosurgical procedures and comparison with the control group when dura is closed with suture alone.

Introduction

INTRODUCTION

Medical adhesives are a material capable of interacting with the tissue to form a strong bond. Fibrin sealants appear to be the first truly successful surgical adhesive technology in medicine, which offer Neurosurgeons and clinicians a valuable and versatile tool in their treatment armamentarium.

Fibrin sealant or glue, a surgical adhesive has gained widespread use for its ability to achieve three major clinical goals: reducing hemorrhage, increasing tissue adherence and allowing drug delivery. A variety of factors are driving interest and movement towards the use of widely manufactured glue. These include improved production methods, enthusiasm for minimally invasive procedures, and aggressive efforts at cost containment. The object of this state of the art review is to clarify the most recent developments in the field from a surgical perspective especially in Neurosurgery.

Commercially available fibrin glue fulfills almost all criteria except that it is not readily available in India at economical rates and most important it is not safe because it is obtained from pooled plasma .The tissue adhesives from blood components or

synthetic chemicals designed to meet these criteria successfully are the subjects of intense commercial interest (20).

Non-commercially produced forms of fibrin glue are becoming increasingly popular. The fibrinogen used in these non-commercial products is derived from blood plasma by cryoprecipitation or chemical precipitation and is then combined with commercially available bovine thrombin to create the adhesive (17). Fibrin glue is thus of significant interest to the surgeons (1).

It was to overcome this problem that the biomedical research wing of Sree Chitra Tirunal Institute for medical sciences and technology developed an indigenously devised version of fibrin glue. The production methods and material characteristics are briefly described in this study. This version is comparable in strength to other formulations, yet is simpler and more convenient to produce. This study was conducted to evaluate the efficacy of the Fibrin Glue when used as an adjunct to dural closure along with primary dural closure alone, sutures with graft and packing with fat and fascia in human being in various neurosurgical procedures and comparison with the control group when dura is closed with suture alone.

Aims
&
Objectives

AIMS AND OBJECTIVES

Thrombosis unit of Biotechnology department of SCTIMST developed indigenous fibrin glue derived from single donor plasma and without Aprotinine. Efficacy of the glue was studied earlier in the laboratory animal and was found to be effective as a biological adhesive. Present prospective study was undertaken to evaluate the clinical feasibility, usefulness and effectiveness of the indigenously and single donor plasma derived fibrin glue as an adjunct to dural closure in varieties of neurosurgical procedures.

The essential aims and objectives of the study were:

1. Clinical human trial of the fibrin glue as a surgical adhesive and sealant.

2. Comparison of fibrin glue with other currently available techniques of dural repair viz, primary dural closure, dural graft with suture, onlay dural grafts.

3. Assess the relative merits and demerits of the fibrin glue with special reference to tissue reaction.

Material and Methods

MATERIALS & METHODS

This prospective study was conducted over a period of about one year. During the period between March 1999 to April 2000, a total of 33 patients were operated in the department of Neurosurgery using fibrin glue as an adjunct to dural closure in order to prevent CSF leakage.

Fibrin glue in this study was supplied from the biomedical and research wing of SCTIMST. The glue was available as component I and component II along with an applicator. The component I (concentrated fibrinogen) prepared by cold precipitate technique from single donor unit of human plasma screened for hepatitis B surface antigen and human immuno-deficiency virus antibody. The concentrated fibrinogen combined with topical bovine thrombin to produce fibrin glue. Both components are applied using dual syringe system.

The criteria for use of fibrin glue, as an adjunct to dural closure was where a watertight closure could not be achieved using conventional methods of dural closure with or without a free graft. Most of the patients in whom fibrin glue was used, were thought to have a high propensity of CSF leakage due to insufficient quantity or quality of the

dural closure or because of the anatomic location like sellar floor, skull base etc.

When sufficient dura was available, closure was done with 3/0 non-absorbable dural suture with simple running stitches. If significant CSF leakage persisted after dural closure fibrin glue was used to seal leakage in one of the two ways. In the first technique small leaks were sealed by keeping the suture line dry with gentle suction and cotton pledget before the application of fibrin glue alone. In the second technique large defect in dura were closed using fascia lata, fat, pericranium graft and suture line were covered with fibrin glue. With all craniotomies the galeal layer were closed using multiple interrupted absorbable suture and skin was closed with running 1/0 silk non-absorbable suture. While in all spinal cases the paraspinal musculature and overlying fascia were closed in two layers using 1/0 monofilament absorbable suture in a water tight fashion and skin was closed using interrupted 1-0 silk, non absorbable suture.

Review of Literature

REVIEW OF LITERATURE

At the end of 17th century, Malpigtis realized that blood clotting is caused by the precipitation of a substance, which was first called fibrin by Chaptal about 100 years later. Going through the textbooks, at random, one finds the following statement as early as in 1890:

"Escaping the living organism blood will soon clot and the protein constituent called fibrin is responsible for this. Fibrin is dissolved in blood but it becomes insoluble outside the blood vessels. Pure fibrin has neither color nor flavour and it resembles albumin".

BERGEL (1909) - First used fibrin to establish haemostasis (2). The use of substances containing fibrin for wound management and haemostasis began as early as in World War I. At that time, GREY and HARVEY used fibrin tampons and patches to control surgical bleeding (9).

Ability of fibrinogen to function as an adhesive was noted in 1940 by YOUNG and MEDAWAR (35). They used it in sealing of peripheral nerves. Fibrin sealant development was further advanced by CRONKITE et al (1944), when fibrinogen and bovine thrombin were mixed to produce a biological adhesive (5). Effectiveness of fibrin sealant

was significantly enhanced in 1972 by MATRAS who developed a more concentrated form of fibrinogen for use in the final adhesive (21).

