Use of Fibrin Sealants in Obstetric Hemorrhage

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INTRODUCTION

In recent years, a variety of methods have been described to arrest bleeding, including a group of compounds which act as fibrin sealants. In the UK, the Confidential Enquiry into Maternal Deaths recommends that all available interventions should be considered, including hemostatic agents. Topical hemostatic agents have been used with excellent results in other surgical specialties, such as neurosurgery, urology and gynecology. While there is no replacement for meticulous surgical hemostasis, the highly viscous gels have been successfully used in cases of PPH. This chapter reviews their uses and explains how they work.

BACKGROUND AND MECHANISM OF ACTION

Fibrin sealants are biological adhesives that mimic the final step of the coagulation cascade. Main components of sealants include fibrinogen, plasmatic proteins and factor XIII, on the one hand, and thrombin, calcium chloride and an antifibrinolytic agent such as aprotinin, on the other. The first three components are extracted from human plasma, whereas calcium chloride and aprotinin both derive from bovine lungs. Mixing fibrinogen and thrombin simulates the final stages of the natural coagulation cascade to form a structured fibrin clot similar to a physiological clot. This clot is naturally degraded by proteolytic enzymes from the fibrinolytic system, such as plasmin. High concentrations of these enzymes are present in response to tissue inflammation. As a result of their hemostatic and adhesive properties, fibrin sealants have been extensively used in most surgical specialties for over the past two decades. They are used to reduce blood loss and postoperative bleeding. However, their uses in obstetrics are more recent and require further evaluation.

Reports published between 2001 and 2003 indicate that fibrin sealants are a safe and highly effective form of surgical adhesive. A survey undertaken in 2000 at the University of Virginia hospital found that over 90% of the surgeons who had used fibrin sealants were pleased with the results. Several studies from the US have reported that fibrin sealants significantly improved surgical outcomes by shortening the time required for operations, lowering the rate of infections and other complications, minimizing blood loss during surgery and reducing the amount of scar tissue formed over incisions. German researchers have found that fibrin sealants containing factor XIII generally give better results than those that do not. Fibrin sealants have several advantages over conventional surgical techniques, such as suture, ligation and cautery. These include speeding up the formation of a stable clot, application to very small blood vessels and areas that are difficult to reach with conventional sutures, reducing the amount of blood lost during surgery, lowering the risk of postoperative inflammation or infection and, finally, convenient absorption during the healing process. They are particularly useful for minimally invasive procedures and for treating patients with blood clotting disorders.

PRODUCTS

Fibrin sealants are prepared and sold under many brand names such as TISSEEL® (Baxter Healthcare Corporation), Evicel® (Ethicon, Somerville, NJ), FloSeal® (Baxter Healthcare Corporation), BioGlue® (CryoLife, Kennesaw, GA), Crosseal® (Ethicon, Somerville, NJ) and Hemaseel APR® (Hemacure Corp., Sarasota, FL). The surgeon and operating room staff must be aware that fibrin sealants are not identical in composition or use. For the individual methods of application, please refer to and follow the individual product information leaflet.

PREPARATION

The preparation and application of fibrin sealants are complex. The thrombin and fibrinogen are freeze-dried and packaged in vials that must be warmed before use. These two ingredients are then dissolved in separate amounts of calcium chloride solution. Next, the thrombin and fibrinogen solutions are loaded into a double-barrelled syringe that allows them to mix and combine as they are sprayed on the incision. Pieces of surgical gauze or fleece may be moistened with the sealant solutions to cover large incisions or to stop
heavy bleeding\textsuperscript{9}. Figure 1 shows the mechanism of action of fibrin sealants.

**SAFETY**

Because the first commercial fibrin sealants relied on a consistent and concentrated source of human fibrinogen, the Food and Drug Administration in the USA revoked the license for the clinical use of pooled commercial fibrinogen concentrates owing to the high risk of hepatitis transmission with the fibrinogen\textsuperscript{10}. In an attempt to resolve this issue, products marketed since that time have adopted various viral inactivation procedures including pasteurization (60\degree C for 10 h, liquid state), solvent-detergent treatment, steam treatment (60\degree C for 30 h, dry state), ultraviolet C (UVC) irradiation, nanofiltration (35 nm) and dry heat treatment (100\degree C for 30 min). Although the risks of viral transmission from fibrin sealants prepared from pooled human plasma are considered to be low, a ‘zero’ risk cannot be guaranteed\textsuperscript{11,12}. Despite their advantages, sealants are not without a major disadvantage in that they must be used topically, as all can cause intravascular thrombosis if injected into the circulation. Furthermore, the risk of air or gas embolism is present when using air- or gas-pressurized spray devices\textsuperscript{13}. The following precautions are advised:

