Topical Hemostatics

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Conflict of Interest

- No conflicts of interest

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Outline

- Introduction
- Four main categories of topical hemostatics
- Highlight commonly used products
  - ?Data
- Basic mechanism of action

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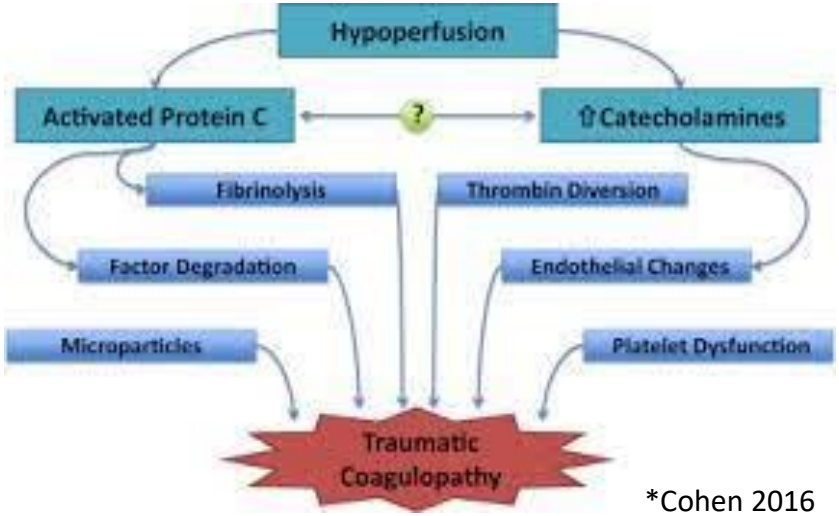
Introduction – Topical Hemostatics

- Exsanguination = leading cause of preventable death among trauma victims
  - 50% in the pre-hospital setting

- Hemorrhage → acute coagulopathy

- 1886 = Earliest use of topical hemostatics
  - Beeswax and petroleum jelly
- 1940s = oxidize cellulose and gelatin
- 1970 = microfibrillar collagen



*Cohen 2016

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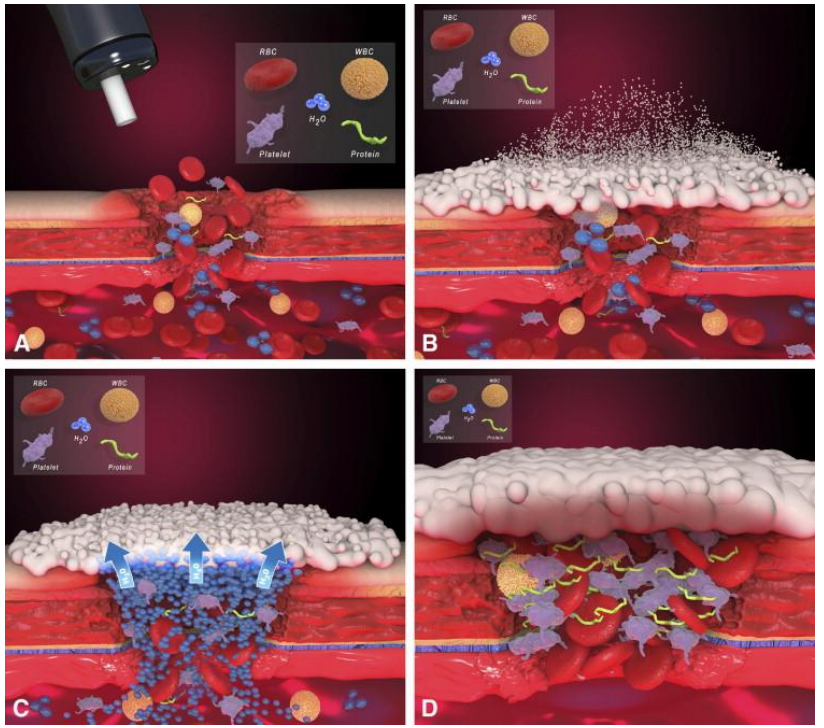
Tompeck et al, 2019 *J Trauma Acute Care Surg*
Gruen et al, 2012 *Lancet*
Sileshi et al, 2008 *Vascular*

Introduction – Topical Hemostatics

- Goal =
  - Enhance and expedite coagulation
  - Minimize adverse effects
- Adjuncts are typically
  - Transportable
  - Increase hemostasis
  - Reduce transfusion need and ~OR times
- Promote coagulation
  - Concentrate innate clotting factors
  - Facilitate clotting cascade
  - Barricade ongoing blood loss



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Tompeck et al, 2019 *J Trauma Acute Care Surg*

Introduction – Ideal hemostatic

(1) Easily accessible
(2) Conform to a variety of wounds
(3) Efficient and effective hemostasis
(4) Limit adverse effect
(5) Self-activating
(6) Removable
(7)Cost effective

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Tompeck et al, 2019 *J Trauma Acute Care Surg*