YOUNG and MEDAWAR (1940) tried to unite severed sciatic nerve in rabbits using fibrinogen, supplemented with chick plasma clotted by chick embryo extract (25).

In the year 1974 Dr. KUNDENNA from traumatology center of Vienna first time used cryoprecipitated fibrin, extracted from patients own blood to reunite severed digital nerve.

GREY and HARVEY produced fibrin sheets for haemostasis in cerebral surgery and as parenchymal tissue dressing (8,16). YOUNG and MEDAWAR initiated the use of fibrinogen as an adhesive in 1940 and CRONKITE et al, were the 1st to use the fibrinogen in plasma in combination with bovine fibrinogen as a biologic glue in 1974 (5).

Fibrin tissue adhesive (Glue) is the name given to products, originally made from plasma protein, that mimic the last step of physiological coagulation cascade to from fibrin clot. The idea dates back to beginning of the century.

A variety of different names have been used to refer to surgical tissue adhesive based on the combination of fibrinogen and thrombin to form fibrin. Numerous references in the literature have used the term fibrin glue. As enthusiasm has grown for the use of commercial products, the term fibrin sealant has become more popular. Clearly the more generic way of referring to this form of surgical adhesive is the term fibrin tissue adhesive (FTA). However this terminology has not yet gained enthusiasm in the literature and at present the most frequent used term is fibrin sealant.

W.D.Spotnitz proposed to use the term fibrin sealant when referring to individual form of specific blood bank-produced or commercially available produced or commercially available products and the term fibrin tissue adhesives when referring to the global family of products that are presently in various stages of development. (22,30,32)

Although surgeons have cut and sewn tissue as far back as 3500 BC (29), the surgical use of glue or adhesives has only been a recent phenomenon (3). Fibrin has been used as a homeostatic agent in neurosurgical procedure since 1915 and in peripheral nerve repair since 1940(30). In Europe commercial fibrin tissue adhesives products have been used

extensively for almost 20 years for a variety of indications including haemostasis, sealing, adhesive (gluing) and slow release of various materials like antibiotics and growth factors. In USA the FDA has still not approved commercial fibrin tissue adhesives due to lack of data on safety and efficacy and risk of transmission of blood born diseases.

CHEMISTRY OF COMPONENTS

Fibrinogen – (Component I) It is the main structural component of fibrin sealants. The monomeric form of fibrin, in conjunction with platelets forms the basis of a clot (4,15). Fibrinogen a 3400 kD plasma protein circulates freely in plasma at a concentration of 2 to 5 mg/ml with a half-life of 7 days. It is produced primarily by hepatocytes and secondarily by platelets. It exists in a dimer form. Each identical unit consist of three polypeptide chains- A: alpha (64kD), B: beta (57kD) and gamma (48kD), which are bound together by 28-29 disulphide bridges predominantly in the N - terminal region. Fibrinogen contains a cell surface receptor (integrin) binding sequence (Arg - Gly- ASP - X) on the X-chain. The molecule is primarily a rod shape at neutral pH and measures 45 nm in length with three globular domains, two at each end, with a diameter of 60 degree and smaller one in the middle, with a

diameter of in 40 degree. These regions are linked together by L-helical regions, which make up 30% of the amino acid sequence. There are two random coiled region of several hundred residues projecting from the D-domains that contains amino acid which participate in fibrin cross linking by factor XIII. The D- domain also contains Calcium binding sites (two with high affinity and four with low affinity.

Fibrinogen is converted from the monomeric to polymeric cross-linked fibrin by a series of reactions. The first step involves proteolytic removal of two fibrinopeptide A and B, located on the alfa and beta chains respectively. This cleavage alters the charge and conformation of the molecule. The fibrinogen is now called fibrin monomer and it begins to aggregate with other monomer .The fiber then elongate and anastomose as well as increases in diameter eventually forming a three dimensional structure.

B. **Factor XIII** (Fibrin stabilizing factor)-Factor XIII (320 kD) produced by hepatocytes, freely circulates in plasma as a zymogen in the form of noncovalently bound tetramer (Alfa 2 Beta 2) (4,15) The platelets also carry factor XIII in small amounts. Plasma concentration of factor XIII is 0.01 -0.02 micro gram /ml. The half-life is 10 days. It becomes active

when calcium binds the alpha 2 subunit and thrombin cleaves the Beta 2 subunit. The active form designated as factor XIIIa. The resultant product catalyses amide bond formation to form alpha glutemyl-e-lysyl linkages between alpha and gamma chain in fibrin. It also covalently cross links alpha 2 plasmin inhibitor, Fibronectin, plasminogen and perhaps collagen to fibrin (6). It also covalently cross links the Gp IIb/IIIa Platelet cell membrane receptor (integrin) which in turn cross links to myosin and actin, thus linking fibrin

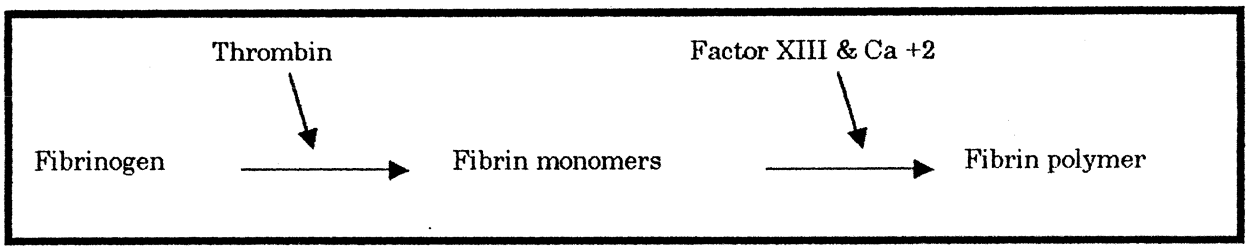
C. **Fibronectin** – It is a large glycoprotein found in both plasma and connective tissue. It has many roles including cell attachment factor, opsonising agent and adhesive. (24). A wide variety of proteins interact with Fibronectin. Collagen, fibrinogen and GPIIb/IIIa cell surface receptor complex all covalently bind to it. Fibronectin complexes with fibrinogen, factor XIII & Von willebrand factor in cryoprecipitation, acts as a nucleus for precipitation. It has a circulating concentration of 0.2 to 0.4 mg/ml & exists as a dimer each subunit of which has a mass of 220kD. Fibronectin is necessary in wound healing as confirmed by reports that Fibronectin free fibrin gels do not support fibroblast growth. (11)

