The Use of Autologous Fibrin Glue in Total Knee Arthroplasty

a report by
Erhan Basad

Assistant Medical Director and Orthopaedic Surgeon, Clinic for Orthopaedic Surgery, Giessen-Marburg University Hospital

Fibrin Glue – A Multipurpose Sealant

Fibrin glue (FG) mimics the last step of the physiological coagulation cascade to form a fibrin clot at the site of application, independent of the patient’s coagulation process. Advantages of FG, include rapid haemostasis, accelerated wound healing and protection against bacterial infections. FG may promote integration of skin grafts in patients with thermal injuries, and provide support for reconstructive surgeries, which may contribute towards improving patient outcome in surgery. FG consists of concentrated human fibrinogen that is activated by the addition of thrombin and calcium chloride. For cartilage repair in orthopaedic surgery, FG provides fixation of cell-carriers without sutures. FG is also applied as a carrier for cells, growth factors and pharmacologic substances, especially as a promising agent for tissue engineering techniques. In the case of allogeneic commercial fibrin glue (CFG) there exist valid concerns about transmitting viral or prion infections, while allergic reaction to bovine-derived factor V may inhibit haemostasis in the previously exposed patient. CFG is also expensive for use in larger quantities, is not biocompatible and is probably cytotoxic, due to some antifibrinolytic ingredients. Aprotinin, for instance, is added into some commercial fibrin glues to provide delayed fibrinolysis of the clot, but also shows a concomitant slower regeneration of granulation tissue, thus indicating that aprotinin is not beneficial for wound healing. For the prevention of adverse effects with aprotinin, alternate substances like nafamostat mesilate are investigated as suitable antifibrinolytic agents.

The non-automated production of autologous fibrin glue (AFG) from single-donation plasmapheresis has been described by Casali et al. As compared with an automated device technique, these non-automated methods are time-consuming and are not suitable within a patient-near unit in a clinical routine environment. The available commercial devices allow the production and use of AFG within a surgical centre. CryoSeal® is an automated device that can produce a 100% autologous fibrin sealant. The CryoSeal system with its plasma processing disposable sets prepares both components of fibrin sealant (FS), cryoprecipitate and thrombin from a single unit of plasma in about an hour.

The CryoSeal FS system consists of two components, a thermodynamic device and a sterile plastic device which together can prepare both components of FS from a single unit of plasma. The thermodynamic device uses a heat transfer plate to control plasma temperature. Freezing and thawing of plasma results in a separation of cryoprecipitate from the cryo-poor plasma. Active thrombin is harvested from a reaction chamber of the Thrombin Activation Device (TAD). The active thrombin and cryoprecipitate are both stored in sterile over-wrapped syringes that can be stored frozen at -18°C or colder until just prior to use. To prepare the FS for use, both the cryoprecipitate and thrombin are thawed for approximately 20 minutes at 30–37°C. In this study, 600ml of whole blood was collected and subsequently separated into plasma and red blood cells. The red blood cell concentrate was re-transfused to the donor. The FG components were produced from platelet-poor plasma using the CryoSeal system. From each production cycle, active thrombin and cryoprecipitate were collected in three pairs (16ml) of sterile over-wrapped syringes and were stored frozen at -80°C until just prior to use.

Total Knee Arthroplasty

The reduction in blood loss and the need for blood transfusion in joint-replacement and spine surgery was always in the interest of orthopaedic surgeons. If cost/benefit relations are taken into consideration, current reviews about pre-operative autologous blood donation show uncertain results, whereas peri-operative blood salvage still shows success in heavy-bleeding surgery. The focus of new research is to develop strategies to avoid the need for blood transfusion. Sealing the bleeding surfaces of a wound with fibrin glue became promising, but was compromised by the risk of infection and high costs of commercially produced fibrin sealants. The effectiveness of allogenetic CFG in reducing blood
loss in total knee arthroplasty (TKA) surgery was investigated by Levy et al. The use of CFG in TKA was shown to be an effective and safe method of reducing blood loss and blood transfusion requirements. However, the risks of infection or immunisation, as well as the economic aspects, have not, so far, been able to be adequately solved in contentment when CFG is applied. In contrast, AFG promises an adjustable solution with virtually no risk of infection, transmission and immunisation. Based on the promising results of Levy et al., the author performed a controlled and randomised pilot study to prove the effectiveness and safety of AFG in TKA surgery. The peri-operative blood loss was reduced by 50%. Patients treated with AFG had better cardiovascular stability, better ROM and less pain as compared with the control group. So far, no adverse effects, such as arthrofibrosis or infection, could be found. Since these can be considered as the early results of a pilot study, there are plans to run a new study with more patients and longer follow-ups.

