TRAUMA, IMPLANTS, AND INORGANIC SURFACES

GALEN D. STUCKY
Department of Chemistry & Biochemistry
Materials Department
Biomolecular Science and Engineering Program
“Sumerian civilization in the southeast of the Tigres-Euphrates river area. Akkadian civilization in the northwest area. The two engage in continual warfare”

www.warscholar.com/Timeline.html

Shia civilization in the southeast of the Tigres-Euphrates river area. Sunni civilization in the northwest area. The two engage in continual warfare

images.thetimes.co.uk/TGD/picture/0,,374645,00.jpg
Uncontrolled hemorrhage continues to be the leading cause of death due to military trauma and the second leading cause of death in the civilian setting.

*Pusateri, Holcomb, Kheirabadi, Alam, Wade, and Ryan, The Journal of Trauma Injury, Infection, and Critical Care, 2006; 60:674*

- Leading cause of death globally among 15–19-year-olds
- Second leading cause of death in the 10–14 and 20–24 year age brackets.

World Health Organization, April 19, 2007

## Trauma Care Needs

### Five Leading Causes of Death, United States, 2005

Ages 1-55 (entire US population)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malignant Neoplasm</td>
<td>Unintentional Injury</td>
<td>Heart Disease</td>
<td>Suicide</td>
<td>Homicide</td>
</tr>
<tr>
<td></td>
<td>79,327</td>
<td>70,494</td>
<td>60,950</td>
<td>23,579</td>
<td>16,229</td>
</tr>
</tbody>
</table>

Blood loss from traumatic injury in United States causes over 50,000 deaths/year in U.S.

[www.cdc.gov](http://www.cdc.gov)
<table>
<thead>
<tr>
<th>Trauma Care Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Civilian</strong></td>
</tr>
<tr>
<td>First Responders: Police, firefighters, EMTs and paramedics</td>
</tr>
<tr>
<td>Emergency Rooms</td>
</tr>
<tr>
<td>Scheduled Surgery (future in U.S.)</td>
</tr>
<tr>
<td>Protection for individuals on anti-coagulants, hemophiliacs</td>
</tr>
<tr>
<td><strong>Homeland Security</strong></td>
</tr>
<tr>
<td>FBI, CIA, ATF, Coast Guard</td>
</tr>
<tr>
<td><strong>Military</strong></td>
</tr>
<tr>
<td>Air Force, Army, Marines, Navy</td>
</tr>
</tbody>
</table>
“The hemorrhage that takes place when a main artery is divided is usually so rapid and so copious that the wounded man dies before help can reach him.” COL H.M. Gray 1919

- Hemorrhage is leading cause of battlefield deaths (>50%)
- 1/3 of KIA considered salvageable
- 80% of hemorrhagic deaths are due to intracavity bleeding
- CCC Research focus on new hemostatatic methods, drugs, devices

% deaths at different times from wounding in Vietnam

Ryan et. al. Army Medical Department Journal PB 8-03-7/8/9, 12\
**Trauma**

**The Challenge**

Average adult male human has approximately 5.6 L of blood. Heart can pump 4-5 L blood /minute. Mortality possible after 1.6-2 L of blood loss.

**NEED RAPID INTERVENTION**

- Leading cause of death in young people
- 37% of deaths from traumatic wounds are caused by hemorrhage
- Hemorrhage is leading cause of preventable battlefield casualties
- Internal Organ and Cranial Surgical Procedures/ Bleeding (clinical trials)
The Challenge - Initial Specs

- Rapid response < 3 minutes major artery
- Thermal Optimization of hemostasis
- High Surface Area Efficacy
  - Light Weight
  - Antibiotic Delivery Agent
  - Therapeutic Delivery Agent
  - Presentation of surface to support thrombosis
- Electrolyte Control
- Active in Presence of Heparin/Coumadin
- Biocompatibility (FDA)
- High Volume, Low Cost Availability, Simple
Army
Chitosan Dressing (HC) HemCon (Tigard, OR)
- Polysaccharide polymer, deacetylated poly-N-acetylglucosamine (chitosan)
  Adheres to tissue strongly, sealing wound site; may secondarily accelerate the concentration of red blood cells and platelets at the bleeding site

Marine, Navy
QuikClot (QC) Z-Medica (Wallingford, CT)
- Granular zeolite
  Adsorbs water, concentrating red blood cells, clotting factors, and platelets at the bleeding site in an exothermic reaction
Positively charged polysaccharide (below pH 6.5) attracts red blood cells which are negatively charged. Coagulation of blood cells source of hemostasis.