D. THROMBIN (component II): is a serine protease (39kD) that enzymatically cleaves fibrinogen to initiate polymerization. Both fibrinopeptide A & B are cleaved (4,15) from fibrinogen chain alfa and beta respectively. Fibrinopeptide A cleavage is associated with end-to-end fibril association & fibrinopeptide B cleavage is associated with lateral fibril association. The enzyme circulates as factor II (prothrombin, 0.15mg/ml plasma). It is cleaved by factor Xa in presence of factor V to form active thrombin near the end of coagulation cascade. Thrombin is mitogenic for fibroblast in wound healing (26)

E. PLASMINOGEN & OTHER FIBRINOLYTIC ENZYME: Plasminogen (93 kD) is the zymogen form of the primary fibrinolytic enzyme plasmin (15). The plasma level of plasminogen is 0.2 mg/ml. Plasminogen is converted to several enzymatic activators like endogenous component urokinase, t-PA, factor XII, kininogen, prekallikrein plasmin itself (autolytic chain reaction) and exogenous activators like streptokinase and recombinant t-PA. Macrophages fibroblast and polymorphonuclear leukocytes also produce proteolytic enzymes that are capable of degrading the fibrin gel

F. Antifibrinolytics: - These can block the conversion of plasminogen to plasmin or directly complex with the active site of plasmin to inhibit fibrinolysis. (19) The primary physiologic inhibitors are alfa-2 macroglobulin (725 kD, 2-5mg/ml), glycoprotein alfa-2 antiplasmin (alfa2-protease inhibitor, 70kD), Antithrombin III & alfa-1 antitrypsin (54 kD)

Exogenous most effective antifibrinolytic agent is Aprotinine used in various fibrin sealant formulations. It is obtained from bovine parotid gland and lung (6.7kD) (33). Another agent is epsilon amino caproic acid. [EACA]. At low concentration it acts as plasminogen activator inhibitor. In various preparations, concentration of at least 10mg/ml in the fibrin clot has been shown to be effective in reducing fibrinolysis (10). Fibrin clot formation requires the simultaneous application and mixing of equal volume of the two separate solutions one containing fibrinogen & factor XIII and the second containing thrombin and calcium chloride. When these two solutions are combined they replicate the final pathway of fibrin clot formation. The basic reaction can be represented as follows



The rate of reaction and strength of the clot formed can be manipulated by altering the concentration of various components. The concentration of thrombin and to lesser extent calcium determines the rate of the reaction, whereas the fibrinogen concentration primarily determines the tensile strength of the clot formed. This characteristic affords a great deal of versatility applicable to a range of clinical needs.

MECHANISM

In general Fibrin tissue adhesives mimic the last step of the physiological coagulation mechanism in which thrombin splits off fibrinopeptide A & B from the fibrinogen chain to form monomer which polymerizes to produce a fibrin clot at the site of application independent of patients coagulation process. Fibrin sealants are biological adhesive derived from blood. These adhesive system exploit the final stage of the coagulation cascade. Fibrinogen the main structural protein in the blood responsible for forming clots is proteolytically cleaved and converted into fibrin monomer by thrombin,

a serine protease that is converted from its inactive form by factor Xa. Fibrin monomer assembles into fibrils, eventually forming fibers in three-dimensional network (gel).

Another serine protease, factor XIII, is proteolytically cleaved by thrombin in the presence of calcium ion into its activated form. The activated factor XIII (XIIIa) then convert noncovalent bonds between the assembled fibrin monomers into covalent bonds by transamination. This renders fibrin gel less susceptible to proteolytic digestion by plasmin and also increases the overall strength and stiffness of the gel. This gel adheres to a variety of adherents such as collagen and cell surface receptors, most notably integrins.

