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Review Article

THE USE OF FIBRIN SEALANT IN UROLOGY

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ABSTRACT

Purpose: Fibrin sealant has been increasingly applied in various surgical fields, including urological surgery, in the last 2 decades. We determined the safety and efficacy of fibrin sealant in urological surgery and identified areas that need further clinical investigation.

Materials and Methods: A MEDLINE search of all available literature regarding the use of fibrin sealant was performed. All articles, including experimental animal studies, prospective and retrospective studies, case series and case reports of fibrin sealant for hemostasis and/or other urological applications, were identified and reviewed.

Results: Prospective randomized studies in the field of thoracic and trauma surgery show the efficacy and safety of fibrin sealant for hemostasis. Based on these data fibrin sealant has been used successfully for hemostasis during partial nephrectomy and traumatic renal reconstruction. A number of experimental animal studies, case series and case reports show the efficacy of fibrin sealant for ureteral anastomosis, microsurgical vasal anastomosis, fistula repair, circumcision and orchiopexy as well as it use as an adjunct in other areas of reconstruction.

Conclusions: Fibrin sealant is an effective and safe topical agent for controlling surface bleeding during elective and trauma related urological procedures. Using fibrin sealant as an adhesive for reconstruction requires further prospective studies. The introduction of laparoscopic procedures in urology may expand the indications for fibrin sealant as an alternative method of tissue reapproximation. Limiting the routine use of fibrin sealant to procedures with demonstrable benefits is desirable and would lead to a cost saving approach.

KEY WORDS: fibrin tissue adhesive, urologic surgical procedures, wound healing, hemostatis, suture techniques

The use of fibrin sealant has increased in numerous surgical fields, including urological surgery, in the last 2 decades. A wide range of commercial or blood bank produced fibrin sealant preparations has been applied.[1] The 2 major areas of fibrin sealant application are as a topical agent for hemostasis and as an adhesive for tissue approximation alone or combined with conventional suturing techniques. In contrast to synthetic materials, fibrin sealant has the advantage of being biodegradable and it does not result in significant inflammation, tissue fibrosis or foreign body reaction. It is absorbed within days to weeks.[2,3] Fibrin sealant may promote angiogenesis, local tissue growth and repair.[1]

Despite increasing applications and extensive research in European countries, Japan and Canada the use of commercial fibrin sealant in the United States was not approved until recently.[4] This delay resulted in the use of various blood bank produced fibrin sealant products with different adhesive and hemostatic properties, which makes data comparison difficult. Varied sealant preparations as well as the lack of prospective randomized studies resulted in individualized use of fibrin sealant for various urological procedures. We reviewed the literature on fibrin sealant for urological surgery and identify the safety and efficacy of this material for the reported procedures. Areas of clear benefit and areas that need further clinical investigation are discussed.

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HISTORICAL DEVELOPMENT

In 1909 Bergel described the use of dry plasma to facilitate hemostasis.[5] Fibrin patches were applied in 1915 for hemostasis in cerebral surgery and for the control of parenchymal organ bleeding during World War I.[6] Initial experimental and clinical use of fibrin sealant as an adhesive was in the field of plastic surgery for microsurgical peripheral nerve anastomosis.[7] However, the quality of the initial fibrin sealant preparations was poor, mainly due to in vivo concentrations of fibrinogen and fibrin. In 1944 researchers accelerated formation of the fibrin clot by mixing fibrinogen with bovine thrombin, which was administered for attaching skin grafts.[8] However, these techniques had limited usefulness due to absent fractionation technologies for producing purified sources of fibrinogen. The lack of a concentrated source of fibrinogen resulted in suboptimal adhesive properties in the early studies and the use of fibrin sealant remained limited.[1] The introduction of advanced purification and fractionation techniques enabled the production of freeze-dried fibrinogen at higher concentrations in the 1970s. Subsequently the high concentration of commercially available fibrinogen and other components, such as thrombin and factor VIII, improved the rheological properties (elasticity, tensile strength and adhesiveness) of modern fibrin sealants.[1]