Introduction – Topical Hemostatics

Four main categories

1. Topical
2. Chemical
3. Physiologic
4. Dressings

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Topical Hemostatics

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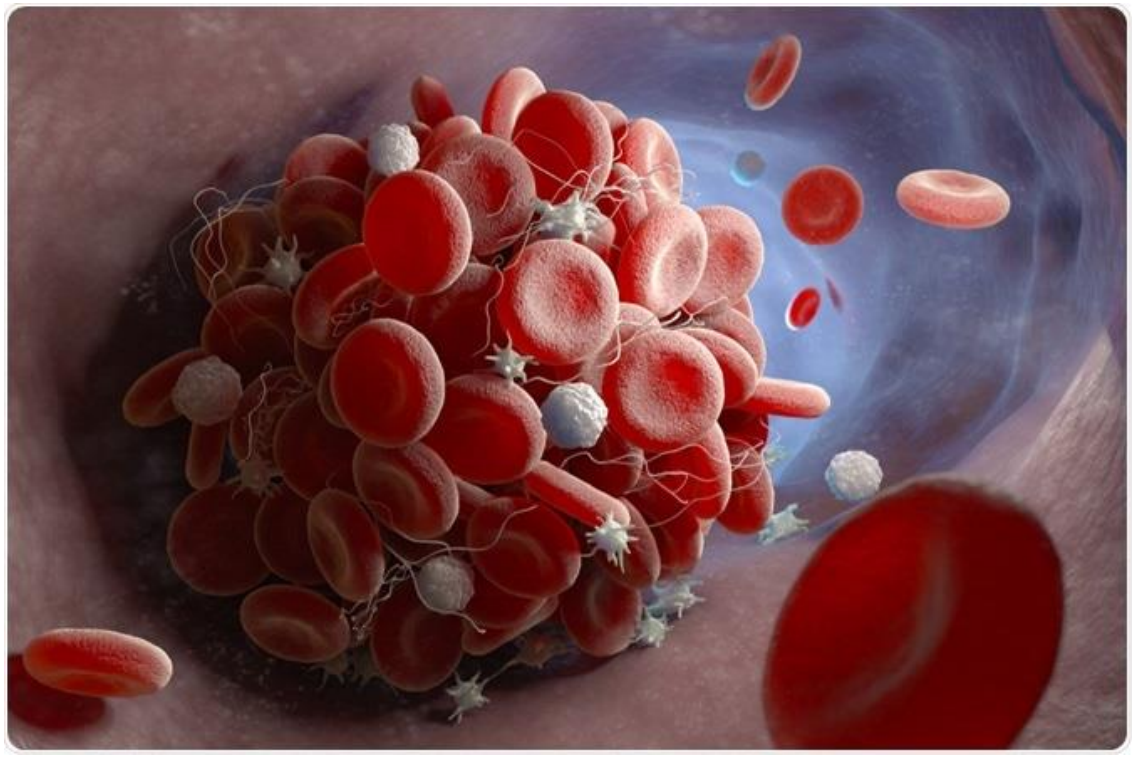

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Topical Hemostatics

Four main categories

1. Topical
    1. Mechanical
    2. Active
    3. Flowable
    4. Sealants
2. Chemical
3. Physiologic
4. Dressings

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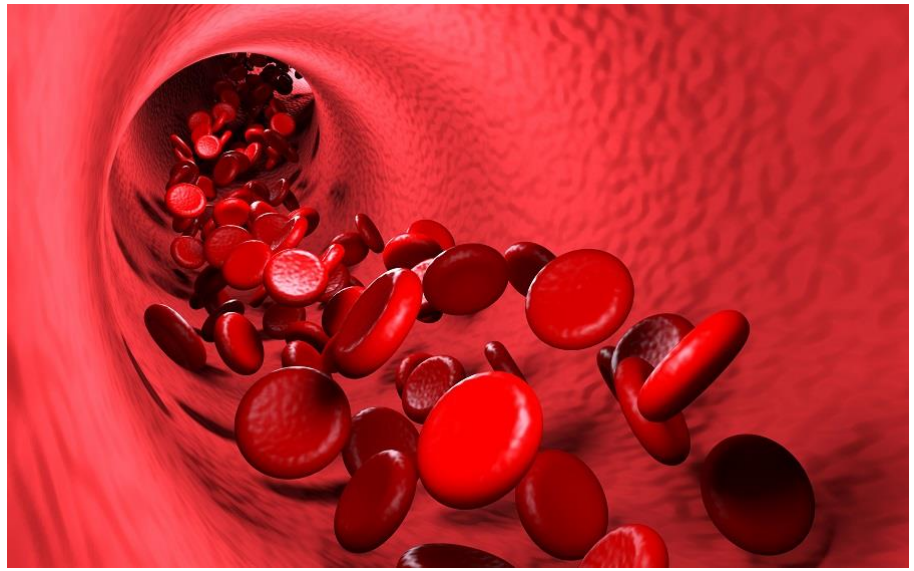
Topical → Mechanical