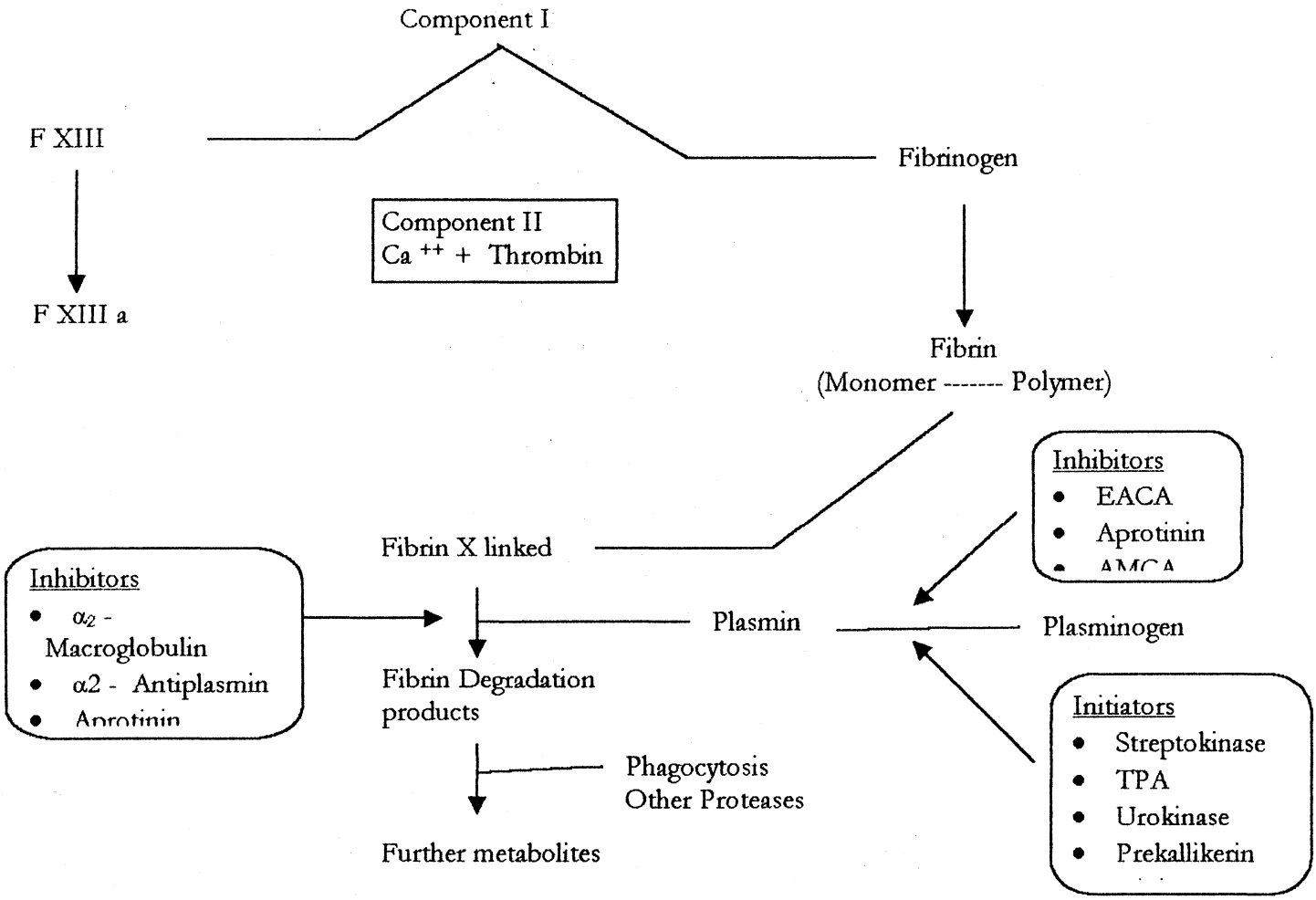
This coagulation process can be readily engineered into an adhesive system, usually by having the fibrinogen and factor XIII as one component analogous to the resin of a two part epoxy kit and thrombin in a calcium chloride solution as the second catalyst component These component may be applied sequentially or simultaneously to the repair site by syringe or by spraying.

Prior to polymerization fibrin glue act as a flowable or sprayable sticky liquid, readily adhering to wet surfaces. Once polymerized in situ by the

addition of thrombin and calcium it becomes a semi rigid, haemostatic, fluid tight adhesive mass, capable of holding tissue or materials in a desired configuration. They offer clinicians a valuable and versatile tool in their treatment armamentarium. Fibrinogen concentrate also contains proteins such as XIII factor, adhesive glycoprotein such as Von Will brand Factor (VWF). Fibronectin (fn) & probably thrombospondin (TSP) and vitronectin (Vi). They also contain plasmin inhibitors including alfa2-plasmin inhibitor (alfa2-PI), alfa2-macroglobulin and plasminogen activator-inhibitor 2.

Thrombin activates factor XIII to XIIIa which catalyses formation of amide cross-linking between glutamine and lysine residues in a variety of proteins. Cross-linking of fibrin polymer stabilizes the clot while the cross linking of the plasmin inhibitors (mainly alfa2-PI) to the chain of fibrin enhances clot resistance against proteolytic degradation by plasmin. Although fibrin cross links directly with collagen, the cross linking between the adhesive glycoprotein and fibrin on one side to collagen and tissue adhesive glycoprotein at the site of injury on the other side, anchors the clot firmly to that site. Platelet may also play a role in contributing would healing and adhesive property.

Coagulation and Degradation Cascade of Fibrin Glue



Neurosurgical application:

1. Dural defect located at the base of skull, over the cortical convexity and along the spinal canal have all been repaired successfully with fibrin sealant (29). This can be done using a suturing sealing technique in combination with fascia and

lyophilized dura. In this situation, the glue simplifies the surgical technique and provides a leak proof dural seal.

2. Fibrin glue has proved useful in the anastomosis of nerves and nerve graft in patients in whom nerves have been injured by trauma or by tumour excision, main advantage over suture is that the procedure is shorter and the anastomosis is easier to perform, especially in areas where access is difficult.

3. Fibrin sealant can help provide haemostasis during the operative treatment of large vascular tumour (30), Intracerebral haematoma or frontobasal injuries (31). The glue has been used to reinforce cerebral saccular aneurysms (32) and to seal intracranial microvascular anastomosis. (31) Carotid cavernous fistula has been repaired using a fibrin adhesive system (33). Two-component fibrin system can be employed in the fixation of bone fragments or in a fibrin bone dust mixture to repair small skull defects.

Risk:

1. Fibrin adhesives are manufactured from blood and are thus associated with the risk of viral blood - borne disease transmission.

These dangers can be eliminated by using autologous sources of fibrinogen, commercially prepared glue using large pools of plasma have dealt with variety of viral sterilization techniques.

