

# The use of Human Fibrin Glue in the surgical operations

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**Abstract.** Human Fibrin Glue (HFG) is made of two components contained in separate vials: a freeze dried concentrate of clotting proteins, mainly fibrinogen, Factor XIII and fibronectin (the sealant) and freeze dried thrombin (the catalyst). The first component is reconstituted with an aprotinin solution that inhibits tissue fibrinolysis. The second component (thrombin), available in 500 I.U. concentration, is dissolved with calcium chloride. It is so a set of substances involved in the hemostatic process and in the wound healing, conferring to the product the following important properties: hemostatic and sealing action, through the strengthening of the last step of the physiological coagulation; biostimulation, which favors the formation of new tissue matrix. The indications for the use of human fibrin sealant are numerous and present in all the surgical branches. A randomized controlled trial of 50 patients undergoing hernia repair according to Lichtenstein's technique under local anesthesia was performed. Patients had concurrent coagulopathies as a consequence of liver disease or long-term treatment with anticoagulants for ischemic heart disease or cardiac rhythm disturbances. Coagulopathies were defined according to the following criteria: prothrombin time <10.5 seconds, activated partial thromboplastin time < 21 seconds, and fibrinogen <230 mg/dL. Patients were randomized in a 1:1 ratio with (group A) or without (control group B) use of human fibrin glue. Postoperative hemorrhagic complications were significantly reduced in group A (4%) compared with group B (24%). This study showed that human fibrin glue is effective in preventing local hemorrhagic complications after inguinal hernia repair in patients with concurrent coagulation disorders.

**Key words:** Human fibrin glue, hemostasis, hernia repair, surgery

## Introduction

The surgical suture, both when realized with the traditional threads and with the most modern mechanical staplers, represents the "classic" method for wound repair. All surgeons, however, sometimes have to deal with wounds hard to recover because, due to stretching and ischemic events of variable extent, complications such as hematomas, granulomata, dehiscences and fistulae may occur, impairing the tissue healing.

Therefore, the ideal solution would be to have wound healing with no need of sutures, capable to sustain a certain mechanical stretching and with optimal conditions for a rapid recovery without leaving foreign substances in the wound area. On the other hand

this concept, even in an empiric way, was already known by the ancient doctors of Great Greece who used vegetal resins for wound healing purposes.

Fibrin's properties, interactions, mechanical strength and resistance to fibrinolysis have been thoroughly studied and described in many publications. Fibrin sealant was developed in 1972 by Matras et al., who successfully used a fibrinogen cryoprecipitate in peripheral nerve anastomoses on animal models. The development of a special cryoprecipitation process enabled the production of a high concentration fibrinogen solution with a high Factor XIII content. Moreover, the introduction of aprotinin, a natural anti-proteasic substance, allowed to solve other problems, such as fibrinolysis inhibition and early fibrin degradation.

## Characteristics, properties and modalities of application

Fibrin sealant is made of two components contained in separate vials: a freeze dried concentrate of clotting proteins, mainly fibrinogen, Factor XIII and fibronectin (the sealant) and freeze dried thrombin (the catalyst). The first component is reconstituted with an aprotinin solution that inhibits tissue fibrinolysis. The second component (thrombin), available in 500 I.U. concentration, is dissolved with calcium chloride.

It is so a set of substances involved in the hemostatic process and in the wound healing, conferring to the product the following important properties:

- hemostatic and sealing action, through the strengthening of the last step of the physiological coagulation;
- biostimulation, which favors the formation of new tissue matrix.

Let's examine the main components of Tissucol and its most important mechanisms of action by evaluating the effects on hemostasis, adhesion and tissue healing.

*Fibrinogen.* It is a high molecular weight protein, precursor of fibrin, which represents the basic element of the clot. The transformation of fibrinogen into stable fibrin occurs by means of thrombin and factor XIII, which in turn are activated by thrombin. Fibrin has a strong affinity with the factors derived from plasma or of cellular origin and with collagen. The fibrin clot that forms in a wound seems to act as a guide to the healing process, attracting the fibroblasts and promoting the formation of granulation tissue.

*Factor XIII.* It is a transglutaminase, carrying out some important functions:

- it catalyzes the formation of intermolecular bridges between a lysin and a glutaminic residue of fibrin molecular chains;
- it stabilizes with the same mechanism the link between fibronectin and fibrin and between fibronectin and collagen, thus increasing the molecular stability of the three-dimensional network of the clot;
- it links alpha<sub>2</sub> antiplasmin to the clot, so slowing down the action of plasmin and consequently regulating the fibrinolysis.

