Low Cost, Locally Prepared Fibrin Glue and Its Clinical Application

Parttraporn Isarangkura

Fibrin glue (FG) (or fibrin sealant [FS] or fibrin tissue adhesive [FTA]) is a group of blood products that leads to the formation of a fibrin clot at the site of application. It consists mainly of fibrinogen and thrombin.

FG represents a revolution for local hemostatic measures for both bleeding and non-bleeding disorders. Tourniquet, pressure and suture have been used for controlling hemorrhage in surgery for hundreds of years. FG has the potential to provide life-saving control of hemorrhage. It is used for local hemostatic measures except arterial bleeding. It can be applied to every organ except eyeballs.

It has been shown to be very useful for local hemostatic measures, a valuable tool for adhesion, sealing, anastomosis, vascular and nerve grafts, etc.[1-3].

Indications for application of fibrin glue are as follows:

1. Local hemostatic measures for both surgical and medical cases.
2. Surgery in patient with bleeding disorders i.e. hemophilia, severe thrombocytopenia and non-bleeding cases with suspected blood oozing.
3. Surgery in nonsuturable organs (e.g. brain, liver, pancreas, thymus) or to repair unhealthy tissue (e.g. irradiated bowel or tissue of elderly patients).
4. Microvascular surgery and vascular grafts (e.g. anurysm repair).
5. Nerve grafts.
6. Skin grafts, particularly plastic surgery.
7. Surgery of small or difficult to reach organs (e.g. tympanoplasty, ENT, eye).
8. Sealing of body cavities, fistulae, pneumothorax, etc.
9. Anastomosis of gastrointestinal, KUB tract and other ductal organs.
10. Sealing of fertilized ovum to the wall of the uterus in animal experiments.

Review of applications and beneficial effects of FG in surgery[4]

CNS surgery:
1. Adhesive agent in CNS tissue surgery. CNS tissue cannot be sutured. FG is almost equivalent to microsurgical suture. FG works as a sealant but not a nerve barrier.
2. Repair of dural defects.
3. Non surgical treatment for postoperative CSF leaks by percutaneous CT guided placement of FG

Eye surgery:
1. Conjunctival closure in strabismus.
2. Wound closure in glaucoma.
3. Lower blepharoplasties (for lower eyelids).
4. Attachment of extraocular muscles.
5. Cataract surgery using FG in radial suture to correct astigmatism.

ENT surgery:
1. Myringoplasty in large persistent tympanic membrane perforation.
2. Repair of laryngotracheal separation with cricoidectomy.
3. Narrowing of nasal fossa in atrophic rhinitis.
4. Routine otologic and neuro-otologic surgery.
5. Vocal fold lateralization in vocal cord defect.
6. Tympanoplasty.

Oral and dental surgery:
1. Local hemostatic measures in patients with bleeding disorders and patients on anticoagulants.
2. Sealing of oro-antral fistula.
3. Correction of periodontal bony defect.
4. Tissue adhesive with bone chips to prevent bone defect.

Head and neck:
1. Parotidectomy closure.
2. Axillary dissection in carcinoma of the breast[5]. Reduces adhesion, bleeding and serous drainage with earlier drain removal from 6.9 ± 1.2 to 3.9 ± 1.7 days ($p < 0.0001$). It reduced serous drainage from 467 ± 138 to 198 ± 83 ml ($p<0.0003$).
3. Prevention of mastectomy seroma.
4. Treatment of chylous leakage after neck dissection, which is found in (5%) of neck resections[6].
5. Axillary lymph node dissection.

Cardio vascular thoracic surgery:
1. Reduced postoperative bleeding and intrapericardial adhesion .
2. Kjaergard's[7,8] review of 2,300 papers in cardiothoracic surgery using fibrin glue showed no worse effect and reduced postoperative bleeding.
3. Repair left ventricular free wall rupture.
4. Aortic valve repair.

Chest surgery:
1. Sealing of prolonged airleak after thoracotomy in lung cancer.
2. Bronchopleural fistula.
3. Percutaneous lung biopsy.
4. Large emphysematous bullae using thoracoscopic technique.

5. Management of postoperative chylothorax in premature babies.
6. Persistent pneumothorax in premature infants.

Vascular surgery:
1. Microvascular anastomosis: Suture may induce vascular narrowing, foreign body reaction, intravascular thrombosis but are less common in those with FG application.
2. Arterial bypass surgery.
3. Aortic aneurysm repair.