2. Fibrin sealant without accompanying antibiotics can serve as a bacterial growth medium potentiating infection.

3. Recent report suggest that bovine thrombin required for use with fibrinogen to produce adhesive can induce antibodies to thrombin and factor V creating significant clotting abnormalities (34).

4. Bovine thrombin inoculation into systemic circulation may have been the cause of hypotension and /or anaphylaxis seen with use of fibrin glue (35). There risks can be minimized using human thrombin. (IgE mediated)

5. Theoretically it can spread via CSF pathway and can cause adhesive arachnoiditis.

Reported uses of Fibrin glue in Neurosurgery practice are:

1.Trans sphenoidal resection of pituitary tumour (including intra operative CSF leak).

2.Trans petrosal resection of skull bone tumour.

3.Orbito zygomatic /frontal craniotomy with exposed frontal sinus.

4.Cavernous sinus aneurysms and tumours.

5.Chiari malformation/pseudo meningioma repair

6.Giant aneurysm with Unclippable neck.

7.Resection of outer layer of sinus wall.

8.E C A - ICA bypass surgery

9.Posttraumatic CSF rhinorrhoea

10.Empty sella with CSF rhinorrhoea

11.Lumbar discectomy with CSF leak.

12.Anterior cervical discectomy with CSF leak.

13.Syringo subarachnoid shunt.

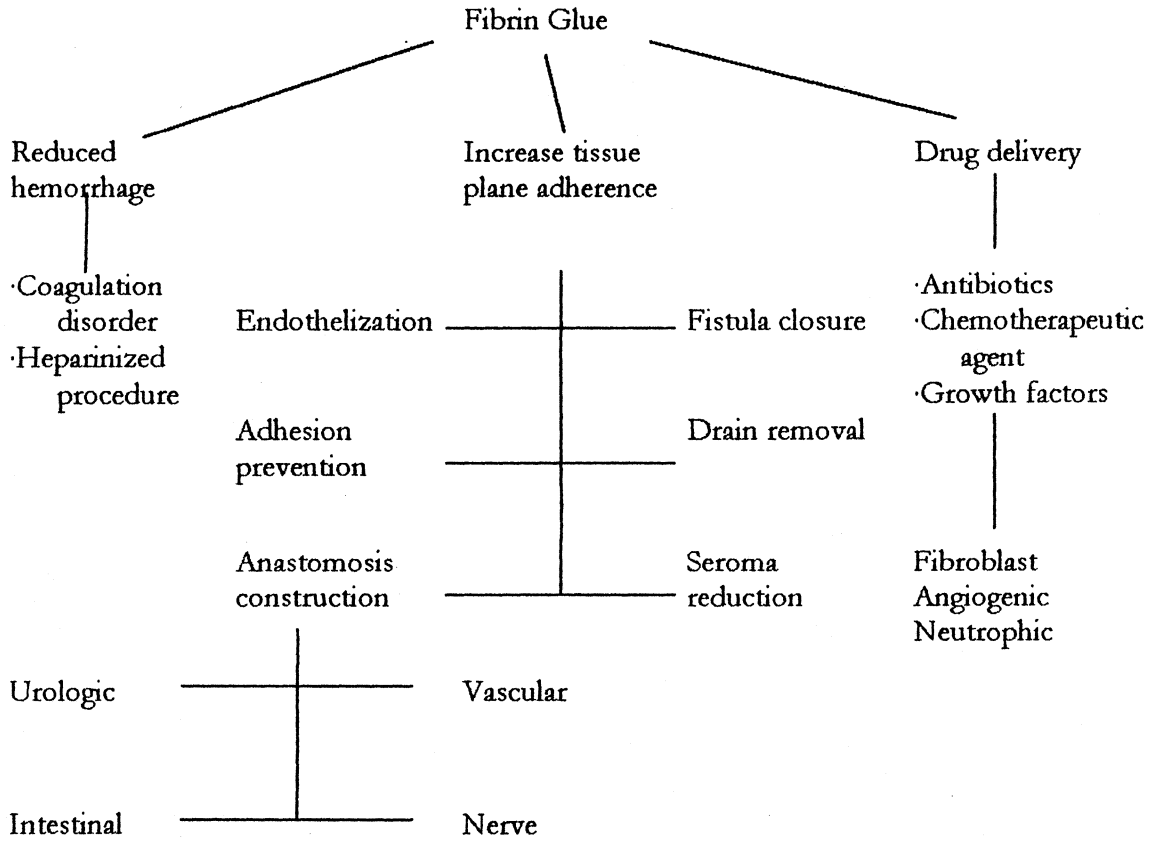
14.Repeat myelomeningocele repair.

15.Trans oral odontoidectomy with CSF leak.

The 1st commercial form of fibrin glue was developed in Europe and currently three different preparations are available for international use. In India it is being marketed by Cedila with the commercial name Beriplast.

Future of surgical tissue adhesives appears bright as progress is continuing in a variety of areas with major clinical implications. The fibrin sealant itself remains a potentially useful agent and modifications of this material as well as development of other new adhesive agents are under way.

Clinical application of fibrin glue



Management Strategy

MANAGEMENT STRATAGY

The ideal Method of application is dependent upon how the adhesive is to be used. Surgical procedures dealing with extremely small areas require an applicator that is capable of delivering micro liters of materials to an exact point. Although only small amount of FTA is required for support adequate distribution and mixing of the FTA component is crucial for clot integrity.

Procedures involving large areas require a spray applicator that is able to deliver large volumes of the components in a uniform, homogenous mixture in order to maximize polymerization and achieve rapid hemostasis. Independent of its use, fibrin glue is applied in a one to one ratio by volume of fibrinogen (component I) to thrombin (component II). Method and amount of glue to be applied is determined by total surface area to be covered and purpose of application (adhesive, sealant, hemostat and carrier). Currently 3 method of glue application have been described.