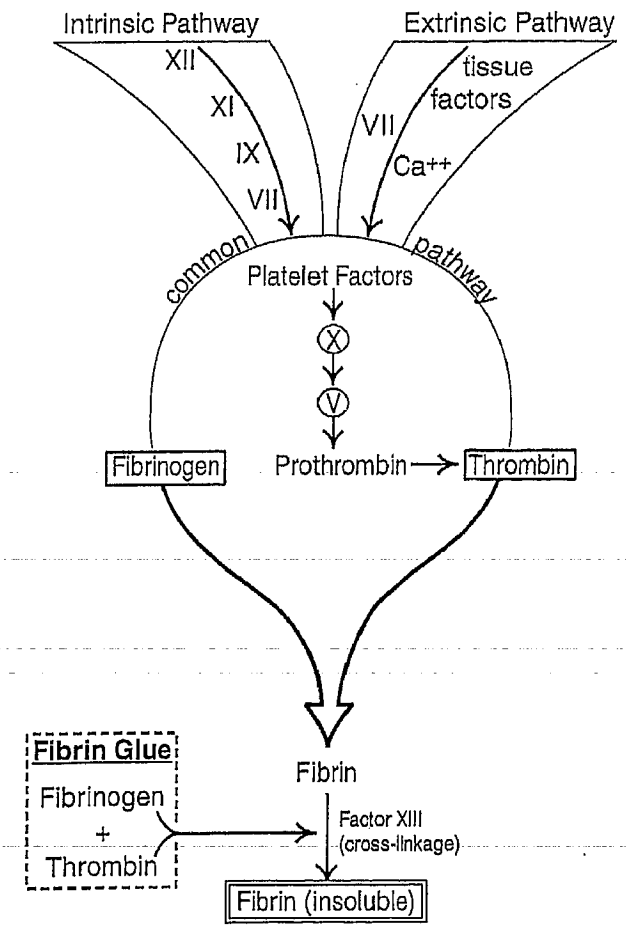
The acceptance of plasma products such as fibrinogen in the United States was decreased due to the risk of viral contamination despite the extensive use of commercially available fibrin sealant in Europe in the early 1970s. Fibrin sealant preparation methods are based on a concentrated

source of human fibrinogen, which historically has been associated with hepatitis B transmission.[2] In 1978 the Food and Drug Administration (FDA) revoked the license for the clinical application of commercial fibrinogen concentrates and prohibited the development of commercial fibrin sealant products until further purification and viral detection methods were developed.[2] This decision resulted in the use of autologous or single donor fibrin sealant preparations in the last 2 decades.[4,9] A theoretical advantage of these products is the lack of disease transmission when autologous fibrin sealant is used. However, the fibrinogen concentration achieved is not uniform and preparation is time-consuming.

Several commercial fibrin sealant preparations are currently available in Europe, Canada and Japan.[1] Tisseel (Immuno, Vienna, Austria) was the first commercially available fibrin sealant approved by the FDA. Subsequently most recent experimental and clinical studies have used this product. Currently in the United States Tisseel (Baxter Healthcare Corp., Irvine, California) and Hemaseel (Hemacure, Sarasota, Florida) are available.

MECHANISM OF ACTION

The figure shows the coagulation cascade. Irrespective of the mode of preparation the effect of fibrin sealant mimics the final step of the coagulation cascade, which involves the conversion of fibrinogen to fibrin and the cross-linking of fibrin monomers into an insoluble complex.[1,8,10] Importantly this process proceeds independently from internal clotting mechanisms, thus, resulting in hemostasis even in the presence of systemic coagulation defects.[3] This process occurs in the presence of thrombin, factor VIII, fibronectin and ionized calcium. Fibrinogen is a soluble blood component that comprises 0.2% of whole blood volume. Fibrinogen is converted into insoluble fibrin in the presence of thrombin as part of the intrinsic and extrinsic coagulation cascade. Fibrinogen is a glycoprotein with 3 pairs of polypeptide chains called Aα, Bβ and γ. The central domain contains fibrinopeptide A and B, which are cleaved during the enzymatic conversion to fibrin. After cleavage the fibrin monomers assemble by noncovalent interaction to form 2-strand fibrils. In the presence of factor XIII, that is fibrin stabilizing factor, fibrin undergoes covalent cross-linking to form a cross-linked network. Optimal cross-linking can be achieved at concentrations of 5 to 20 mM. calcium chloride at an ionic strength of 0.015 M.[1]



Coagulation cascade showing site and mechanism of fibrin sealant action. *XII, XI, IX, VII, X* and *V*, factors.

VARIOUS FIBRIN SEALANT PREPARATIONS

Fibrin sealant can be produced from pooled blood sources or from a single blood donor. The single donor blood can be allogenic or autologous. The use of pooled blood products is the basis for the commercially available fibrin sealant.