- Matrix for rapid clot formation → impedes blood loss → tamponade
- Must have an intact coagulation cascade
  - Platelet aggregation
  - Fibrin production
- Pros =
  - Affordable
  - Easy to use
    - Manual pressure with saline soaked gauze
  - No specific storage needs



Tompeck et al, 2019 *J Trauma Acute Care Surg*
Spotnitz WD. 2012, *Am Surg.*
Gabay M, et al, 2013
Neveleff et al, 2012 *AORN J.*

Topical → Mechanical

Class	Brand	Distributor
Physical Agents	Bone wax, Ostene	Ethicon, Baxter Healthcare
Porcine Gelatin	GELFOAM SURGIFOAM, Sponge	Ethicon
Oxidized regenerated cellulose (ORC)	SURGICEL (original, FIBRILLAR, NU-KNIT, SNoW, Powder), WoudClot, bloodSTOP	Ethicon, CoreScientific Creations, LifeScience
Bovine collagen	Avitene, Helistat, Helitene, INSTAT MCH	Bard, Davol Inc., Tengra, Ethicon
Polysaccharide spheres	Arista, VITASURE, PerClot, EndoClot PHS	Bard, Stryker, Cryolife, EndoClot Inc.

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Tompeck et al, 2019 *J Trauma Acute Care Surg*

Topical → Mechanical – Bone Wax

- Use:
  - USDA approved for bleeding from bony surfaces
  - Derm surgery
- Adverse Effects:
  - Cannot use in contaminated field
  - Impedes bacteria clearance
  - Impairs osteogenesis
- Cannot leave in the spinal canal/spinal fusion sites

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Howe N et al. 2013 *J Am Acad Dermatol*
Gabay M. 2006 *Am J Health Syst Pharm*
Simo KA et al, 2012, *ISRN Surg*

Topical → Mechanical – SURGICEL

- Use:
  - RP bleed (original), solid organ (NU-KNIT), Craniotomy (FIBRILLAR), contaminated field
- Adverse Effects:
  - Foreign body reaction
- Do not apply onto periosteum, perichondrium, or graft beds

Howe N et al. 2013 *J Am Acad Dermatol*
Gabay M. 2006 *Am J Health Syst Pharm*
Simo KA et al, 2012, *ISRN Surg*

Topical → Mechanical – Arista

- Use:
  - Surgical procedures with arteriolar, capillary, or venous bleeding
  - Anastomotic sites
- Adverse Effects:
  - Hyperglycemia → avoid over 50g in DM patients
  - Embolism following intravascular injection
- Do not use in optho or neuro procedures

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Tompeck et al, 2019 *J Trauma Acute Care Surg*
Simo KA et al, 2012, *ISRN Surg*

Med Devices (Auckl). 2017 Nov 30;10:273-279. doi: 10.2147/MDER.S140663. eCollection 2017.

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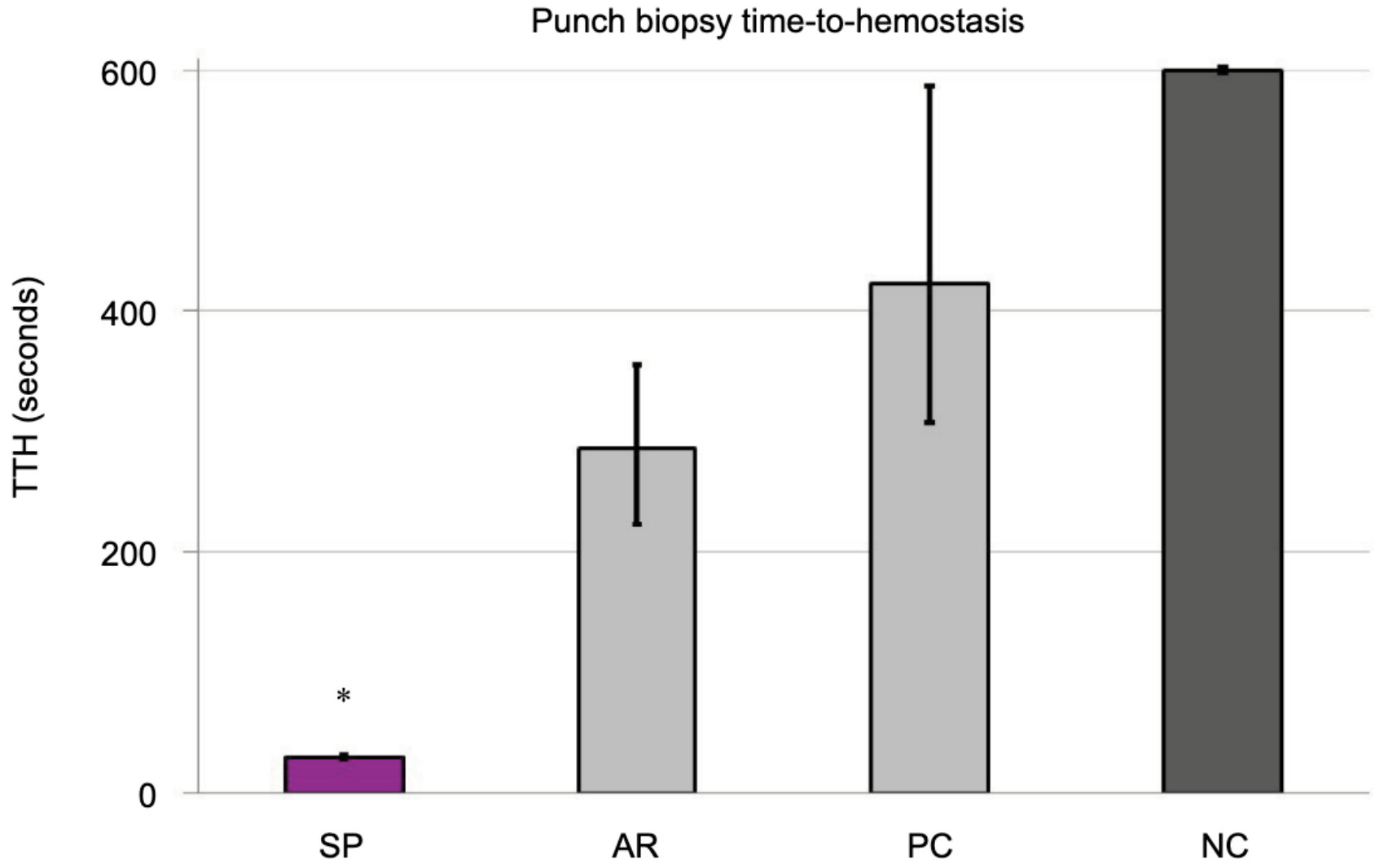