1.Sequential delivery

2.Spray application

3.Dual syringe injection.

We use dual syringe system, which involve a two-syringe system joined by needle. The plungers of each syringe are attached by the plastic connection that insures equal application of both components. This system would inhibit mixing of two components prior to site of application. One of major draw back of this system is that the needle can get obstructed with clot.

In our BMT department cryoprecipitation method has been standardized to concentrate the coagulation proteins from single donor unit of plasma collected and screened for transfusion. This method yields high concentration of fibrinogen. Up to 95% of plasma fibrinogen is recovered in the concentrate. Each batch prepared has been consistent as tested by sterility checking, estimation of clottable fibrinogen, clotting time assay and clot stability in test tubes.

In this prospective study, during the period between March 1999 to April 2000, in 33 patients indigenously prepared fibrin glue was used as an adjunct to dural closure to prevent CSF leak and the outcome was reviewed. Fibrin glue in this study was supplied from BMT department of our hospital as component I and component II along with the applicator. The component I [concentrated fibrinogen] was prepared by

cold precipitation technique from single donor unit of human plasma screened for hepatitis B surface antigen and human immunodeficiency virus antibodies. The concentrated fibrinogen is combined with topical bovine thrombin to produce fibrin glue. Both components are applied using dual syringe system.

Always it is the aim of the surgeon to do water tight dural closure. The fibrin glue was used as an adjunct to conventional dural closure to achieve a watertight closure where conventional methods of dural closure with or without a free graft were felt not adequate by the surgeon, or not possible. Most of the patient in whom fibrin glue was used there were generally thought to have a high risk for CSF leakage due to insufficient quantity or quality of the dural closure or because of the anatomic location like sellar floor, skull base etc.

When sufficient dura was available, closure was made with 3/0 nonabsorbable dural suture with simple running stitches. If significant CSF leakage persisted after the dural closure, fibrin glue was used to seal the leakage in two ways. In first technique small leaks were sealed by keeping the suture line dry and gentle suction and cotton pledget before the application of glue. In second technique large defect was

closed using fascia lata, fat, pericranium graft and suture line were covered with glue.

With all craniotomies the galeal layer were closed using multiple interrupted 2/0 absorbable suture and skin was closed with continuous interlocking stitches 1/0 silk suture. While in all spinal cases the paraspinal musculature and overlying fascia were closed in two layers using 1/0 monofilament absorbable suture in a watertight fashion and skin closed using interrupted 1/0 silk nonabsorbable suture.

Results and Analysis

RESULTS AND OUTCOME ANALYSIS

During the period March 1999 to April 2000, a total of 33 patients were operated in the department of Neurosurgery using fibrin glue as an adjunct to dural closure in order to prevent CSF leakage. These patients formed the "case group " in our study. In order to compare the results of the study group, "control group" patients were selected from patients, operated during the same period of time. During the selection an attempt was made to choose appropriate cases in majority of aspects i.e.: gender, age, associated medical problems, disease and other variables. An attempt was also made initially to obtain a second control group where the currently available imported fibrin glue was used. Due to the high cost of the product and the relative nonavailablity in the market this attempt had to be aborted.

Fibrin glue in this study was supplied from the biomedical and research wing of SCTIMST. The glue was available as component I and component II along with an applicator. The component I (concentrated fibrinogen) prepared by cold precipitate technique from single donor unit of human plasma screened for hepatitis B surface antigen and human immuno-deficiency virus antibody. The concentrated fibrinogen

combined with topical bovine thrombin to produce fibrin glue. Both components are applied using dual syringe system.

The selection criteria for including patients in the case group was as follows:

1. Patients being operated primarily for CSF leaks.

2. In all elective cranial and spinal operations where the surgeon felt that a watertight closure could not be achieved using conventional methods of dural closure with or without a free graft.

3. Patients likely to have a high propensity of CSF leakage due to insufficient quantity or quality of the dural closure or because of the anatomic location like sellar floor, skull base etc.

When sufficient dura was available, closure was done with 3/0 non-absorbable dural suture with simple running stitches. If significant CSF leakage persisted after dural closure fibrin glue was used to seal leakage in one of the two ways. In the first technique small leaks were sealed by keeping the suture line dry with gentle suction and cotton pledget before the application of fibrin glue alone. In the second technique large defect in dura were closed using fascia lata, fat, pericranium graft and suture line were covered with fibrin glue. With all craniotomies the

galeal layer were closed using multiple interrupted absorbable suture and skin was closed with running 1/0 silk non-absorbable suture. While in all spinal cases the paraspinal musculature and overlying fascia were closed in two layers using 1/0 monofilament absorbable suture in a water tight fashion and skin was closed using interrupted 1-0 silk, non absorbable suture.

The various parameters assessed were as follows:

1. Incidence of CSF leak either as a) CSF rhinorrhoea, otorrhoea b) CSF leak from the wound c) Subgaleal collection d) pseudomeningocele formation.