Commercial fibrin sealant. Commercial products, such as Tisseel and Periplast (Behringwerke AG, Marburg-Lahn, Germany), have been extensively applied in Europe. A primary component of the synthetic fibrin sealant is highly concentrated human fibrinogen. The vial also contains fibronectin, factor XIII and plasminogen. It is reconstituted in a solution containing aprotinin, which is a bovine derived protease inhibitor. The other component is a catalyst solution containing bovine thrombin suspended in calcium chloride solution.

The reaction proceeds by thrombin cleavage of fibrinopeptides A and B from the fibrinogen molecule, which results in the formation of fibrin monomers. Thrombin also activates factor XIII, which in turn enables stable fibrin cross-linkage and the formation of a firm nonfriable clot. Fibronectin is also a participant in fibrin cross-linkage. Its inclusion in the fibrin sealant system appears to promote cellular migration and fibroblastic growth into areas of fibrin seal application.

Single donor and autologous fibrin sealant. Previously restricted access to commercial fibrin sealant resulted in the development of alternative techniques for fibrin sealant production in the United States. Various methods have been described for preparing fibrin sealant from autologous or single donor blood.[4,9,11,12] The principle of all methods involves the isolation of fibrinogen from whole blood or platelet rich plasma, as achieved by initial centrifugation of blood products combined with cryoprecipitation, or chemical precipitation with ammonium sulfate, polyethylene glycol or ethanol.[2] Cryoprecipitation is the gold standard for fibrinogen preparation, while for small amounts of autologous blood chemical methods may be more feasible for concentrating the fibrinogen.[13] The advantage of chemical concentration is that processing time is minutes versus hours for cryoprecipitation techniques. However, it has the disadvantage of chemical additives. These concentrated fibrinogen solutions are then mixed with bovine thrombin and used as fibrin sealant. The clotting reaction is enhanced when thrombin is reconstituted with calcium chloride. Autologous fibrinogen cryoprecipitate eliminates the risk of viral transmission, although it produces limited amounts of fibrinogen. Comparative studies show that commercially prepared products from pooled human blood generally contain the highest concentration of 75 to 115 mg./ml. fibrinogen.[2] Cryoprecipitation and centrifugation methods with autologous or single donors yield a fibrinogen concentration of 21.6 to 40 mg./ml. Experimental data imply that the fibrinogen content of fibrin sealant is critical to sealant tensile strength. The thrombin content of fibrin sealant affects the rapidity of hemostasis and has a major

role when the hemostatic and sealing properties of the sealant are the most important clinical considerations.[1-3, 13] Various fibrin sealant preparations using different techniques, including cryoprecipitation and chemical methods or commercial fibrin, make comparison of previous studies difficult.

Methods of application. The 2 components of fibrin sealant are applied sequentially or simultaneously to the surgical field by a dual syringe system with or without an endoscopic delivery system, spraying or sponges. A common mode of application is the double-barreled Duplojet syringe apparatus (Immuno), which enables simultaneous application of equal amounts of the fibrinogen and thrombin solutions through a blunt tipped needle. A laparoscopic applicator is also available. Alternatively the material can be applied by spraying with forced sterile gas by mixing equal proportions of the solutions on application. A sandwich technique using a layer of fibrinogen followed by a layer of thrombin has also been used in oral surgery and for applying collagen fleece to wound surfaces.[12]

Proper fibrin sealant application is required for optimal adhesive function. After fibrin sealant is applied to 2 surfaces for approximation the 2 surfaces should be brought in contact immediately before polymerization of the fibrin sealant. If fibrin is applied to 1 surface and allowed to polymerize, it will act as anti-adhesive, preventing adherence of the 2 surfaces.

APPLICATIONS OF FIBRIN SEALANT IN UROLOGY

Fibrin sealant has proved to be an effective hemostatic agent in several surgical fields, including cardiovascular, thoracic and abdominal surgery. In a large multicenter prospective study at 11 institutions in the United States the effect of fibrin sealant for hemostasis in cardiac surgery was compared with other conventional techniques.[14] In this study hemostasis using fibrin sealant was achieved at a significantly higher rate and in a shorter period than with other conventional topical agents. Subsequently others observed the efficacy of fibrin sealant for hemostasis during liver and spleen trauma. In a controlled prospective study from University of California-Los Angeles administering fibrin sealant resulted in decreased mortality and morbidity due to traumatic injury to the spleen and liver.[15, 16] Despite this use of fibrin sealant in the fields of cardiothoracic and general surgery the use of fibrin sealant in urology has been limited to animal experimental studies, retrospective reviews, case series and case reports. While the efficacy and safety of fibrin sealant has been reported for some urological procedures in animal models or clinical studies (see table), in other areas its usefulness has not been demonstrated.