Ethicon funded study**

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Topical → Active

- Thrombin based

- Application of concentrated thrombin to a bleeding surface = coagulation
  - Rapid conversion of native fibrinogen into a fibrin clot
  - Activation of Factor V, FVIII, and FXI
  - Promotion of platelet aggregation and adherence

- ↑ [thrombin] = ↑ efficacy

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Tompeck et al, 2019 *J Trauma Acute Care Surg*
Barkum et al 2013 *Gastrointest Endosc.*

Topical → Active

Class	Brand	Distributor
Bovine Thrombin	THROMBIN-JMI	Pfizer
Human pooled plasma thrombin	EVITHROM, GELFOAM PLUS	Ethicon, Baxter
Recombinant human thrombin	RECOTRHOM	Mallinckrodt

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Tompeck et al, 2019 *J Trauma Acute Care Surg*

Topical → Flowable

- Gelatin particles + thrombin = superior stable fibrin matrix and clot
- Crosslinked gelatin particles swell = tamponade effect and conform to irregular spaces
- Thrombin activates FV, FVIII, FXIII, and platelets
- Converts fibrinogen to fibrin monomers to hasten clot formation
- Thrombin acts at the terminal portion of the coagulation cascade = effective despite clotting factor deficiencies

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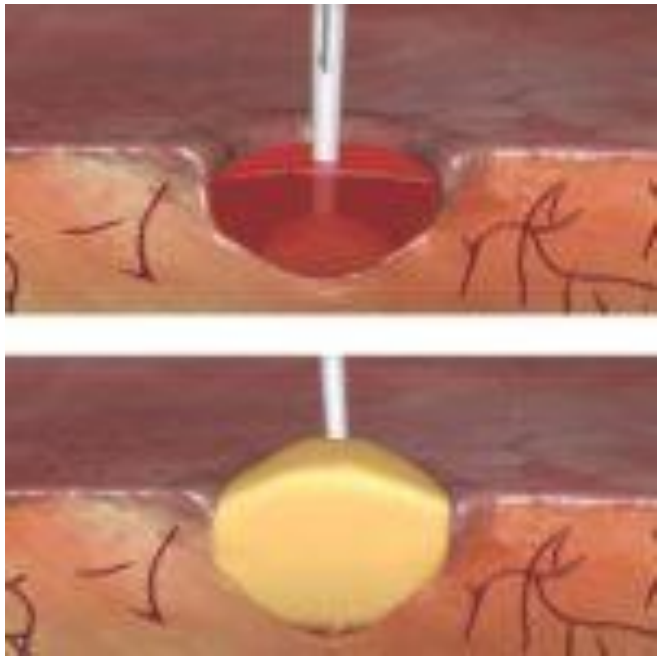
Howe N et al. 2013 *J Am Acad Dermatol*

Topical → Flowable

- Must reconstitute the thrombin component
  - Takes up to 3 minutes
  - Foam like consistency
  - Expands up to 20% over 10 min
  - Last 6-8 weeks



Howe N et al. 2013 *J Am Acad Dermatol*

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Topical → Flowable

Class	Brand	Distributor
Bovine gelatin and human pooled plasma thrombin	FLOSEAL Hemostatic matrix	Baxter
Porcine gelatin +/- human thrombin	SURGIFLO	Ethicon

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Tompeck et al, 2019 *J Trauma Acute Care Surg*

J Med Econ. 2015;18(9):735-45. doi: 10.3111/13696998.2015.1044994. Epub 2015 Jun 8.