2. Ease of preparing the components.

3. Ease of handling and loading the applicator.

4. Settling time.

5. Incidence of any visible tissue reaction.

6. Antibody formation against bovine thrombin (component II)

PATIENTS PARAMETERS :

None of the reported studies available so far indicate any influence of either sex or the age on the efficacy of fibrin glue. No attempt was therefore made to restrict recruitment of patients based on these parameters. Thus we include a total of thirty-three patients of whom thirteen were males and twenty were females. (Table 1)

TABLE I: AGE DISTRIBUTION

(n = 33)

Age group	No
0-10	2
11-20	5
21-30	5
31-40	5
41-50	9
> 50	7

Although selection of patient was entirely dependent on surgeon's discretion, but specifically glue was being used for skull base and trans-sphenoidal surgeries. Majority of patients presented with CSF rhinorrhoea while the second commonest group included patients operated for pituitary adenoma by a transphenoidal route. (Table -2)

The control; group also included a similar group of patients (Table 2a). However once the trial was on and the efficacy of fibrin glue fairly well accepted none of the surgeons wanted to risk operating on primary CSF rhinorrhoea patients without fibrin glue. Hence it was not possible to include patients of primary CSF rhinorrhoea in the control group.

TABLE: 2 DIAGNOSIS (INDICATIONS)

CSF Rhinorrhoea	9
Meningioma	5
Aneurysm	3
Pituitary	9
Craniopharyngioma	1
Post Fossa Lesion	1
Spine	4
AVM	1

The indigenously prepared fibrin glue was found to be relatively safe during the animal trails on rabbits. However we independently assessed the possibility of any inherent risk factor compounding our final analysis. Six of 33 patients had a risk factor in form of hypertension and diabetes mellitus but no patient had renal, respiratory or other problems. (Table-3). None of this risk factor could be found to have any influence on the final outcome

TABLE: 3. RISK FACTORS

Hypertension	5
Diabetes Mellitus	1
Cardiac Illness	0
Pulmonary Dysfunction	0
Renal Disease	0
GIT disturbances	0

The study group included patients operated for different conditions and hence the surgical technique adopted was also different. (Table 4). Out of 8 patients of anterior cranial fossa floor repair, 5 patients were operated by Bifrontal craniotomy and anterior cranial fossa floor repair, 2 underwent Trans Sphenoidal repair of sellar floor and 1 underwent postcraniectomy CSF leak (paradoxical rhinorrhoea) repair. Out of eleven patients operated by craniotomy, 5 had meningioma, 3 had aneurysm and one each was operated for pituitary adenoma, craniopharyngioma and AVM. Three of patients developed CSF leak (one aneurysm and two meningioma). All were managed conservatively.

Of the two patients who underwent craniectomy (one for acoustic neurinoma and one for medulloblastoma), one developed CSF leak, which was managed initially by putting EVD. As patient had

hydrocephalus, later it was converted to shunt. Two of eight patients operated for pituitary adenoma by transphenoidal route developed CSF rhinorrhoea, of which one subsided spontaneously and other underwent re-exploration and packing of sellar floor.

Among 4 spinal cases one patient of paraganglioma developed CSF leak from the wound, which subsided with conservative measures.

TABLE - 4: SURGICAL PROCEDURE-STUDY GROUP

Surgery	Total	Success	Failure
Craniotomy	11	8	3♣
Craniectomy	2	1	1♥
Skull base repair	8	8	0
Trans-sphenoidal	8	6	2♦
Spine Laminectomy	4	3	1♣

♣ : Conservative
♦: Re-exploration
♥: EVD / Shunt

Seven patients developed CSF collection / leak. Out of these three patients were managed conservatively with antiedema measures, bed rest and repeated aspiration. 1 patient underwent reexploration of posterior fossa wound and repair, but her leak was persisting, so lastly

underwent EVD followed by shunt. In one patient operated for pituitary adenoma CSF leak persisted in spite of conservative measures, so re-exploration and packing of sphenoid sinus and sellar floor was done.

In all 33 patients glue was used as an adjuvant to dural closure. Fibrin glue was never used alone as the sole occlusive agent. In seven patients the primary dural repair was fairly sufficient except for few areas of leak in between sutures. In these patients glue was used along with primary dural closure. In ten patients dura was deficient and a dural graft had to be applied which was sutured and reinforced with glue. In four patients graft was put, as on lay and glue applied at margin, as suturing watertight was difficult. In twelve patients glue was used along with fat /fascia to pack sphenoid sinus (Table - 5)

TABLE-5: REPAIR RESULTS

Procedure	Total	Success	Failure
Primary closure + Glue	7	7	0
Duroplasty + Glue	10	6	4
Onlay Fascia + Glue	4	4	0
Glue + Fat + Fascia	12	9	3
Glue only	0	0	0
Total	33	26	7

In this project we have not used fibrin glue alone in any of the cases. Results of above are better seen in cases of floor repair (Onlay fascia and Glue) and Pituitary adenoma cases (Glue + Fat + Fascia).

In order to compare the results of the study group, control group patients were selected randomly, operated during the same period of time. During the selection an attempt was made to choose appropriate cases in majority of aspects i.e.: gender, age, associated medical problems, disease and other variables. But due to the fact that we had not operated any case of anterior cranial fossa floor repair without using the glue following the availability of the glue, so appropriate control were not available for this group. The following table shows the results without using the glue in the control group. (Table - 6)

TABLE 6: CONTROL GROUP

Surgery	Total	Success	Leak/Collection
Craniotomy	11	6	5
Craniectomy	2	1	1
Transphenoidal	8	5	3
Spine	4	2	2
ACF Repair	0	0	0

Out of 33 patients 6 had developed complications in the form of meningitis (1) and fever (5). The patient with meningitis was operated for pituitary adenoma and postoperatively had CSF leak. He was managed conservatively with appropriate sensitive antibiotics and he recovered with no deficits. However none of the other six patients where the fibrin glue had failed developed features of CNS infection. Five of the patients developed unexplained fever. Out of these five patients four were surgical failures with three having subgaleal CSF collection and one having frank CSF rhinorrhoea. They however had no other evidence of hypersensitivity reaction (Table -7) Serum from sixteen patients where fibrin glue was used were analyzed for the formation of

antibodies. No significant titers were documented in any of these sixteen patients.