Gastrointestinal surgery:
1. Gastrointestinal anastomosis-stent FG, sutureless.
2. Esophagus perforation.
3. Esophago-jejunal anastomosis.
4. Recurrent tracheo-esophageal fistula.
5. Upper gastrointestinal tract fistula: endoscopic obliteration
6. Cholecysto-jejunostomy (sutureless) using absorbable intraluminal stent.
7. Repair pancreatic fistula in pancreatic transplantation and pancreatectomy.
8. Peptic ulcer bleeding.
9. Seal peritoneal dialysis catheter leakage.
10. Recto-vaginal and ano-rectal fistula
11. Improved healing of irradiated bowel anastomosis

Liver sugery:
1. Liver resection in benign and malignant diseases.
2. Liver transplantation.

KUB system:
1. Colpofixation in stress urinary incontinent.
2. Intractable transplant-ureteral fistula.
3. Transvaginal colpo-urethropexy.
4. Vaso-vasostomy (FG replaces two-layer suture technique).
5. Laparoscopic ureteral re-anastomosis.
6. Partial nephrectomy.
7. Laparoscopic closure of ureterotomy in porcine model.

Gynecological surgery:
1. Recto-vaginal and ano-rectal fistula.
2. Anastomosis of the fallopian tube in animals.

Bone & Orthopedic surgery:
1. Joint replacement.
2. Brachial plexus injury repair.
3. Fracture and other surgery.
4. Bone graft.
5. Multiple surgical joint correction in hemophilia.

Plastic surgery:
1. Face lift procedure. FG reduces major hematomas and ecchymoses. No drain of postoperative dressing is required.
2. Musculo facial plastic surgery, dorsal hand burns, infected skin graft.
3. Decrease wound contraction in skin graft.
4. Hemostatic effect on graft of donor site.
5. Used as skin graft of contaminated wounds in areas difficult to immobilize, i.e. perineum, gluteal folds, axilla.

In 1909, FG was first introduced as a fibrin powder in the operative field for hemostatic measure. A crude form of FG containing fibrinogen and thrombin was first utilized in the military field in 1940[9]. The improved product was used to promote wound healing, skin grafting and dural sealing and etc. Since 1978, commercial products have been licenced licensed in the USA and Europe that have improved viral safety and clinical efficacy.

Before 1996, FG was used to a very limited extent in Thailand due to its enormous expense. By the request of the author, technology for locally prepared FG and surgical application was transferred to the Bangkok International Hemophilia Training Center of the World Federation of Hemophilia (WFH) at Ramathibodi Hospital in July 1996 by Prof. Uri Martinowitz and the late Prof. Henri Horoszowski with the support of WFH and Israeli government. Since then FG has been widely used and proved to be very useful in Thailand.

The aim of this paper is to describe: 1) methodology in preparation and application of locally prepared FG for developing world, 2) the experience in clinical applications of locally prepared FG in various surgical and medical conditions 3) its usefulness, advantages and cost effectiveness.

Methodology of preparation and applications of locally prepared FG

Preparation of FG

FG is prepared in two solutions being kept in two different vials with completely sterile technique in the laminar air flow.

Solution 1. One mL contained 40 mmol/calcium chloride solution, gentamicin 2 mg and thrombin. Human thrombin (Omrix Pharmaceutical Co, Belgium) has been used since 1997 at a concentration of 100 IU/mL for dental surgery and 250,500 IU/mL for other procedures. Bovine thrombin was used in the first 14 months.

Solution 2. One mL is composed of cryoprecipitate with fibrinogen content of 10-12 mg/mL and tranexamic acid 15 mg/mL (Daiichi Pharmaceutical, Tokyo, Japan) as antifibrinolytic agent. The source of lyophilized cryoprecipitate is prepared from single random donor, screened for VDRL, HBsAg, anti-HCV, HIV p24Ag and anti-HIV. It is kept for 3 months as delay release (quarantine) plasma to prevent contamination of HIV during window period. The frozen cryoprecipitate is lyophilized, then heat treated at 60°C for 72 hours.

During 1996-1997 both solutions were prepared at Ramathibodi Hospital and since 1997 the solutions have been prepared on a large scale by the National Blood Center. Solutions are kept at -20°C and are utilized within 6 months.

The technology of locally prepared FG is modified for a few items according to the limited resources in Thailand. Locally prepared lyophilized cryoprecipitate from delayed release plasma is used as the source of fibrinogen. Medical accessories are locally modified and made in Thailand at low cost. The application set includes a syringe holder, syringe bridge, 3-way connector with 3-lumen tube, and two syringes. An air pump is used only for spraying in large surgical areas.