Similar patient outcomes yet different hospital costs between flowable hemostatic agents

Guy David [1], Sangtaeck Lim, Candace Gunnarsson, Richard Kocharian, Sanjoy Roy

Affiliations + expand

PMID: 25907200 DOI: 10.3111/13696998.2015.1044994

- New England National Database review evaluating outcomes and costs → FLOSEAL vs SURGIFLO
- Average of $349.8 for FLOSEAL vs. $222.66 for SURGIFLO
  - $21 reduction in hospital cost for each additional hour of surgery
- No difference in surgical complications
- Limitations

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Topical → Sealant

- Four categories:
  - Fibrin
  - Polyethylene glycol (PEG) polymer
  - Albumin with glutaraldehyde
    - i.e. BioGlue
  - Cyanoacrylate (CA)
    - i.e. DERMABOND

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Tompeck et al, 2019 *J Trauma Acute Care Surg*
Spotnitz WD 2017, *Am Surg*
Gabay M et al, 2013, *Pharmacotherapy*
Neveleff D. 2012, *AORN J*

Topical → Fibrin Sealant

Class	Brand	Distributor
Human pooled plasma +human pooled plasma fibrinogen	TISSEEL, EVICEL, ARTISS	Baxter, Ethicon, Baxter
Human fibrinogen +thrombin, ORC	EVARREST Patch	Ethicon
Human fibrinogen + thrombin, equine collagen	TachoSil Patch	Baxter
Autologous fibrinogen and thrombin	CryoSeal	Asahi Kasei Pharma
Autologous fibrinogen and thrombin + bovine thrombin	Vitagel	Stryker

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Tompeck et al, 2019 *J Trauma Acute Care Surg*

Topical → Fibrin Sealant

- Typically composed of fibrinogen, thrombin (human or bovine), and FXIII or an anti-fibrinolytic agent

- Final pathway = cross-linked insoluble fibrin matrix
  - Decreases clot breakdown by limiting plasmin generation

- Higher [Fibrinogen] = stronger clot over time

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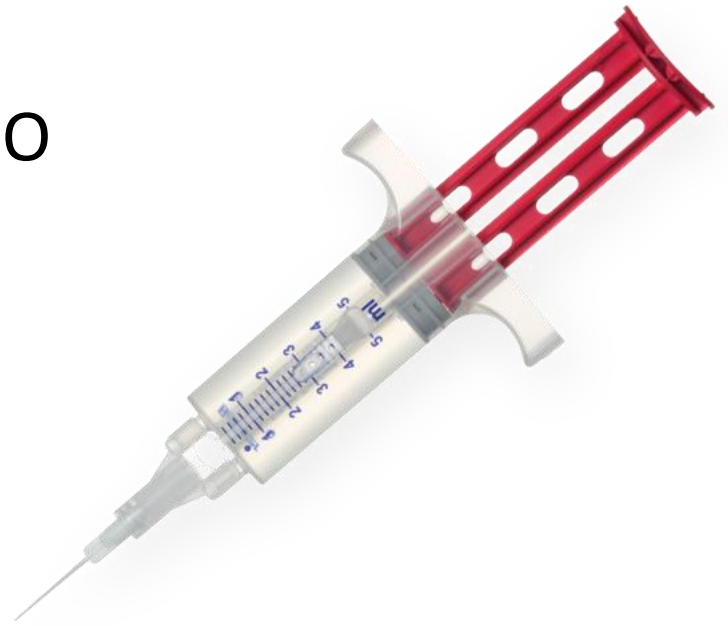
Howe N et al. 2013 *J Am Acad Dermatol*
Gabay M. 2006 *Am J Health Syst Pharm*
Simo KA et al, 2012, *ISRN Surg*

Topical → Fibrin Sealant - TISSEAL

- Can be used in open or laparoscopic surgery
- Possible reduction in multiple fluid collections PO
- Can be used in optho sx
- Can cause bovine spongiform encephalitis
- Cannot use in IgA deficiency