Importantly fibrin sealant is currently approved for 3 on-label uses in the United States, including splenic trauma, colon sealing and cardiac surgery. All urological applications of fibrin sealant are not FDA approved at this time. We present the use of fibrin sealant in urology.

RENAL SURGERY

Early animal studies showed the effectiveness of fibrin sealant for hemostasis.[17] In renal surgery no randomized prospective studies are available on the usefulness of fibrin sealant for hemostasis. Several single institution studies indicate the efficacy of fibrin sealant for hemostasis during renal surgery.[18, 19] These groups applied fibrin sealant during renal trauma and renal sparing surgery. Urlesberger et al used fibrin sealant for renal surgery.[20] In their study 33 partial nephrectomies, 9 nephrotomies and 4 renal ruptures were managed with fibrin sealing. Their technique involved a commercial fibrin adhesive system, including fibrinogen cryoprecipitate, thrombin, factor VIII and a proteinase inhibitor. Fibrin sealant was applied to the cut surface of the renal parenchyma with manual compression for 5 minutes and then covered with a collagen patch. Sutures were placed for

Urological applications of fibrin sealant

References	Procedure	Indication	Animal Studies	Clinical Studies
Braun,[17] Kram,[18] Levinson,[19] Urlesberger,[20] Lapini,[21] Pfab[22] and Janetschek[23] et al	Renal sparing surgery	Hemostasis	Effective	Effective
Eden[24, 25] and Barrieras et al[26]	Pyeloplasty	Anastomosis	Inconclusive	Effective in limited cases combined with sutures
Schultz,[27] and McKay,[28] Wolf[29] and Anidjar[30] et al	Ureteral surgery	Anastomosis	Inconclusive, ineffective without additional sutures in 1 study	Effective in limited cases combined with sutures
Tostain,[35] Papadopoulos,[31] Schneider,[32] Welp,[33] Rossi,[34] Yashi,[36] Grumbl[37] and Morita[38, 39] et al	Fistula repair	Closure	Effective	Effective in case reports, case series
Wagenknecht,[47] Silverstein and Mellinger,[41] Weiss and Mellinger,[42] and Bach,[40] Niederberger,[43] Shekarriz[44] and Vankemmel[45, 46] et al	Vasovasostomy	Anastomosis	Effective	Effective
Shekarriz et al[48, 49]	Vasoepididymostomy	Anastomosis	Effective	Not available
Taneli et al[51]	Reflux surgery	Bulking agent	Effective	Not available
Noeske[52]	Orchiopexy	Adhesive	Not available	Effective
Maier,[57] and Avanogmacr,[53] Martinowitz[54, 55] and Tock[56] et al	Circumcision	Hemostasis	Not available	Effective mostly in hemophilia cases
Kokesch-Hauser et al[59]	Transplant surgery	Hemostasis (lymphocele)	Not available	Not effective
Gilly,[62] Moore,[63] Vaxman[64] and Furrer[65] et al	Lymph node dissection	Hemostasis (lymphocele)	Not available	Inconclusive
Jolic,[69] and Volz,[66] Wallwiener,[67] Kiilholma[68] and Kjolhede[70] et al	Bladder neck suspension	Adhesive	Not available	Not effective
Vecsey,[72] and Gasser,[71] Boeckmann[73] and Lobel[74] et al	Prostatectomy	Hemostasis	Not available	Inconclusive

collecting system closure, arterial hemostasis and renal capsule closure. For managing traumatic renal rupture a collagen patch was placed without additional sutures. There was no delayed hemorrhage and 5 cases of urinary fistula closed spontaneously. Kram et al applied fibrin sealant to treat renal trauma in 14 patients.[18] Sealant was sprayed over the lacerated area. For deep penetrating injuries fibrin was injected into the wound, creating a fibrin plug. There was no renal loss, infection, delayed bleeding or urinary leakage. They concluded that fibrin sealant was effective for hemostasis. Levinson et al used fibrin sealant for partial nephrectomy in 7 patients.[19] Sealant was applied to the cut surface of the kidney. There was no delayed hemorrhage or infection. In their experience fibrin sealant was effective for controlling venous bleeding from the cut surface of the kidney and it resulted in excellent hemostasis. Lapini et al used fibrin sealant in 67 cases of partial nephrectomy for renal tumors.[21] In their study fibrin sealant was applied to the cut surface in addition to at least 1 parenchymal suture. No postoperative hemorrhage was observed. A reported advantage of fibrin sealant in these studies was that the sealant was broken down and rapidly removed from the body by macrophages within 2 to 4 weeks, allowing normal wound healing. Conventional hemostatic agents are associated with increased infection, chronic inflammation and associated fibrosis.

