HEMOSTATIC AGENTS AND TISSUE SEALANTS IN UROLOGY

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History

* Raw meat! ➔ Ancient Egypt
* Dried plasma ➔ WW1
* Thrombin powder ➔ WW1 (high viral hepatitis transmission)
* Traditional ➔ pressure / electrocautery / sutures / clips
Types

- Topical
- Fibrin Sealant
- Tissue Adhesives
Topical

- Surgicel – cellulose
- Gelfoam -- gelatin
Surgicel

- Many types
- Acidification → low pH leads to vasoconstriction
- Platform for platelet adhesion
- Absorbed at around 4 weeks
Gelfoam

- Thrombin + gelatin (bovine)
- Platelet adhesion, matrix formation, fibrin clot formation
- Flowable vs simple contact (flowable better coverage i.e. 75%)
- Expensive
- Absorbed between 4 – 8 weeks
What is it?

- Mixture of coagulation factor (human fibrinogen/thrombin (human or bovine) / aprotinin/ CaCl$_2$/ Factor XIII/synthetic)
History

* Fibrin emulsion 1\textsuperscript{st} described by Bergel (1909)
* Purified thrombin available in 1938, combined with fibrinogen in 1944 (for tx of burned soldiers in WW1)
* In Europe widely used since 1970’s
* In USA, FDA only approved in 1998 (Tisseel) (worry of prion & viral transmission)
* Uro → Shekarriz & Stoller described use in 2002
**Figure 1** – Mechanism of action of liquid fibrin sealant in recapitulating the terminal portion of the coagulation cascade.
Fibrin Sealant

Safety

* Donor screening
* Serum testing and retesting at 90 days storage
* 2-step vapor heating process

As of 2005, no reported viral transmission in USA using FDA approved sealants

In Japan 1 case of parvovirus B19 transmission using non-FDA approved sealant
Risks of Fibrin Sealant

- Transmission of hepatitis A, B, C and HIV
- Bovine thrombin → bovine spongiform encephalitis, IgE mediated allergic reaction (significant hemorrhage)
- Thromboembolic events if introduced into large vessels
Fibrin Sealant

Delivery Method

* Dual chamber delivery system
* One chamber with fibrinogen & Factor XIII mixed with another chamber of thrombin at site of application → immediate conversion to fibrin, complete in 3 minutes
* Clot broken down in 2-4 weeks by macrophages without fibrosis or FB reaction
* Variety of catheters used for open, endoscopic and laparoscopic applications
Fibrin Sealant

Application in Urology

- Hemostatic agent
- Urinary Tract sealant
- Tissue adhesive

Table 2 – Urological applications of fibrin sealant.

I. Hemostasis
Partial nephrectomy
Open
Laparoscopic (13-16)
Percutaneous nephrolithotomy (22)
Management of splenic injury (23)
Hemophilia and other coagulopathy (24)
Circumcision (25)
Hemorrhagic cystitis (27)

II. Urinary Tract Sealant
Laparoscopic and open pyeloplasty (31-34)
Ureteral anastomoses (31-34)
Urethral reconstruction (37)
Simple retropubic prostatectomy (35)
Radical retropubic prostatectomy (36)
Bladder injury (24)
Lymphadenectomy (38,39)
Percutaneous nephrolithotomy tract closure (22)

III. Tissue Adhesion
Fournier’s gangrene reconstruction (41,42)
Fistula closure (24,45,46)
Skin grafting (42)
Complex urethroplasty (37)
Partial Nephrectomy

* OPN (Urlesberger H et al. Eur Urol 1979)
* 68% of members of World Congress of Endourology use for LPN (Finley DS et al. J Urol 2005)

Renal Trauma

* 14 pts with traumatic renal injury → renal salvage with no urinoma/ delayed bleed/ infection (Kram HB et al. Urology 1989)
Fibrin Sealant for Hemostasis

Miscellaneous Applications

* Tubeless PCNL → 2-3mL instilled into parenchymal defect at removal of sheath

  Noller MW et al. J Urol 2004

* Splenic injury during left nephrectomy → avoids splenectomy


* Buccal donor graft site

  Riccabona M. Tech Urol 1999

* Post cystodiathermy for refractory radiation cystitis post supravesical urinary diversion

  Ouwenga MK et al. J Urol 2004

* For urology procedures (eg. Circumcision) in ptts with coagulation disorders

Ureteral anastomosis (iatrogenic and traumatic injuries)