*Fibronectin.* It is a high molecular weight glycoprotein, which:

- interacts with fibrinogen and preferentially with polymerized fibrin, forming covalent links catalyzed by Factor XIII, which lead to the concentration of both molecules: fibronectin is then an integral part for adhesion and migration of fibroblasts to the wound area;
- it gets linked to collagen with molecular affinity interactions: this link favors the interaction of collagen with other repair structures, favoring the regeneration of a new matrix;
- it interacts with the cells, and this adhesion to fibronectin seems to be very important for various types of cells;
- it is also a substrate for Factor XIII.

The main characteristics of fibronectin consist of participating in the formation of the mixed fibrin clot, of increasing the adhesive property between cells and substrate and between one cell and another, and of favoring their growth and migration.

*Aprotinin.* It is a polypeptide that blocks plasmin and other serin-proteases. Through the addition of aprotinin, it has shown to be the best inhibitor of fibrinolysis which can be delayed, resulting in a significant increase of the healing processes, enhancing the formation of connective tissue. Thus, the survival of fibrin sealant can be controlled through suitable dosages of aprotinin, after having evaluated the fibrinolytic activity of the relevant area.

*Thrombin.* It is a serum protease with important functions: the transformation of fibrinogen into fibrin, activation of Factor XIII and stabilization of the network formed by fibrin and other proteins are the main ones.

*Calcium chloride.* Ca<sup>++</sup> ions are indispensable in various coagulation steps, for example in the transformation of prothrombin into thrombin and in the activation of Factor XIII; the polymerization processes are accelerated by the presence of Ca<sup>++</sup> ions.

In order to make the preparation and application of Tissucol easier and more effective, in the various indications, special devices and methods have been developed (application needle, Tissuspray, DuoFlo, Duplo-Tip and catheters), enabling to use the product in different areas – constricted, large or difficult to access.

## Indications

The properties of the main components, the possibility to add variable quantities of antifibrinolytic substances and to influence the consolidation time, the availability of special application devices, make the product extremely easy to handle and with practically limitless application fields in surgery. Its therapeutical significance and tolerability have been demonstrated at the international level in many fields of general and specialistic surgery, both as the sole suture element and as adjuvant of other means of surgical synthesis and hemostasis. In the light of its peculiar characteristics, many authors have specifically evaluated this product in patients with coagulation disorders, with absolutely specific problems and risks in case of surgical treatments.

The indications for the use of human fibrin sealant, also thanks to evident practical and economic advantages of the product, are numerous and present in all the surgical branches. The most significant are the following ones.

### – *Abdominal and general surgery*

The adhesive, sealing and hemostatic properties of Tissucol are particularly useful in this kind of surgery. The hemostatic property, in particular, is helpful in parenchymal surgery, mostly in liver, pancreas and spleen surgery, above all in case of partial resections and when it is necessary to favor the hemostasis of large injured areas, with massive bleeding. The considerable reduction of blood loss, correlated to seeping hemorrhages, diminishes blood transfusions or even makes them unnecessary. The use of the preparation also allows to avoid additional traumas to the residual parenchyma, reducing the suture stitches that strongly harm such friable tissues (1-5). In pancreatic surgery, fibrin sealant has been used also to treat the pancreatic stump with no panereo-digestive anastomosis (6).

The adhesive action of Tissucol is very useful in intestinal surgery, where it is necessary to carry out a complete and tight suture of the walls, which is not always possible. The use of Tissucol allows to obtain a complete and integral reparation of the tunicae, optimally resuming the continuity and tightness of the intestinal tract: many authors have carried out experi-

mental and clinical researches which have demonstrated a reduction in the rate of dehiscences, both in the manual and mechanical anastomoses (7). Human fibrin glue has also been used to treat fistulous complications of digestive anastomoses in a conservative way, without having to re-operate (8). The use of Tissucol, for the same reasons, has shown to be particularly useful for the non-surgical treatment of anal and perianal fistulae (9).

Moreover, excellent results have been described for the prevention of axillary lymphorrhoea after breast surgery (10), as well as for the prevention of complications in prosthetic surgery of hernias, both tension-free and laparoscopic (11).

### – *Thoracic and cardiovascular surgery (12-15)*

These types of specialistic surgery benefit by the adhesive, hemostatic and sealing properties of Tissucol in many indications.