- Use the applicator, spray set and pressure control device or regulator as recommended in the labeling or information for use (IFU) of the hemostatic agent
- Use an air or gas pressure setting within the range recommended by the manufacturer of the sprayer
- Ensure that distance between the spray head and the tissue surface is not less than the minimum recommended by the manufacturer of the sprayer
- Monitor blood pressure, pulse, oxygen saturation and end tidal CO\textsubscript{2} for signs of an air or gas embolism.

**USES IN PPH**

Although no large trial data are available to date about their safety in obstetric patients using fibrin sealant to deal with PPH is now appearing in the literature. Most of the data come from single case reports with a successful outcome.

Reports of uses of fibrin sealants to manage cases of PPH are shown in Table 1 (see Chapter 58 for discussion of case reports).

Fibrin sealants may be an excellent adjuvant in the Jehovah’s Witness patient experiencing PPH, for example, a 30-year-old nulliparous patient underwent cesarean section for dystocia and suspected chorioamnionitis, and subsequently developed PPH that required management with oxytocin, ergometrine, carboprost, uterine artery ligation and Hayman compression sutures. The patient ultimately required two additional visits to the operating room, culminating in hysterectomy. Use of tranexamic acid, recombinant factor VIIa and TISSEEL was instrumental in halting the ongoing hemorrhage\textsuperscript{18}. The use of fibrin sealants is a matter of personal choice for Witnesses and should be discussed in the preoperative period as outlined in Chapter 72\textsuperscript{19,20}.

Palacios-Jaraquemada has written extensively about the uses of fibrin glue with external uterine elastic bandages in patients with severe PPH\textsuperscript{21}. After circulatory stabilization by external aortic compression, laparotomy and identification of the source of bleeding, compression sutures were applied and intruterine fibrin glue was administered; immediately thereafter, an external elastic bandage was wrapped around the uterus to compress it. After hemostasis had persisted for some time, the bandage was removed, and uterus and abdomen were then closed. Application of external uterine elastic bandage resulted in hemostasis within 45 min after aortic compression. Hysteroscopy 6 months after the procedure showed no signs of uterine ischemia or endometrial adhesions. The application of endouterine fibrin provided the placental bed with an excellent hemostatic substrate to avoiding oozing and re-bleeding. Hysteroscopic examination at a later date showed complete recovery of the endometrial cavity without synechiae\textsuperscript{21}. This is an important factor as most of the women are young and desire more children. Table 2 shows the risk of developing synechiae after different techniques used to treat PPH.

The procedure for applying the fibrin sealant, FloSeal, is outlined below:

1. Identify the source of the bleeding at the tissue surface. Apply FloSeal Hemostatic Matrix FAST to the deepest part of the wound or lesion, i.e. the source of bleeding at the tissue surface.

2. This is the target site for FloSeal Hemostatic Matrix application. Do not inject FloSeal into...
blood vessels. Do not apply FloSeal in the absence of active bleeding.

(3) The flowable nature of FloSeal allows it to conform to any irregular wound geometries and be applied in difficult-to-reach locations.

(4) After creating a cone-like mound of FloSeal over the bleeding site, immediately gently place FloSeal to the bleeding surface with a moistened gauze sponge for 2 min.

(5) FloSeal granules allow high concentrations of thrombin to react rapidly with the patient’s fibrinogen and form a mechanically stable clot.

(6) FloSeal granules have a maximum, controlled swell volume of approximately 20%, which is achieved within about 10 min and physically, restricts the flow of blood.

(7) FloSeal can be reapplied, if necessary. Reapply at the base of the wound and backfill the lesion. Once hemostasis is achieved, gentle irrigation should always occur to remove excess product that has not been incorporated into the clot. Do not disrupt the clot by physical manipulation or suction.

(8) FloSeal allows visualization of the surgical site both during and after application.

(9) FloSeal is biocompatible and fully resorbs within 6–8 weeks, consistent with normal wound healing.

An example of the mechanism of action and usage technique is shown in Addendum A.