Discussion and Perspectives

Buchta et al. investigated biochemical and mechanical properties of AFG produced with commercially available devices and compared these parameters with the industrially produced FG. The study demonstrated that the mechanical properties of FG are influenced by the presence of different components, such as fibrinogen, fibronectin, factor VIII, factor XIII, thrombin and the presence of anti-fibrinolytic agents. Gille et al. demonstrated that even partially autologous FG contains significantly higher amounts of transforming growth factors – beta 1 and 2 – which were proven favourable with respect to migration pattern, morphology and viability of cells. Buchta et al. also demonstrated that there were variations in the composition of the final product AFG derived from commercially available devices, which may be due to the natural variation of concentrations of coagulative proteins in plasma. The concentration of thrombin, for instance, influences the speed of clot formation when it is below a threshold level. This means that the quality of AFGs can differ from patient to patient or even within the same donor, depending on the donor’s current state, unless the device achieves this level of thrombin. A standardised composition of thrombin and fibrinogen is available in commercially produced FG, because these products are fractionated from a large pool of allogeneic plasma. The significance, if any, of these variations in composition must be addressed in the clinical setting.

A potential disadvantage of allogeneic FG is the possible development of immune-mediated adverse effects, including coagulopathies or anaphylactic shock. Besides bovine thrombin, it is also known that serious immune-mediated injury can occur due to allergic reactions with bovine-derived aprotinin used in some pooled allogeneic FS as an anti-fibrinolytic. The reported adverse effects associated with aprotinin immunogenicity range from mild skin rashes to fatal anaphylaxis after local application of fibrin glue. From 1990 to 1998, reports of five allergic reactions following one million exposures to fibrin sealant were reported. Allogeneic FG carries a risk of pathogen transmission including viral infections. To prevent exposure to allogeneic materials and the risk of blood transmitted diseases, the use of self-produced AFG is an attractive alternative to CFG. The availability of AFG as a safer product in high amounts opens new fields for the application of fibrin adhesives in orthopaedic surgery. During TKA surgery, the amount of blood loss can be influenced by several factors, including a bloodless field, non-traumatic preparation, the surface of open spongous bone not covered by the implant and achieving proper haemostasis prior to wound closure. In addition, post-operative blood loss can occur during the application of controlled vacuum to the drain and by controlling blood pressure through adequate pain management. As a result of this, the application of FG only addresses one of several issues that impact blood loss. Therefore, the surgical procedure has to be adapted for the use of FG. Thermodynamic devices, dedicated disposable sets, applicator devices and trained personnel are all requirements for the successful production and use of AFG.

Current studies show that the use of AFG in orthopaedic surgery provides clinical benefits for patients, and economic benefits due to a reduced need for post-operative intervention, reduced hospital stay and early rehabilitation. A study with a larger number of patients and longer observation periods is necessary to confirm these results.

In summary, the advantages of AFG are autologous derivation, lack of bovine products and the possibility of its production and storage close to the patient in a clinical environment. With the increasing availability of AFG, its use will continue to evolve into almost every field of surgery and tissue engineering. AFG is a safer and more biocompatible successor to CFG, which encourages surgeons to use it in broader application areas. Optimisation and more compact devices for the production of AFG in the intra-operative setting will have to accompany this development.

A longer version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchbriefings.com).
Cryoseal Fibrin Sealant components (cryoprecipitate and thrombin) are prepared from one unit of 100% human-derived autologous or single-donor retested plasma, eliminating the risks associated with pooled plasma products.

The 100% Human Alternative

- No bovine or other animal derived components
- No synthetics (glutaraldehyde, cyanoacrylate)
- No antifibrinolytic agents
- Easy to use. Easy to apply. Simply thaw, attach a tip and apply. No reconstitution. No mixing.

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Tel: +1(916) 858-5100
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Cryoseal Fibrin Sealant is not available for sale in the United States.