In cardiosurgery, the hemostatic and adhesive properties, are particularly crucial especially in coronary surgery, in case of valve plasty and in congenital cardiac pathologies, both with or without the use of prostheses. Furthermore, the preparation has enabled to obtain extraordinary therapeutical results in the surgery of dissecting aneurysms. Tissucol has shown to be a valuable tool to solve contingent situations and technical problems, sometimes life-threatening.

In peripheral vascular surgery, the sealing property is particularly useful. This type of surgery could be in practice compared to microsurgery, where the possibility to avoid sutures is certainly advantageous. Moreover, a rapid sealing allows to obtain a stable consolidation within short time, certainly sooner than with the traditional sutures.

In thoracic surgery, the indications to the use are mainly bronchial and parenchymal sutures, where the control of air leak through the sealing properties results in a post-surgical rapid and safe course. In pulmonary surgery, if a complete aerostasis is not achieved, the time of hospitalization increases because of the necessity to perform thoracic drainages.

### – *Urological surgery (16)*

Also in this field, fibrin sealing can represent a valid technical tool in many procedures. The complete

compatibility with the tissues, as well as the hemostatic and sealing effects for anastomoses, confer to this product some irreplaceable peculiarities, allowing to realize tissue synthesis in the best possible way. In urological surgery, in fact, it is necessary that sutures, being in direct contact with urines, are carried out in such a manner to avoid the possible occurrence of an urinose fistula. Just the adhesive property of Tissucol for any tissue allows to consolidate within a very short time the traditional sutures, making them more airtight. It is also extremely important the possibility to obtain a safe and perfect hemostasis in the presence of parenchymal sections, as in the conservative kidney surgery, or of large injured areas with seeping bleedings, as for example in the pelvic excavation after total cystectomy.

– *Plastic surgery (17-20)*

In this field there are many indications mostly related to the adhesive property. The take of the free flaps of transplanted skin is conditioned by two factors: the adhesion of the flap that has to be as much complete as possible and immediate, and the absence of hematomas that cause the failure of the take. Fibrin sealant, due to its sealing property, together with the hemostatic property, thus represents an ideal tool. Moreover, it can allow the biological cover in large injured areas, so representing a biologically favorable bed for skin transplantation. At last, the application of the product is particularly suitable for suturing delicate areas such as face or eyelids, or to be used in the skin cover of fingers.

**Personal experience (21)**

Our purpose was to establish the efficacy of human fibrin glue in preventing coagulative complications after inguinal hernia repair in patients with coagulation disorders.

A randomized controlled trial of 50 patients undergoing hernia repair according to Lichtenstein's technique under local anesthesia was performed. Patients had concurrent coagulopathies as a consequence of liver disease or long-term treatment with anti-coagulants for ischemic heart disease or cardiac rhythm disturbances. Coagulopathies were defined according to the following criteria: prothrombin time

<10.5 seconds, activated partial thromboplastin time <21 seconds, and fibrinogen <230 mg/dL. Patients were randomized in a 1:1 ratio with (group A) or without (control group B) use of human fibrin glue.

Postoperative hemorrhagic complications were significantly reduced in group A (4%) compared with group B (24%).

This study showed that human fibrin glue is effective in preventing local hemorrhagic complications after inguinal hernia repair in patients with concurrent coagulation disorders. This implies that the use of human fibrin glue reduces the costs of prolonged hospitalization related to such complications.

**Conclusions**

The important role of the biological sealant in surgery is highlighted by the long experience acquired on international level: in fact, so far more than 3,000 scientific papers have been published and millions of patients have been treated. The literature has always confirmed the effectiveness of the product and has also demonstrated the excellent local tolerability and the complete absence of undesirable effects and contraindications.

The authors often report also the favorable cost-benefit ratio, mainly due to the reduction of the hospitalization time, thanks to the rapid wound healing, to the early drainage removal and to the reduction of complications such as hematomas, sepsis, dehiscences and formation of fistulae (21, 22).

In conclusion, it is possible to affirm that Tissucol has to be considered a product with an excellent efficacy-safety ratio, as a result of more than 30 years of experience and experimentation. We can certainly declare that thanks to its properties, it has allowed to obtain considerable advantages, for example the possibility to improve the surgical procedures and in some cases to realize new techniques, hard to achieve until then.

**References**

1. Tokunaga Y, Tanaka K, Uemoto S, et al. Fibrin sealant of the cut surface of partial liver grafts from living donors. *J Invest Surg* 1995; 8: 243-51.