**CONCLUSION**

Fibrin sealants are new tools to arrest bleeding in patients with PPH. Early reports of their use are promising. Fibrin sealants have thrombin and fibrinogen which form a stable clot and arrest bleeding. This is independent of the patient clotting mechanism; hence, they are ideal in the patient with coagulopathy. Fibrin sealants have been called a ‘clot in a bottle’. Their use has been reported with traumatic PPH and in patients with placenta previa and Jehovah’s Witnesses. Staff need to be trained in its use as well as its preparation. More research is needed to determine its safety and efficiency in managing PPH.

**PRACTICE POINTS**

- Fibrin sealants are new tools in treating PPH
- Their use mimics the final steps of the physiological clotting cascade, thus achieving hemostasis
- Fibrin sealant produces a fast, effective, clear stable clot
- Sealants function independently of patient’s own clotting mechanism
- Early case reports are promising. More studies and training are needed for fibrin sealant evaluation in the management of PPH.

**References**


**Table 1** Reports of uses of fibrin sealants to manage cases of PPH

<table>
<thead>
<tr>
<th>Report</th>
<th>Year</th>
<th>Sealant</th>
<th>Success rate</th>
<th>Special consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhulkotia</td>
<td>2009</td>
<td>TISSEEL</td>
<td>1/1</td>
<td>Vulval hematoma and vaginal laceration</td>
</tr>
<tr>
<td>Whiteside</td>
<td>2010</td>
<td>TISSEEL</td>
<td>1/1</td>
<td>Vaginal laceration</td>
</tr>
<tr>
<td>Law</td>
<td>2010</td>
<td>FloSeal</td>
<td>1/1</td>
<td>Placenta previa</td>
</tr>
<tr>
<td>Moriarty</td>
<td>2008</td>
<td>FloSeal</td>
<td>1/1</td>
<td>Vault hematoma</td>
</tr>
<tr>
<td>Arab</td>
<td>2010</td>
<td>TISSEEL</td>
<td>1/1</td>
<td>Bleeding in a Jehovah’s Witness</td>
</tr>
<tr>
<td>Palacios-Jaraquemada</td>
<td>2010</td>
<td>TISSEEL</td>
<td>6/6</td>
<td>External elastic bandages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No uterine synchiae</td>
</tr>
</tbody>
</table>

HSC, hysteroscopy; HSG, hysterosalpingogram

**Table 2** Uterine synechiae following different techniques to manage PPH

<table>
<thead>
<tr>
<th>Report</th>
<th>Year</th>
<th>n</th>
<th>Management of PPH</th>
<th>HSC or HSG</th>
<th>Synchiae</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poujade</td>
<td>2011</td>
<td>119</td>
<td>Uterine compression sutures</td>
<td>32</td>
<td>18% (6/32)</td>
<td>13</td>
</tr>
<tr>
<td>Poujade</td>
<td>2011</td>
<td>33</td>
<td>Uterine compression suture (Hackethal technique)</td>
<td>15</td>
<td>26.7% (4/15)</td>
<td>—</td>
</tr>
<tr>
<td>Sentilhes</td>
<td>2010</td>
<td>101</td>
<td>Uterine embolization</td>
<td>8</td>
<td>8% (8/111)</td>
<td>26</td>
</tr>
<tr>
<td>Palacios-Jaraquemada</td>
<td>2010</td>
<td>10</td>
<td>Fibrin glue and uterine external elastic bands</td>
<td>8</td>
<td>0% (0/8)</td>
<td>—</td>
</tr>
</tbody>
</table>

HSC, hysteroscopy; HSG, hysterosalpingogram
Addendum A: Example of how to use a fibrin sealant

From Baxter Healthcare Corporation, with permission

Step 1  Get FloSeal to the site of bleeding. Deliver to base of wound allowing it to conform to the shape of wound

Step 2  Use enough FloSeal to cover the site

Step 3  Apply sealant quickly. Extrude at a faster rate than the bleeding to prevent product from being washed away by brisk bleeding

Step 4  Keep FloSeal at the site with a moistened swab, and approximate with fingers to hold in place

Step 5  Wait 2 min before inspection (brisk bleeding/coagulopathic patients may require longer) to confirm hemostasis. Reapplication may be required

Step 6  Once hemostasis is achieved, gently irrigate excess granules that are not incorporated into the clot.
Step 7  FloSeal is reabsorbed by the body within 6–8 weeks, consistent with the time frame of normal wound healing.