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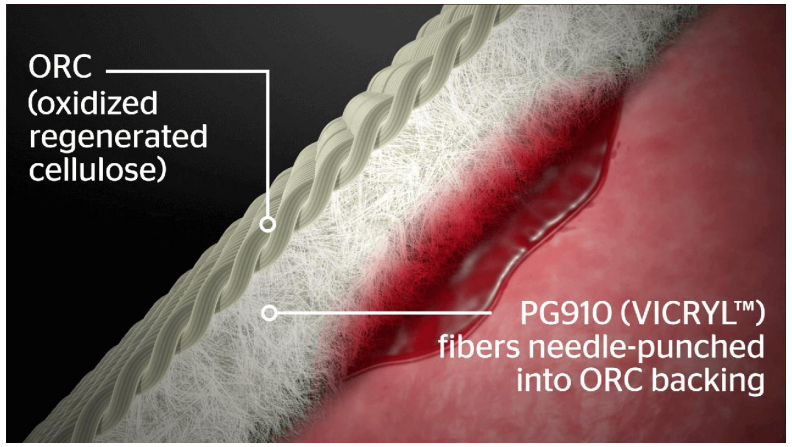
Achneck er al, 2013 *Ann Surg*
Gabay M et al, 2013, *Pharmacotherapy*

Topical → Fibrin Sealant - EVARREST patch

- Soft tissue bleeding during open surgery
  - Good adjunct in hepatic surgery
- Do not use for bleeding from large vessel injuries alone
- ? Reduction in postoperative biliary or fluid collections
- Can cause Hypersensitivity to human blood or horse proteins



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Achneck er al, 2013 *Ann Surg*
Gabay M et al, 2013, *Pharmacotherapy*
Koea JB 2013, *HPB*

J Invest Surg. 2014 Dec;27(6):360-5. doi: 10.3109/08941939.2014.941444.

Hemostatic efficacy of EVARREST™, Fibrin Sealant Patch vs. TachoSil® in a heparinized swine spleen incision model

John P Matonick [1], Jeffrey Hammond

Affiliations + expand

PMID: 25361019 DOI: 10.3109/08941939.2014.941444

- EVARREST vs TachoSil in swine models
- AC with heparin + Injury
- At 3 minutes 86% vs 0% hemostasis (p<0.001)
- At 10 minutes 100% vs 4% TachoSil (p<0.001)
- 100% adherence with EVARREST

Randomized Controlled Trial > HPB (Oxford). 2016 Mar;18(3):221-8.
doi: 10.1016/j.hpb.2015.12.006. Epub 2016 Feb 1.

A multicentre, prospective, randomized, controlled trial comparing EVARREST™ fibrin sealant patch to standard of care in controlling bleeding following elective hepatectomy: anatomic versus non-anatomic resection

Jonathan B Koea [1], Jonathan Batiller [2], Nicolas Aguirre [2], Jessica Shen [2], Richard Kocharian [2], Grant Bochicchio [3], O James Garden [4]

Affiliations + expand

PMID: 27017161 PMCID: PMC4814597 DOI: 10.1016/j.hpb.2015.12.006

- RCT EVARREST vs SOC during hepatic resection
- At 4 minutes 96% hemostasis vs 46% (p<0.001)
- No difference in anatomic vs non anatomic resection

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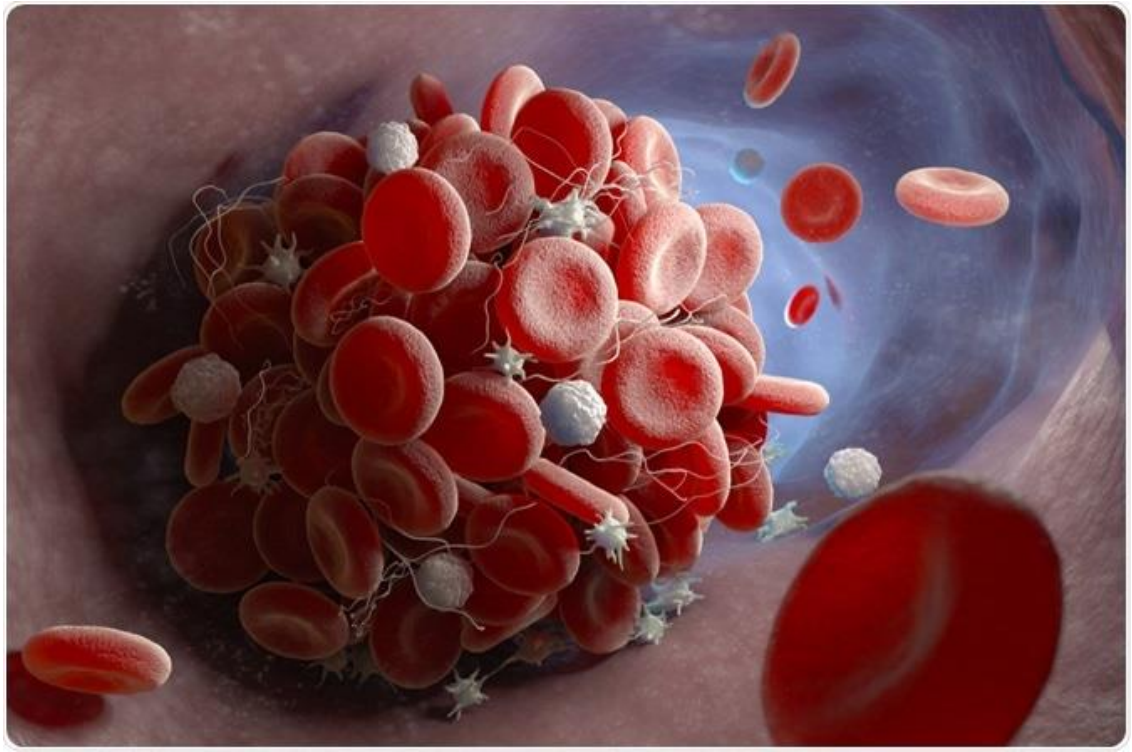

