Topical Hemostatics

Chelsea R Horwood MD, MPH
48th Annual Rocky Mountain Trauma and Emergency Medicine Conference
August 2, 2022
Conflict of Interest

• No conflicts of interest
Outline

• Introduction

• Four main categories of topical hemostatics

• Highlight commonly used products
  • ?Data

• Basic mechanism of action
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

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
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
Introduction – Topical Hemostatics

Four main categories
1. Topical
2. Chemical
3. Physiologic
4. Dressings
Topical Hemostatics

Four main categories

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

Four main categories

1. Topical
   1. Mechanical
   2. Active
   3. Flowable
   4. Sealants

2. Chemical
3. Physiologic
4. Dressings
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
Neveleff et al, 2012 AORN J.
### Topical → Mechanical

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

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

Tompeck et al, 2019 J Trauma Acute Care Surg
Simo KA et al, 2012, ISRN Surg
Punch biopsy time-to-hemostasis

- SP
- AR
- PC
- NC

Ethicon funded study**
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
## Topical ➔ Active

<table>
<thead>
<tr>
<th>Class</th>
<th>Brand</th>
<th>Distributor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine Thrombin</td>
<td>THROMBIN-JMI</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Human pooled plasma thrombin</td>
<td>EVITHROM, GELFOAM PLUS</td>
<td>Ethicon, Baxter</td>
</tr>
<tr>
<td>Recombinant human thrombin</td>
<td>RECOTRHOM</td>
<td>Mallinckrodt</td>
</tr>
</tbody>
</table>
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

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
## Topical ➔ Flowable

<table>
<thead>
<tr>
<th>Class</th>
<th>Brand</th>
<th>Distributor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine gelatin and human pooled plasma thrombin</td>
<td>FLOSEAL Hemostatic matrix</td>
<td>Baxter</td>
</tr>
<tr>
<td>Porcine gelatin +/- human thrombin</td>
<td>SURGIFLO</td>
<td>Ethicon</td>
</tr>
</tbody>
</table>
Similar patient outcomes yet different hospital costs between flowable hemostatic agents

Guy David, Sangtaeck Lim, Candace Gunnarsson, Richard Kocharian, Sanjoy Roy

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
Topical → Sealant

• Four categories:
  • Fibrin
  • Polyethylene glycol (PEG) polymer
  • Albumin with glutaraldehyde
    • i.e. BioGlue
  • Cyanoacrylate (CA)
    • i.e. DERMABOND
## Topical → Fibrin Sealant

<table>
<thead>
<tr>
<th>Class</th>
<th>Brand</th>
<th>Distributor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human pooled plasma + human pooled plasma fibrinogen</td>
<td>TISSEEL, EVICEL, ARTISS</td>
<td>Baxter, Ethicon, Baxter</td>
</tr>
<tr>
<td>Human fibrinogen + thrombin, ORC</td>
<td>EVARREST Patch</td>
<td>Ethicon</td>
</tr>
<tr>
<td>Human fibrinogen + thrombin, equine collagen</td>
<td>TachoSil Patch</td>
<td>Baxter</td>
</tr>
<tr>
<td>Autologous fibrinogen and thrombin</td>
<td>CryoSeal</td>
<td>Asahi Kasei Pharma</td>
</tr>
<tr>
<td>Autologous fibrinogen and thrombin + bovine thrombin</td>
<td>Vitagel</td>
<td>Stryker</td>
</tr>
</tbody>
</table>
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
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

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

Achnecker et al, 2013 Ann Surg
Gabay M et al, 2013, Pharmacotherapy
Koea JB 2013, HPB
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

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
Topical Hemostatics

Four main categories

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

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

Tompeck et al, 2019 J Trauma Acute Care Surg
Kakimoto M et al, 2010 Jn Palliative Medicine
# Topical Hemostatics ➔ Chemical

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc Paste</td>
<td>• Pain and local irritation at application site&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ferric Subsulfate</td>
<td>• Dyspigmentation&lt;sup&gt;8,14&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Increased erythema&lt;sup&gt;8,14&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Infection&lt;sup&gt;8,14&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Delayed wound reepithelialization&lt;sup&gt;8,14&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Dermal fibrosis&lt;sup&gt;8,14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Silver Nitrate</td>
<td>• Decreased healing to surrounding tissues&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Silver particle deposition&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Stinging sensation&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aluminum Chloride</td>
<td>• Paresthesia&lt;sup&gt;8,14&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Tissue Irritation&lt;sup&gt;8,14&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Larger scars&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
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

Tompeck et al, 2019 J Trauma Acute Care Surg
Palm MD et al, 2008 Dermatol Surg
Topical Hemostatics

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Topical Hemostatics ➔ Physiologic

- Mechanism
  - “Mimics” later steps in the coagulation cascade
  - Vasoconstriction

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

<table>
<thead>
<tr>
<th>Physiologic</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>• Tachyarrhythmia's(^{8,83})</td>
</tr>
<tr>
<td></td>
<td>• Rebound Hyperemia(^{8,83})</td>
</tr>
<tr>
<td>Cocaine</td>
<td>• Myocardial infarction(^{8,14})</td>
</tr>
<tr>
<td></td>
<td>• Syncope(^{8,14})</td>
</tr>
<tr>
<td></td>
<td>• Central nervous stimulation (including seizures)(^{8,14})</td>
</tr>
<tr>
<td></td>
<td>• Stroke(^{8,14})</td>
</tr>
<tr>
<td></td>
<td>• Death(^{8,14})</td>
</tr>
<tr>
<td>Hydrogen Peroxide</td>
<td>• Delayed wound healing(^{14})</td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>• Myopathy(^{51,52})</td>
</tr>
<tr>
<td></td>
<td>• Hypotension (IV route)(^{51,52})</td>
</tr>
<tr>
<td></td>
<td>• Nephrotoxicity(^{51,52})</td>
</tr>
<tr>
<td></td>
<td>• Intravascular thrombosis (deep vein thrombosis, myocardial infarction, stroke, death)(^{51,52})</td>
</tr>
<tr>
<td></td>
<td>• Increased thrombin time(^{51,52})</td>
</tr>
</tbody>
</table>

Tompeck et al, 2019 J Trauma Acute Care Surg
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

Tompeck et al, 2019 J Trauma Acute Care Surg
Schexneider KL. 2003 Curr Opin Hematol
Topical Hemostatics

Four main categories

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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

Tompeck et al, 2019 J Trauma Acute Care Surg
### Topical Hemostatics ➔ Dressings

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

Tompeck et al, 2019 J Trauma Acute Care Surg
Comparative analysis of hemostatic agents in a swine model of lethal groin injury

Hasan B Alam, Gemma B Uy, Dana Miller, Elena Koustova, Timothy Hancock, Ryan Inocencio, Daniel Anderson, Orlando Lorente, Peter Rhee

Affiliations + expand
PMID: 12813325 DOI: 10.1097/01.TA.000068258.99048.70

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

Peter Rhee, 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

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Reported Efficacy for Hemorrhage Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt trauma</td>
<td>6/8</td>
</tr>
<tr>
<td>Blast (artillery, rockets, improvised explosive devices)</td>
<td>21/22</td>
</tr>
<tr>
<td>Penetrating</td>
<td></td>
</tr>
<tr>
<td>Stab wound</td>
<td>3/5</td>
</tr>
<tr>
<td>Gunshot wounds</td>
<td>65/68</td>
</tr>
</tbody>
</table>
Conclusion

• Four main categories of topical hemostatics

• Hemostatic choice → available and fits desired intent

• Paucity of data

• Can help adjunct hemostasis