Application of FG

Solutions 1 and 2 are thawed at room temperature (20-25°C), then solution 1 is drawn up into the first syringe and solution 2 into the second syringe. The two syringes are fixed with the syringe bridge and holder and connected to the sterile spray delivery.

FG is applied either by direct syringe push for a small area such as sockets of dental extraction sites or sprayed with air pump machine through 0.2 μm filter for major surgery in large areas such as in cardiovascular surgery.

Special mouth rinse for dental surgery

After dental surgery, each patient receive local and systemic antifibrinolytic drug as a special mouth rinse. One capsule (250 mg) of tranexamic acid (Daiichi Pharmaceutical Tokyo, Japan) is disolved in 50 mL of drinking water which is used by swishing and swallowing all amount every 6 hours for one week.

Clinical application of low cost locally prepared FG :: Experience in 264 cases

Patients

From November 1996 to May 1999, FG was applied to 264 patients with bleeding and non-bleeding disorders at Ramathibodi Hospital. Their ages ranged from 1 month to 87 years, with 98 pediatric and 166 adult cases. There were 171 males and 93 females.

Table 1. Type of surgical and medical procedures using FG and the amount of FG used.

Type of procedures	No. of cases	Percent of procedures	FG used mL/case
Dental	87	32.95	1-8
Neurology	53	20.08	2-6
Cardiovascular	41	15.53	9-20
ENT	29	10.99	2-3
Orthopedic	20	7.57	2-80
Plastic	7	2.66	2-5
DHF	6	2.27	2
Liver	2	0.75	2-5
Eye	2	0.75	2
Severe bleeding in hemophilia A with inhibitor	1	0.38	4
Other	16	6.07	2-4
Total	**264**	**100**	**1-80**
Total amount of FG used			**1,324 ml**

Clinical procedures using FG included dental surgery, open heart surgery, ENT, orthopedic including 3-4 joint corrections in one session in hemophiliacs, neurology, plastic, liver, eye surgery, uncontrolled bleeding in dengue shock syndrome and others.

Types of surgical and medical procedures using FG and the amount of FG used are shown in **Table 1**.

Dental surgery was performed in 87 cases as shown in **Table 2**. Most of them were for local hemostatic measures in patients with bleeding disorders (85%). The other applications were used for sealing the oro-antral fistula instead of using a flap procedure to close the fistula, and serving as a matrix for bony chips to correct bony defects in periodontal disease. It was used as tissue adhesive with bone chips to prevent the bone defect of the distal part of the second molar.

Cardiovascular surgery was performed in 41 cases, aged 1 month to 70 years, with neonate 5, infant 12, children 10 and adult 14 cases. The type of operation was shown in Table 2. Most of them were used for local hemostatic measure and few cases were used as sealing , e.g. to repair lymph leakage.

Neurosurgical: FG was applied in 53 cases aged from 1 month to 83 year old (**Table 3**). It was implremented for lacal local hemostatic measure in patients with transient coagulopathies, sealing and adhesiveness in CSF leakage, fistula or repair of dura defect.

Ear, nose, and throat (ENT) surgery: FG was used in 29 cases aged 13-63 years: chronic otitis media 10, allergic rhinitis with nasal obstruction 7, tympanoplasty 3, myringoplasty 1, malignant inverted papilloma 1 and others 7 cases.

Orthopedic surgery using FG was performed in 20 cases, aged 7-53 year: brachial plexus injury 9, hemophilia with multiple joint correction in one session 5, fracture 3, aneurysmal bone cyst 1, herniated nucleus pulposus 1 and skin muscular defect 1 cases.

Plastic surgery was performed in 7 cases including myeloplasty (facial lift) 3, cavernous hemangioma 3 and laceration wound 1 cases.

Pediatrics. FG was first applied to dengue hemorrhagic

Table 2. Dental surgery with fibrin glue application.
Total 87 cases aged 5 months - 87 years

Diseases

1. Bleeding disorders 74 cases (85%)
   - Hemophilia A, B and von Willebrand's disease
   - Thrombocytopenia—ITP, leukemia, aplastic anemia, SLE, etc.
   - Acquired coagulation defect— liver disease, biliary atresia
   - Glanzmann thromblasthenia
   - On anticoagulant (ASA, coumadin)

2. Non bleeding disorders 13 cases (15%)
   - Periodontal surgery with bone graft who received immunosuppressive drugs
   - Sealing of oro-antral fistula
   - Surgical removal of impacted molar

fever (DHF) with dengue shock syndrome in 6 cases with thrombocytopenia and coagulopathies with severe complications i.e. hepatic, renal failure or pulmonary hemorrhage. FG was used for local hemostatic measure at the uncontrollable bleeding from the tube drain of peritoneal dialysis, intercostal drainage in pulmonary hemorrhage with hemothorax, and applied to cutdown wounds for exchange transfusion. Gauze packing was put on top of the glue. Satisfactory hemostasis was achieved in all cases.