Fibrin sealant is most effective for controlling surface hemorrhage and slow venous oozing. A relatively dry surface is essential before applying the sealant. If it can be achieved, the sealant can also be used for controlling minor arterial bleeding. Only Pfab et al described injecting fibrin sealant into a nephrostomy tract to prevent hemorrhage after percutaneous nephrolithotomy.[22] Although good results were achieved, no control group was mentioned. The advantage of this technique remains to be proved.

Recently the advent of laparoscopic nephron sparing surgery has resulted in the increase use of fibrin sealant for hemostasis in renal surgery.[23] Hemostasis represents a challenge when performing laparoscopic resection. Although fibrin sealant has been applied with good results, the fact that argon beam and bipolar coagulation are often used with the sealant makes evaluation of the relative merit of fibrin sealant confusing.

URETERAL SURGERY

Pyeloplasty. Fibrin sealant has been applied for pyeloplasty. Initial animal studies of fibrin sealant for laparoscopic pyeloplasty showed favorable results.[24] Based on these results Eden et al performed fibrin sealant pyeloplasty in 9 patients, which was exclusively laparoscopic in 8.[25] Approximating sutures were placed and fibrin sealant was applied to seal the anastomosis. Mean operative time was 180 minutes. Followup imaging at 1 to 2 years revealed satisfactory drainage. They concluded that this technique was more rapid than sutured laparoscopic pyeloplasty only. In contrast, in a porcine model comparing the efficacy of fibrin sealant and laser soldering for open pyeloplasty Barrieras et al noted that fibrin sealant pyeloplasty had a higher failure rate than laser soldering after 4 weeks.[26] The reason for this discrepancy is unclear. An explanation may be the number and location of the additional sutures placed before fibrin sealant application. It may be that fibrin sealant combined with a limited number of approximating sutures results in shorter operative time and comparable patency rates in cases of laparoscopic pyeloplasty. However, further clinical studies with a larger number of patients are necessary to evaluate this technique.

Ureteral anastomosis. In the early 1980s Schultz investigated fibrin sealant for ureteral repair after open stone surgery.[27] He did not find any advantage of fibrin sealant in addition to sutures, which was attributed to early detachment of the fibrin clot from the ureteral surface due to ureteral peristalsis movement. More recently, several animal studies have been done to examine the feasibility of fibrin sealant ureteral anastomosis for laparoscopic application with controversial results. McKay et al reported experimental studies in 10 pigs that compared fibrin sealant and conventional anastomosis with comparable results.[28] However, no long-term results were mentioned. Eden and Coptcoat compared fibrin sealant and laser assisted anastomosis in a porcine model.[24] In their experience the 2 techniques were comparable in regard to tensile strength but sealant was superior with respect to time and ease of surgery. Wolf et al compared alternative techniques and standard sutured anastomosis in a porcine model.[29] In 5 laparoscopic ureteral anastomoses using a commercial fibrin sealant no acute urinary leakage was observed, while urinary leakage occurred in 33%, 38% and 66% of anastomoses performed with a laser, a mechanical suturing device and free needle suturing, respectively. Fibrin sealant anastomosis was associated with less hydronephrosis proximal to the anastomosis and a significantly larger lumen compared with laser assisted anastomosis. Histological evaluation revealed significantly fewer abnormal features when using fibrin sealant versus conventional suturing techniques. Overall in their experience fibrin sealant was superior to laser soldering and the mechanical suturing device. In contrast, Anidjar et al reported an experimental study using fibrin sealant only for ureteral anastomosis.[30] In that study retrograde ureteropyelography in 10 pigs immediately after anastomosis revealed minimal evidence of leakage in 2. However, 2 pigs included in the survival model died of massive urinoma a few days postoperatively. They concluded that fibrin sealant ureteral anastomosis is unsafe without additional sutures. In another series fibrin sealant combined with sutures was applied in 3 patients with trauma related ureteral anastomosis with satisfactory results.[18] To our knowledge no other human studies of fibrin sealant for ureteral anastomosis are available to date. These experimental and clinical data indicate that using only sealant for ureteral anastomosis is unsafe. However, fibrin sealant applied with a limited number of approximating sutures may achieve results comparable to those of sutured anastomosis and it decreases operative time, especially for laparoscopic approaches, in which suturing can be a challenging task. Further clinical trials with a larger number of patients are necessary to determine the efficacy of fibrin sealant assisted ureteral anastomosis.