2. Suzuki Y, Kuroda Y, Morita A, et al. Fibrin glue sealing for the prevention of pancreatic fistulas following distal pancreatectomy. *Arch Surg* 1995; 130: 952-5.
3. Noun R. Fibrin glue effectiveness and tolerance after elective liver resection: a randomized trial. *Hepato-Gastroenterol* 1996; 43: 221-4.
4. Uranues S, Mischinger HJ, Pfeifer J, et al. Hemostatic methods for the management of spleen and liver injuries. *World J Surg* 1996; 20: 1107-12.
5. Katkouda N. Laparoscopic management of benign solid and cystic lesions of the liver. *Ann Surg* 1999; 229: 460-6.
6. Marczell AP. Indications for fibrin sealing in pancreatic surgery with special regard to occlusion of a nonanastomosed stump with fibrin sealant. In *Surgical Technology Int. VIII* (Szabo Z et al eds.), 1999: 32-6.
7. Fernandez Fernandez L, Tejero E, Tieso A. Randomized trial of fibrin glue to seal mechanical oesophagojejunal anastomosis. *Brit J Surg* 1995; 83: 40-1.
8. Pross M, Manger T, Reinheckel T, Mirow L, Kunz D, Lipfert H. Endoscopic treatment of clinically symptomatic leaks of thoracic esophageal anastomoses. *Gastrointest Endosc* 2000; 51: 73-6.
9. Patrlj L, Kocman B, Martinac M, et al. Fibrin glue – antibiotic mixture in the treatment of anal fistulae: experience with 69 cases. *Digest Surg* 2000; 17: 77-80.
10. Moore M, Burak WE Jr, Nelson E, et al. Fibrin sealant reduces the duration and amount of fluid drainage after axillary dissection: a randomized prospective clinical trial. *J Am Coll Surg* 2001; 192: 591-9.
11. Katkhouda N, Mavor E, Friedlander MH, et al. Use of fibrin sealant for prosthetic mesh fixation in laparoscopic extraperitoneal inguinal hernia repair. *Ann Surg* 2001; 233: 18-25.
12. Koveker G. Clinical application of fibrin glue in cardiovascular surgery. *Thorac Cardiovasc Surg* 1982; 30: 228-9.
13. Rousou J, Levitsky L, Gonzalez-Lavin L, et al. Randomized clinical trial of fibrin sealant in cardiac surgery patients undergoing re sternotomy or reoperation: a multicenter study. *J Thorac Cardiovasc Surg* 1989; 97: 194-203.
14. Giovannacci L, Renggli JC, Eugster T, Stierli P, Hess P, Gurke L. Reduction of groin lymphatic complications by application of fibrin glue: preliminary results of a randomized study. *Ann Vasc Surg* 2001; 15: 182-5.
15. Rousou JA, Engelman RM, Breyer RH. Fibrin glue: an effective hemostatic agent for nonsuturable intraoperative bleeding. *Ann Thorac Surg* 1984; 38: 409-10.
16. Canonico S, Selvaggi F, Santoriello A, Campitiello F, Petraroia F. L'impiego di una colla di fibrina umana negli interventi urologici per calcolosi. *Minerva Chir* 1986; 41: 569-72.
17. Achauer BM, Miller SR, Lee TE. The hemostatic effect of fibrin glue on graft donor sites. *J Burn Care Rehabil* 1994; 15: 24-8.
18. Horch RE, Bannasch H, Kopp J, Andree C, Ihling C, Stark GB. Keratinocytes suspended in fibrin glue (KFGS) restore dermo-epidermal junction better than conventional sheet grafts (CEG). *Plast Surg Forum* 1996; 19: 23-5.
19. Kulber DA, Bacilius N, Peters ED, Gayle LB, Hoffman L. The use of fibrin sealant in the prevention of seromas. *Plast Reconstr Surg* 1997; 99: 842-9.
20. Horch RE, Bannash H, Andree C, Kopp J, Stark GB. Single cell suspensions of cultured human keratinocytes in fibrin glue reconstitute the epidermis. *Cell Transplantation* 1998; 7: 309-17.
21. Canonico S, Sciaudone G, Pacifico F, Santoriello A. Inguinal hernia repair in patients with coagulation problems: prevention of postoperative bleeding with human fibrin glue. *Surgery* 1999; 125: 315-7.
22. Szucs TD, Haverich A, Odar JO (eds): *Economics of surgical procedures*. J.A. Barth Verlag, Heidelberg, 2000.

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