A 4-year-old boy with hemophila A and a high inhibitor titre had severe bleeding from a cut on his tongue that could not be controlled by recombinant factor VIIa infusion. FG was applied at the bleeding point twice. The bleeding could not be controlled by FG, which suggested that it was due to arterial bleeding. Surgical suture under general anaesthesia was then carried out and the bleeding stopped after suture.

Liver surgery: FG was used in a liver transplant and in a case of hepatic failure with bleeding.

Eye surgery. FG was applied in 2 cases: conjunctival papilloma in 87-year-old with senile unhealthy tissue and excision with amniotic graft at left limbus.

FG was applied in other 16 procedures.

No complications of FG were noted in any case. The beneficial effects of FG were satisfactory in most cases.

The usefulness, advantages and cost effectiveness of locally prepared FG

Fibrin glue has been commercially available and widely used for two decades. But it has been rarely used in developing countries because of the cost. Since July 1996 low cost locally prepared FG has been available in Thailand at about 10% of the commercial price. It has became widely used in patients with bleeding and non-bleeding disorders all over the country.

Over a 2-year and 7-month period, the total amount of FG used at Ramathibodi Hospital was 1,324 ml, which would have cost US dollars 260,000 (10 million baht) if purchased commercially. The locally made product cost 10 times less than the commercial one. In addition, the concentration of thrombin and volume of glue can be prepared altered according to the needs of uers.

Since July 1998, the National Blood Center, Thai Red Cross Society has prepared for large scale production of FG to serve the whole country. It is available 24 hours stored at -20°C.

The viral safety of blood products used for the preparation of FG is stated in the package brochure. Human thrombin is prepared by solvent detergent extract which acts as viral inactivation. Locally made fibrinogen is partially treated lyophilized cryoprecipitate from delayed release plasma that is safe from HIV but not completely safe from hepatitis if the donor is in window period of infection. It is emphasized that FG should be used only for indicated cases.

Dental surgery in patients with hemostatic disorders can be performed without preoperative blood component therapy. Only 7% required blood component therapy postoperatively with only 1 or 2 doses compared to all of the control no-FG 50 cases (100%) who required multiple doses of systemic blood components pre and post operatively. For non hemostatic disorders, FG is used for sealing and tissue adhesion to induce the regeneration of periodontal tissue.

One dental surgery session for a thrombocytopenic patient requires FG (2 ml 100 IU) which cost US $15 for the locally prepared product. If FG is not used, the cost of platelet concentrate in an adult of 50 kg body weight would be US $150 for the whole process. (The cost of blood component is partially subsidized by the government to the National Blood Center.) The expense of FG is only 10% of the cost of blood product. In addition, it reduces the hazards of blood transfusion complications and risk of viral transmission.

The cost effectiveness of FG relating to reducing use of blood products is clearly demonstrated, particularly in dental surgery for patients with bleeding disorders and in multiple surgical orthopedic procedures in one session in hemophiliacs. FG is even more essential and useful for the countries with the shortage of blood products.

The beneficial effect of FG in cardiovascular surgery lies in its local hemostatic effects in the operative field. It reduces post operative bleeding and no patients required repeat surgery to stop bleeding including the neonates and infants. FG has proved very useful for hemostatic measure in open heart surgery of small infants with multiple suture lines at the posterior surface of the heart. Suture is difficult to perform in a small narrow space.

For neurosurgery, FG was applied in 3 major areas (**Table 4**):

1. Local hemostatic measure at the raw surface of surgery showed excellent result in all cases particularly in patients with transient coagulopathies due to long operating

Table 3. Open heart surgery in which fibrin glue was used.

Type of surgery	No. of cases
Adult	
Coronary arterial disease	6
Valvular heart disease	5
Atrial septal defect	1
Others	2
Total adult	14
Pediatric	
Ventricular septal defect	12
Atrial septal defect	4
Total anormaly of great vessel	3
Complex anormalies	1
Total anormaly of pulmonary venous return	2
Pulmonary stenosis and ventricular septal defect	1
Tetralogy of Fallot	1
Others	3
Total pediatric	27

time or in severe trauma patients.

2. In treatment of CSF leakage or fistulae due to trauma or removal of tumor, FG was applied to close the defect in order to prevent CNS infection. The result was good in most cases. A few cases that failed were due to inadequate pressure packing or large dural defects.