URINARY FISTULA

Vesicovaginal. In 1985 Papadopoulos et al applied fibrin sealant to close artificially created vesicovaginal fistulas in a rabbit model.[31] In 10 animals a conventional suture technique was used and in another 10 they used a combination of suturing and fibrin sealant. There was a 30% recurrence rate in the suture only group, whereas no recurrence was noted in the sealant group. More recently, Schneider et al reported the results of endoscopic treatment of vesicovaginal fistula using fibrin sealant in 6 patients.[32] They noted a 66% success rate with fibrin sealant injection compared with an 88% primary success rate with conventional suturing. Welp et al described 3 cases of successful vesicovaginal fistula closure using sealant exclusively.[33] Rossi et al successfully treated 3 postoperative cases of urinary fistula.[34] Tostain reported 2 vesicovaginal and 2 ureterovaginal cases of successful closure with fibrin sealant and urinary diversion.[35] A case of recurrent colovesicovaginal fistula was closed successfully by endoscopic fibrin sealant application.[36] A vesicoperineal fistula,[37] a fistula between an ileal conduit and the skin after cystectomy[38] and a radiation induced colovesical fistula[39] have been treated successfully with fibrin sealant.

Overall the use of fibrin sealant for urinary fistula closure

is limited to case reports and small case series. Although results have been satisfactory, it appears that applying fibrin sealant for fistula closure should be individualized. No general recommendation can be made.

INFERTILITY

Vasovasostomy. In 1980 Bach et al applied fibrin sealant for vasal anastomosis in a rabbit model.[40] Subsequent experimental studies confirmed the suitability of fibrin sealant for immediate and delayed vasal anastomosis in animal models.[41–46] Although various numbers of additional sutures have been applied,[41,44,46] 2 transmural sutures combined with fibrin sealant application had results comparable to those of standard 2-layer sutured anastomosis.[41,44] Sutureless vasovasostomy is associated with the poorest results.[44] Wagenknecht reported experience with fibrin sealant for vasovasostomy in humans with good results.[47] To our knowledge no other human data are currently available. Briefly, experimental studies show that fibrin sealant assisted vasal anastomosis is feasible and results in shorter operative time with results comparable to those of sutured anastomosis. Prospective randomized studies are necessary to evaluate the efficacy of fibrin sealant vasovasostomy in humans.

Vasoepididymostomy. Limited data are available on fibrin sealant for vasoepididymostomy. In experimental studies in rats we noted that fibrin sealant assisted vasoepididymostomy using the invagination technique resulted in patency rates comparable to those of standard microsurgical end-to-side vasoepididymostomy.[48,49] A modification of the invagination technique was used clinically in humans with good clinical results,[50] although no sealant was applied. To our knowledge no clinical data are available on fibrin sealant for vasoepididymostomy in humans.

PEDIATRIC APPLICATIONS

Vesicoureteral reflux. Taneli et al reported an experimental study in dogs using fibrin sealant for treating reflux.[51] Fibrin sealant was injected via endoscopy at a subureteral location and compared with polytetrafluoroethylene injection. Reflux resolved in each group. Histological evaluation of the sealant injected area revealed increased collagen fiber deposition, whereas at polytetrafluoroethylene injected sites there was a mass of granulation tissue. They concluded that fibrin sealant may be a suitable material for the endoscopic treatment of reflux. To our knowledge no clinical data are available to date.

Orchiopexy. There are few studies of fibrin sealant application for orchiopexy after spermatic cord torsion. Noeske described good fixation after placing fibrin sealant into the scrotal sack with manual compression for 5 minutes.[52] No recurrences were reported. The theoretical advantage of sealant is the avoidance of suture material, which may be traumatic. However, to our knowledge no prospective randomized clinical studies are available and a cost comparison with the conventional technique has not been performed.