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Topical Hemostatics → Chemical

- 1852 → French military used Ferric Subsulfate for hemostasis
- Caustic to tissue
- Hemostatic
- Stable at room temperature

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Tompeck et al, 2019 *J Trauma Acute Care Surg*
Kakimoto M et al, 2010 *Jn Palliative Medicine*

Topical Hemostatics → Chemical

Chemical	Adverse Effects
Zinc Paste	• Pain and local irritation at application site[14]
Ferric Subsulfate	• Dyspigmentation[8,14] • Increased erythema[8,14] • Infection[8,14] • Delayed wound reepithelialization[8,14] • Dermal fibrosis[8,14]
Silver Nitrate	• Decreased healing to surrounding tissues[8] • Silver particle deposition[8] • Stinging sensation[14]
Aluminum Chloride	• Paresthesia[8,14] • Tissue Irritation[8,14] • Larger scars[14]

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Tompeck et al, 2019 *J Trauma Acute Care Surg*

Topical Hemostatics → Chemical – Silver Nitrate

- Formulations:
  - Topical stick applicator
  - 10% solution

- Elaborates free silver ions → bind to tissue proteins for hemostasis

- Binds bacterial proteins = antibacterial properties

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Tompeck et al, 2019 *J Trauma Acute Care Surg*
Howe N et al, 2013 *J Am Acad Dermatol*
Palm MD et al, 2008 *Dermatol Surg*

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Topical Hemostatics → Physiologic

- Mechanism
  - "Mimics" later steps in the coagulation cascade
  - Vasoconstriction

- Hydrogen peroxide
  - Unknown mechanism
  - Nonallergenic
  - Noncaustic
  - Nontoxic
  - Cheap

Physiologic	Adverse Effects
Epinephrine	• Tachyarrhythmia's[8,83] • Rebound Hyperemia[8,83]
Cocaine	• Myocardial infarction[8,14] • Syncope[8,14] • Central nervous stimulation (including seizures)[8,14] • Stroke[8,14] • Death[8,14]
Hydrogen Peroxide	• Delayed wound healing[14]
Tranexamic Acid	• Myopathy[51,52] • Hypotension (IV route)[51,52] • Nephrotoxicity[51,52] • Intravascular thrombosis (deep vein thrombosis, myocardial infarction, stroke, death)[51,52] • Increased thrombin time[51,52]

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Tompeck et al, 2019 *J Trauma Acute Care Surg*
Howe N et al, 2013 *J Am Acad Dermatol*
Palm MD et al, 2008 *Dermatol Surg*

Topical Hemostatics → Physiologic - TXA

- Derivative of Lysine

- Mechanism
  - Competitively inhibits plasminogen activation
  - Higher concentrations = noncompetitively inhibits plasmin
  - Prevents degradation of fibrin clots

- Can be used IV, topical or nebulized

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Tompeck et al, 2019 *J Trauma Acute Care Surg*
Ferraris VA et al, 2011, *Ann Thorac Surg*
Schexneider KI. 2003 *Curr Opin Hematol*

Topical Hemostatics

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Topical Hemostatics → Dressings

- Designed for rapid application
- Incorporate gauze or other material impregnated with active hemostatic ingredients
- Common in first aid kits and combat

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Tompeck et al, 2019 *J Trauma Acute Care Surg*

Topical Hemostatics → Dressings

Product	Brand	Manufacturer
p-GlcNAc	Syvek Patch	Marine Polymer Technologies, Inc. Burlington, MA
	mrdh	Marine Polymer Technologies
Chitin/Chitosan	Celox	MedTrade Products, Ltd, Crewe, UK
	ChitoSeal	Luna, Inc., Charlottesville, VA
	HemCon Patch PRO	Tricol Biomedical Inc., Portland, OR
	ChitoGauz[e] PRO	Merit Medical, Jordan, UT
	Clo-Sur P.A.D.	Gel-E, Inc., College Park, MD
	gel-e	
p-GlcNAc-containing Glycosaminoglycans (MPH)	TraumaDEX	Medafor, Minneapolis, MN
	HemaDerm	
Mineral Zeolite	QuikClot Combat Gauze	Z-Medica Corp., Wallingford, CT
Dry Fibrin	DFSD	American Red Cross Holland Laboratory, Rockville, MD
Hydrophilic Polymers of Potassium Salts	WoundSeal	Biolife L.L.C., Sarasota, FL