- Bolster over suture line (Kramm 1989)
- Drain free (Evans 2006)
- Use in laparoscopic pyeloplasty/repair of collecting system
Prostatectomy

- Drain free simple retropubic prostatectomy (sealant outside tract over sutured prostatic capsule closure or at urethrovesical anastomosis)
- Faster recovery and earlier home discharge
Fibrin Sealant for Urinary Tract Sealing

Urethroplasty

* Used at pendulolus urethra reconstruction surgery
* Faster healing, earlier catheter removal, improved ptt satisfaction
Complication Management

- Iatrogenic bladder injury during transvaginal hysterectomy (direct transvaginal application with bolster interposition) avoids need for bladder repair or tissue interposition (flap)
- To prevent lymphocele after lymphadenectomy
- Sclerosant for postoperative lymphocele drainage (75% success)
- Percutaneous transrenal application for persistent calyceal leak d/t gunshot wound
Fibrin Sealant for Tissue Adhesion

Tissue Planes

* Increase issue healing due to better adherence, accelerating revascularization, prevents seroma
* Panurethroplasty
* Fournier’s gangrene
* Closure of urinary fistulae (promotes ingrowth of fibroblasts)
For infertility → vasovasotomía & vasoepididymostomía (animal models now)

* All the above mentioned are only case reports or series (not standard of care) and must be informed to ptts (furthermore in our social background)
Available Fibrin Sealants

- Tisseel (Baxter, USA)
- Hemaseel (Haemacure, USA)
- Beriplast P (Aventis, Germany)
- Bolheal (Fujisawa, Japan)
- Quixil (Omrix, Belgium)
Composition

- Thrombin and a proprietary gelatin matrix (manufactured from bovine collagen extracted from corneal tissue)
- Thrombin (also bovine origin) is supplied as a sterile freeze dried powder reconstituted in 0.9% NaCl and mixed with the gelatin in OT just before use
- Prep time 1 minute, can use within 2 hours
Mechanism of Action

* The granules fill the wound and swell up on contact with blood/fluid → tamponade → matrix for clot formation
* Thrombin activates plts; factors V, VII, XII; and promotes conversion of fibrinogen → fibrin → stabilizes the matrix complex
* Absorption at 6-8 weeks
* Requires blood for activation
Gelatin Matrix / Thrombin Sealants (FloSeal)

- FDA approved for CT, vascular and GS
- Use in urology → trauma and PN (animal models and clinical case series)
Risks

- Bovine spongiform encephalitis
- Thromboembolic events
- Immunologically mediated coagulopathy
- IgE mediated anaphylaxis
Open and laparoscopic PN
Used as adjunct for LPN (Gill and co., Richter and co.) → no hemorrhagic complications
Trauma (Renorrhapy)
Proven in animal models, however, in clinical series in humans
In PCN, nephrostomy tract occluded with balloon catheter and filled with Floseal → no bleeding BUT is it cost effective? Danger of obstruction?
Cyanoacrylate

- First used as a tissue sealant in 1940s (pure form causes significant inflammation thus limited usage)
- Synthetic form (Dermabond by Ethicon, USA) approved by FDA in 1998 for skin closure (low SE)
- Small series shows safe to use for closure of urinary fistulas (Bardari et al), further studies needed
Bovine Serum/Albumin/Glutaraldehyde (Bioglue)

- Approved in 2000 by FDA as adjunct to std methods of hemostasis for vascular surgery
- MoA: 2 component system (purified bovine serum + glutaraldehyde) → binds to bovine albumin to target tissue (no absorption or inflammation)
- Mixed at time of application, needs dry field, works within 3 minutes
Bovine Serum/Albumin/ Glutaraldehyde (Bioglue)

Usage

- Efficacy in CTS and peripheral vascular surgery
- Usage in urology needs to be studied
- Issues of inflammation due to glutaraldehyde
Polyethylene Glycol Hydrogels

- CoSeal (Cohesion Technologies) & AdvaSeal-S (Genzyme Corp)
- Polymerize at site
- Approved by FDA in 2000 as pulmonary sealants
- Reconstituted in syringe
- Degrades at 30 days
- For urology → animal studies in PN showed no bleed and no humoral or cell mediated immune response
Efficacy of some has been established while others need further evaluation & confirmation.

Must ensure that when and if a product is used in lieu of std procedure, results should be equal or better.

Costs, pitfalls and potential complications?

Future development and refinement needed.
THANK YOU