Circumcision. Circumcision in patients at high risk, namely those with hemophilia A or B, or von Willebrand's disease, requires factor replacement, which is associated with significant cost. Others have used fibrin sealant for circumcision in patients with hemophilia.[53–56] Martinowitz et al reported on 10 patients with hemophilia who underwent circumcision with topical fibrin sealant applied for hemostasis, including 3 with bleeding postoperatively and only 2 who required factor VII infusion.[54] They concluded that this approach results in a decreased rate of blood factor transfusion with cost savings. Similarly Avanogmaer et al compared the cost of factor replacement in 22 patients with hemophilia treated with or without sealant application for circumcision.[53] The cost of factor replacement in the group treated conventionally was $12,875 compared with $8,898 and $4,868 in those treated with fibrin sealant and 2 blood factor replacement protocols, respectively. The advantages of fibrin sealant as a hemostatic agent for surgical procedures in patients with hemorrhagic diathesis has been demonstrated in other areas, such as tooth extraction and orthopedic procedures.[55] Furthermore, the use of fibrin sealant for circumcision has been reported in the normal pediatric population.[57] Maier applied fibrin sealant after circumcision using a clamp for approximating the edges of the preputial skin layers to avoid bleeding or early separation with good cosmetic results.[57]

It appears that fibrin sealant is beneficial for circumcision in patients with hemorrhagic diathesis and should be considered. Although good results have been reported in the normal population, to our knowledge no controlled studies have been performed regarding the benefits of fibrin sealant application and no cost comparison data are available.

Miscellaneous. Fibrin sealant has been reported as an adjunct to surgical closure techniques for hypospadias, epispadias and bladder exstrophy repairs for hemostasis, and for improving wound healing.[58] The relative contribution of fibrin sealant in these cases of reconstruction is unclear.

MISCELLANEOUS

Renal transplantation. Studies of the usefulness of fibrin sealant for renal transplantation are limited. A prospective randomized study was performed studying the efficacy of sealant application during transplantation for postoperative prevention of lymphocele in 100 patients.[59] In that series no benefit of the sealant was identified. Heimbach et al reported preservation of a transplant kidney after rupture using fibrin sealant as an adjunct to collagen foam and polyglactin mesh with good results.[60] Closure of an intractable transplant kidney-ureter fistula using fibrin sealant has also been described.[61]

Lymphocele prevention. Several clinical studies are available of the efficacy of fibrin sealant for lymphatic drainage after inguinal or axillary lymph node dissection with controversial results. Gilly et al reported a randomized prospective study of 40 patients who underwent axillary or inguinal lymph node dissection.[62] They noted a significant decrease in lymphatic drainage and hospital stay. Furthermore, Moore et al observed that fibrin sealant resulted in a decreased rate of seroma and earlier drain removal after radical axillary dissection.[63] In contrast, in a recent prospective randomized study Vaxman et al noted no difference in lymphatic drainage using sealant.[64] Furrer et al had similar results in another prospective series of 30 patients comparing the efficacy of fibrin sealant and conventional techniques.[65] Briefly, current data on fibrin sealant for preventing lymphocele after inguinal or axillary dissection are inconclusive and its routine use cannot be justified.

Bladder neck suspension. Few studies have shown the successful use of fibrin sealant for bladder neck suspension.[66–70] A modified Burch procedure was performed via an open or laparoscopic approach with sealant used to replace sutures.[67,68] Although short-term results were promising,[68] long-term followup was disappointing.[70] In a recent prospective study of the long-term efficacy of fibrin sealant suspension in 43 patients the subjective 1 and 3-year success rates were 72% and 55%, and the corresponding objective success rates were 64% and 60%, respectively.[70] Therefore, this treatment cannot be currently recommended.

Prostatectomy. Gasser et al performed a randomized study of fibrin sealant for decreasing blood loss after suprapubic prostatectomy.[71] Sealant combined with collagen fleece resulted in significantly decreased blood loss compared with conventional techniques. Furthermore, the need for blood transfusion was decreased in the postoperative period. Similar results were achieved by Vecsey, who reported decreased

blood loss during the first 24 hours.[72] These data support the hemostatic effect of fibrin sealant for controlling venous oozing. Boeckmann and Jakse applied sealant for reconstructing the urethra after perineal prostatectomy in 17 patients.[73] The urethral anastomosis was covered with fibrin sealant and no urinary leakage or anastomotic stricture was noted. However, the control group had undergone radical retropubic prostatectomy. Lobel et al applied fibrin sealant during radical prostatectomy.[74] Application in the area of pelvic lymph node dissection or at the urethral anastomosis did not result in improved sealing or decreased lymphocele formation after radical prostatectomy compared with conventional techniques. Based on their results they concluded that routine fibrin sealant use was not justified during radical prostatectomy. An experimental study has been done of the transurethral application of fibrin sealant for controlling radiation related hemorrhagic cystitis.[75] No clinical studies are available.