3. Prophylaxis of dural closure in tumor removal. There were some cases of dural defects after removal of brain or spinal tumors. FG was applied if the repair of dura (with or without duraplasty) could not be accomplished by suture. The result was good in 75%. Some cases failed because of large defects or transient increased intracranial pressure postoperatively.

FG has been useful for operation of small organs i.e. in ENT surgery. In plastic surgery its use resulted in less suturing, better wound healing and minimised scar appearance.

The beneficial effect of FG in medical and surgical procedures has given much satisfaction to physicians, nurses, patients and relatives. It has proved to be useful in many aspects: local hemostatic measures, adhesion, sealing, anastomosis, microvascular suture for brain, nerve, vessel and skin grafts. sealing and repairing of defect in body cavities, subarachnoid space, tears of dura mater, operating on difficult or non-suturable organs and tissue of elderly patients. Multiple surgical procedures in one session, i.e. 3-6 joints operation in one session, in hemophiliacs cannot be achieved without fibrin glue.

Advantages of fibrin glue are:

1. Minimize or no blood component required for surgery.
2. Reduce risk of transfusion complications e.g.
   - Infection such as HIV, hepatitis
   - Isoimmunization
   - Inhibitor in hemophilia
   - Transfusion reactions
3. Reduce pre- and post-operative bleeding and blood oozing.
4. Reduce clotting factors used intra- and post-operation in hemophilia and allied diseases.
5. Multiple surgical procedures can be done in one session, e.g. 2-6 joint operation at one session in hemophilia, which reduces cost of surgery.
6. Reduce workload for physicians and nurses.
7. Reduce duration of hospitalization.
8. Reduce cost of treatment.
9. Sustain release of antibiotics or growth factor in the surgical wound, increase wound healing, reduce adhesion and infection.
10. Reduce discomfort and number of sutures in many surgeries.

Table 4. Neurosurgery using fibrin glue in 53 cases aged 1 month - 83 years

Disease	Cases
Brain tumour	27
Trigeminal neuralgia	2
Hemifacial spasm	5
Subarachnoid hemorrhage	1
Ruptured aneurysm	5
Post traumatic CSF leakage	1
Intracerebral hematoma	4
Rt temperal lobe cyst	1
CSF rhinorrhea	3
Traumatic optic nerve compression	1
Cerebellar AVM	2
Syringomyelia	1

The complications of FG are:

1. Infection of the surgical wound.
2. Separation of anastomoses.
3. Adhesion in the GI tract.
4. Bleeding of the surgical wound.
5. Risk of transfusion transmitted disease if using unsafe blood product for preparation.

New forms of fibrin sealant have been produced and developed despite the frozen liquid form, e.g. dry fibrin sealant bandage, spray powder, self-expanding sealant foam for non compressible haemorrhage, and recombinant FG to avoid risk of transfusion transmitted diseases[10-13].

The value of fibrin glue in medical field in Thailand has been compared to the value of cement and glue for the construction of buildings or the “elephant” brand household glue that repairs everything in the house from diamond rings to old shoes.

Summary

FG is a group of blood products that lead to the formation of a fibrin clot at the site of application. It is very useful for local hemostatic measure, sealant, adhesive tool and tissue repair. Technology for locally prepared FG was transferred to Ramathibodi Hospital by Prof. Uri Martinowitz in 1996.

The paper describes the indication and beneficial effects of FG; methodology of preparation and application of locally prepared FG in the developing world; the experience in clinical applications of FG to various surgical and medical conditions and its usefulness, advantages and cost effectiveness.

A total of 264 cases with age range from 1 month to 87 years, which included 98 pediatric cases and 166 adult cases (171 males and 93 females). Clinical procedures included dental surgery (87), open heart surgery (41), ENT (29), orthopedic (20) including 3-4 joint correction in one session in 6 hemophiliacs, neurology (53), plastic repair (7), liver (2), eye (2), severe bleeding in dengue shock syndrome (6), and others (17). The result of local hemostatic, adhesive and sealant effect of FG was satisfactory in most cases and no complication was observed.

FG has proved to be very useful and cost effective in many aspects, e.g. minimizing blood product usage, decreasing medical workload, and reducing medical cost. Low-cost locally prepared FG is very useful for developing countries.

It is even more essential for countries with a shortage of blood products. The blood product for preparation should be free from viral contamination and should be used only for indicated cases.

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*Bangkok International Hemophilia Training Center, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand,
**National Blood Center, Thai Red Cross Society,
***The Chaim Sheba Medical Center, Tel-Hashomer, Israel.

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