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Tompeck et al, 2019 *J Trauma Acute Care Surg*

Topical Hemostatics → Dressings – Mineral Zeolite

- Microporous inorganic granular powder derived from lava rock
  - Minerals → silicon, aluminum, magnesium, sodium
  - Absorption of tissue fluid through molecular sieves concentrates coagulation factors = hemostasis

- QuickClot
  - 2002
  - Kaolin impregnated polyester gauze

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Tompeck et al, 2019 *J Trauma Acute Care Surg*

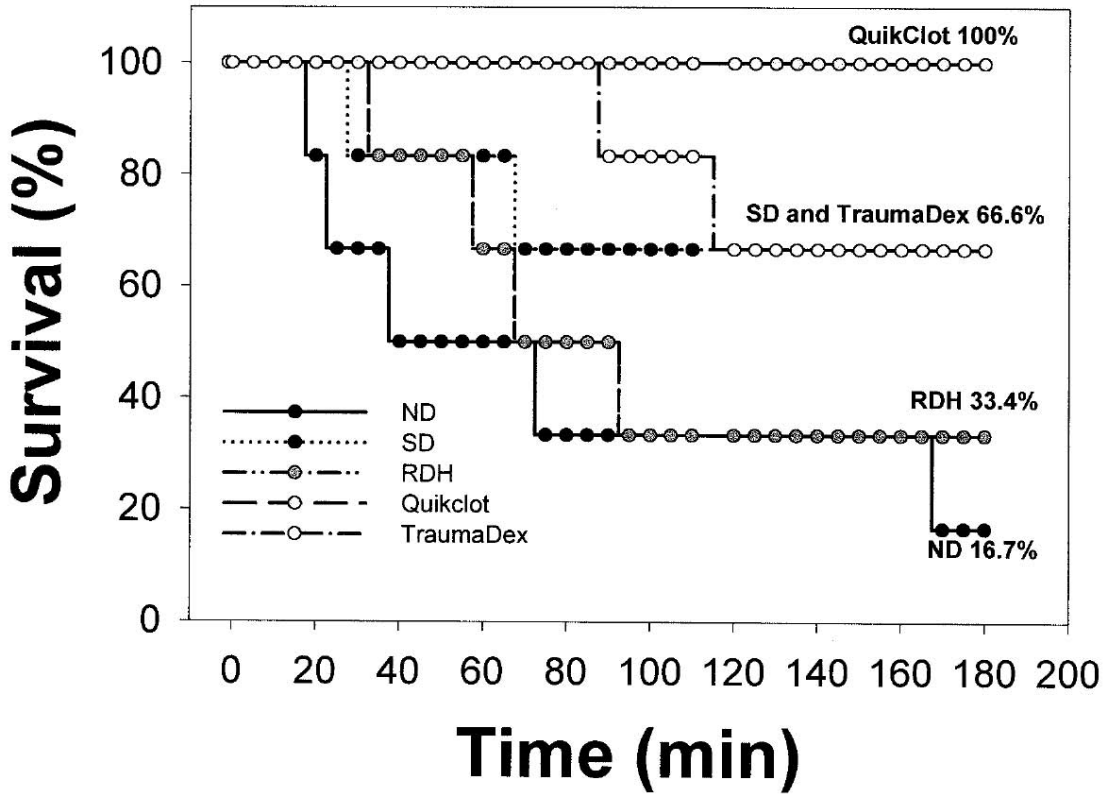
Comparative Study > J Trauma. 2003 Jun;54(6):1077-82.
doi: 10.1097/01.TA.0000068258.99048.70.

Comparative analysis of hemostatic agents in a swine model of lethal groin injury

Hasan B Alam [1], Gemma B Uy, Dana Miller, Elena Koustova, Timothy Hancock, Ryan Inocencio, Daniel Anderson, Orlando Llorente, Peter Rhee

Affiliations + expand

PMID: 12813325 DOI: 10.1097/01.TA.0000068258.99048.70



> J Trauma. 2008 Apr;64(4):1093-9. doi: 10.1097/TA.0b013e31812f6dbc.

QuikClot use in trauma for hemorrhage control: case series of 103 documented uses

Peter Rhee [1], Carlos Brown, Matthew Martin, Ali Salim, Dave Plurad, Donald Green, Lowell Chambers, Demetrios Demetriades, George Velmahos, Hassan Alam

Affiliations + expand

PMID: 18404080 DOI: 10.1097/TA.0b013e31812f6dbc

Table 3 Effectiveness by Mechanism

Mechanism	Reported Efficacy for Hemorrhage Control
Blunt trauma	6/8
Blast (artillery, rockets, improvised explosive devices)	21/22
Penetrating	
Stab wound	3/5
Gunshot wounds	65/68

Conclusion

- Four main categories of topical hemostatics
- Hemostatic choice → available and fits desired intent
- Paucity of data
- Can help adjunct hemostasis

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