POTENTIAL COMPLICATIONS

Fibrin sealant should not be injected directly into large blood vessels to avoid the possibility of thromboembolic complications. Bovine thrombin causes a risk of allergic reactions. Immunologically induced coagulopathy has been described.[1] In cases of known allergy hypersensitivity reactions may develop and bovine protein is contraindicated. IgE mediated anaphylactic reaction to bovine thrombin is an extremely rare reaction. Sudden and severe hypotension resulting in death has been reported after applying bovine thrombin to a deep hepatic wound.[3] Replacing bovine thrombin with human thrombin in most recent commercial products should avoid this potential complication.

Others reported the usefulness of antibiotics with fibrin sealant for facilitating tissue healing without infection.[76,77] These studies were based on data on the increased risk of colonic dehiscence when using fibrin sealant for anastomosis.[78,79] However, except for this application current data do not indicate a clear benefit of the routine use of antibiotics with fibrin sealant.

Like any other blood product, commercial fibrin sealant causes a theoretical risk of viral transmission. This concern caused delayed approval of a commercial product in the United States. In the last decade advances in viral inactivation technology have resulted in a decreased risk of transmission of hepatitis A, B and C, and HIV. Various viral inactivation techniques, including vapor heating, steam treatment, pasteurization, irradiation, solvent detergent extraction and nanofiltration, have been applied.[1] Tisseel, which is the currently available commercial fibrin sealant in the United States, uses a vapor heated method for viral inactivation. This process involves the exposure of plasma concentrates to hot vapor under high pressure. Despite this technology the risk of thermoresistant and nonenveloped viruses, such as hepatitis A and provirus B19, is not eliminated.[1] Another factor contributing to the decrease risk of viral transmission is careful donor selection strategies. Subsequently in large European studies there has been no case of disease transmission using this product.

Blood bank produced fibrin sealant can eliminate the risk of viral transmission only when autologous blood is used. Otherwise the risk is comparable to that of other blood products tested in standard fashion. A case of HIV transmission after cryoprecipitated fibrinogen was applied as an adhesive was reported. While no case of viral transmission using bovine thrombin has been described, bovine spongiform encephalitis is a theoretical risk.[3]

OTHER SYNTHETIC SEALANTS

Other types of synthetic sealants have been reported for wound closure and other reconstructive procedures.[80,81] Cyanoacrylate sealants are synthetic monomers that have mainly been applied to close skin laceration wounds with excellent results.[82] These synthetic sealants contain monomers that polymerize after application to form an adhesive layer over superficial wounds. Their adhesive property appears to be strong. Early studies showed good results after experimental and clinical use of this sealant for renal lacerations.[83–86] However, the use of this form of sealant in the urological field remains limited. Absorbable and biodegradable cyanoacrylate sealants are necessary for internal use. In contrast, fibrin sealant has the advantage of being biodegradable with minimal tissue reaction.[87] Other commercially available products include collagen, bovine thrombin, albumin cross-linked with glutaraldehyde and hydrogel. Urological applications of these products has been limited.

CONCLUSIONS

It has been more than 2 decades since the initial use of fibrin sealant for urological application. Many experimental and clinical studies for various indications have been reported. Controlled clinical trials have proved the efficacy of fibrin sealant for liver and splenic trauma with excellent hemostatic effect. Furthermore, a cardiac surgical trial was the pivotal trial, resulting in FDA approval of fibrin sealant in the United States. This approval resulted in the acceptance of fibrin sealant for hemostasis for renal trauma and selected renal surgery, although no prospective randomized studies for renal surgery have been performed. Similarly in the area of reconstruction fibrin sealant application has been limited to personal experience, experimental and retrospective studies. A reason for the slow introduction of this material has been concern about disease transmission by commercial sealant. With the recent introduction of commercial fibrin sealant in the United State as well as increasing applications for laparoscopic surgery fibrin sealant may prove to be an alternative material for tissue approximation and hemostasis. Therefore, it is expected that fibrin sealant may be increasingly used in urology in the future. Prospective clinical trials are necessary to justify the routine application of fibrin sealant for many types of reconstructive urology and for avoiding its misuse for unproved indications.

Commercial fibrin sealant preparations available in Europe, Canada and Japan are also manufactured by CRTS-Lille, Lille, France, France. Currently in the United States Tisseel is distributed by Baxter Healthcare Corp., Irvine, California.

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