TABLE - 7: COMPLICATION AND MANAGEMENT

Meningitis	1♥
Fever	5♦

♥ : Pituitary adenoma with CSF leak
♦: 1 patient- CSF leak
3 patient –Collection
1 patient -No problem.

All the thirty-three patients were operated by a team of seven consultants. There response on the ease of preparing and using the glue was obtained by a verbal questionnaire. In the initial 5 patients there was a problem in mixing of component with their solvent as quantity of component used were 0.7ml and 1ml Later on accepting our suggestion the components were made available in equal quantity (2ml). (Table - 8)

TABLE - 8: SURGICAL HANDLING

Good	28
Satisfactory	5
Not Satisfactory	0

In most of the cases of our series we used 1 ml or 2ml of glue.

TABLE - 9: GLUE VOLUME

Volume	No of Patients
1 ml	15
2 ml	17
3 ml	1

Settling time in majority of cases was 1 or 2 minutes. In only initial 5 patients it was more. Our discussion with the scientist of BMT wing, it was found to be due to some procedural defect, which was corrected later.

TABLE -9: SETTLING TIME

Settling time	No. of Patients
< 1 mt.	3
1-2 mt.	20
2-3 mt.	5
3-4 mt.	5
>4 mt.	0

Discussion

DISCUSSION

The successful completion of the animal trials of the Fibrin glue indigenously prepared at SCTIMST led to the final phase of clinical trials on human beings.

The indigenously prepared glue differed from the commercially available product in that in the present product, Aprotinin was not used. Avoidance of its use will help in reducing the cost and makes composition much simpler. In this study the glue has been used as an adjunct to dural closure and it is seen that there is definite advantage in preventing CSF leak or subgaleal collection in cases of skull basal lesions, CSF rhinorrhoea cases and Pituitary transsphenoidal surgery. Although it has not been found to be equally beneficial in other cases as the results does not show significant difference between study and control group. Similar kind of results had been mentioned in literature also.

Age and sex were apparently found not to have any influence on the efficacy of glue. Of the seven failures neither age nor sex appeared to have any contributing factors.

Primary condition of the patient too was found not to have any bearing on the outcome. The result of the glue was directly dependent on the type of surgery and the surgical procedure adapted for dural closure. Thus in patients where primary closure of dura could be achieved, glue was found to be very effective in sealing minor site of leakage, which is usually seen through the suture line. Similarly cases where the dural defect could be covered with an onlay patch, fibrin glue was found to be very effective in tightly retaining the onlay patch in preventing the CSF leak.

Procedure	**Total**	**Success**	**Failure**
Primary closure + Glue	7	7	0
Duroplasty + Glue	10	6	4
Onlay Fascia + Glue	4	4	0
Glue + Fat + Fascia	12	9	3
Glue only	0	0	0
Total	33	26	7

Fibrin glue was found to be very effective in trans-sphenoidal surgery where intra-operative CSF leak had occurred. In this study where three out of eight patients of trans-sphenoidal surgery in control group had postoperative CSF leak, only two in the study group had CSF leak.

Similarly of the eleven patients who underwent craniotomy in control group, five had CSF leak, where only three patients in the study group had CSF leak. None of the patients who underwent surgery for primary CSF rhinorrhoea had post-operative leak and glue was found to be very effective. With the proven efficacy of fibrin glue in the ACF repair, none of the patients admitted for CSF rhinorrhoea, were denied the benefit of fibrin glue.

Procedure	**Study group (Failure / Total)**	**Control group (Failure / Total)**
Craniotomy	3/11	5/11
Craniectomy	1/2	1/2
Trans-sphenoidal	2/8	3/8
Spinal Surgery	1/4	2/4
ACF Repair	0/8	0/0

Indigenously available glue is economically significantly cheaper and on large-scale production, the cost of one ml of glue would approximately be around Rs. 350/- to Rs. 400/-, compared to commercial glue (Rs. 5000/- per ml.).

The ease of handling the applicator and the glue is found to be fairly satisfactory.

The major drawbacks encountered are as follows :

1. Mixing of component II takes a longer time.

2. Presence of moisture in the applicator syringe tip makes the glue less viscous and as repeated application might be required, multiple needles have to be used and irrigation of the needles would retain the moisture.

3. Although the settling time could be reduced considerably with modification in component II, but the time it takes is still longer than commercially available glue.

4. In the initial part of the study component I and II were supplied in different quantities (0.70ml and 1ml), so that mixing and application of this different quantity was little cumbersome. More over the glue could not be applied at uniform rate. This defect was however rectified by supplying the equal volume of both components (2ml).

The modifications that have been suggested to improve the efficacy of glue are as follows :

1. Glue to available in different proportions (1ml, 2ml, 5ml packages)
2. To provide multiple needle tip with applicators.
3. To provide longer needles for application at depth like in trans-sphenoidal surgery
4. To reduce settling time further

Few of the drawbacks of present study are

1. There is no data for comparison of present indigenous glue and commercially available glue (which is very expensive), but results of indigenous glue seems satisfactory.
2. Following the availability of glue, no anterior cranial fossa repair (for CSF leak) was done without using glue, so appropriate control cases were not available for the study.

3. In present study the availability of the glue was subject to various technical hitches like fund problem, storage difficulty, manpower etc. and caused scarcity of glue at times.

Conclusion

CONCLUSION

1. Fibrin glue developed at Biomedical technology department is a very effective tissue sealant when used as an adjunct to dural closure in neurosurgical procedures.

2. The glue is relatively free of any side effects.

3. The glue is economically available and on large scale production would reduce the cost still further.

4. The performance can be further enhanced by the suggested modifications.

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