New releases being tested
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dry Fibrin Sealant Dressing</th>
<th>Rapid Deployment Hemostat</th>
<th>HemCon Chitosan Dressing</th>
<th>QuikClot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ready to use</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Simple to apply</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lightweight and durable</td>
<td>?</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stable over long periods</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Safe to use/training requirements</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>?</td>
</tr>
<tr>
<td>Cost</td>
<td>$$$</td>
<td>$$$</td>
<td>$$</td>
<td>$</td>
</tr>
</tbody>
</table>

Other products recently disclosed -- being tested

TraumaStat

WoundStat

OMRIX, (Israel) Fibrin Sealant
Z-Medica Products
www.zmedica.com

**Quik Clot and QuikClot ACS™**
--- problem with excessive heat release

**QuikClot ACS+™ and QuikClot 1st Response™**
--- heat release solved, some sacrifice of blood-clotting efficacy

**QuikClot® Sport™ & QuikClot® Sport™ Silver**
--- heat release solved, antibiotic delivery of Ag+ as antibiotic

**QuikClot® Combat Gauze™**
-- no heat release, best *in vivo* survival and clotting efficacy
QUIKCLOT® COMBAT GAUZE™

100 % *in vivo* test survivability

How did we get there?
How to most efficiently promote or inhibit blood coagulation, prevent infection, heal wounds, and regenerate tissue?

- Surface Area
- Surface Charge
- Heat Release
- Surface Chemistry
- Particle Morphology
- Particle Size
- Pore Structure
- Supported Enzyme Activity and Delivery
- Electrolyte Transport
- Antibiotic Delivery
Activated Platelet
In Vitro
Intrinsic Pathway

Negatively Charged Surfaces Activate FXII

Activated Platelet

Venous Rupture
Extrinsic Pathway

Common Pathway

Resting Platelet

copyright 1996 M.W. King


Hydration capacity  20%
BET SA  515 m²/gm
α Cage  11.4 Å

NaCa$_{5.5}$(SiO$_2$)$_{12}$(AlO$_2$)$_{12}$•27H$_2$O (when fully hydrated)

Dehydrated in QC

www.z-medica.com/quikclot/hemostat_quikclot.asp

XRD Pattern of QuikClot™
Hypothesis: Accelerated clotting due to:

Dehydration of blood concentrates clotting factors and platelets

Heat does not influence clotting
The Zeolite Story

Host: Guest structures: tunable, inexpensive, light weight, high utility

Media concentration control

Control release/adsorption electrolytes

Selective surface adsorption of clotting reactants

Tunable heat profile with high hemostasis efficacy?? (rxn acceleration w/o burning)

- Adsorption/Separation: H$_2$O, H$_2$S, CO$_2$ removal, Gas Storage, CH$_4$, O$_2$/N$_2$ Separation
- Paper Making: 480,000 tons/yr
- Catalysis: Petroleum Processing, NO$_x$ Abatement: 700,000 tons/yr
- Ion Exchange: Radioisotope Separation, Detergent Builders: 35,000 tons/yr
- Construction Industry: Europe: 150,000 tons/yr
- Fish/Animal Culture: 80,000 tons/yr
- Solar Energy Storage: 700,000 tons/yr
- Ceramic Precursors: 150,000 tons/yr
Solving the 2nd/3rd degree burn problem

QuikClot ACS+™ and QuikClot 1st Response™
--- heat release solved, some sacrifice of blood clotting efficacy

Marines, Navy, Air Force, Army

QuikClot® Sport™ & QuikClot® Sport™ Silver
--- heat release solved, delivery of Ag⁺ as antibiotic

First Responders, Individual Protection

Z-MEDICA CORP LAUNCHES FIRST TWO BLOOD CLOTTING PRODUCTS FOR CONSUMERS – INCLUDING FIRST ANTIMICROBIAL FORMULATION QuikClot Sport™ & QuikClot Sport Silver™ Created for Sports and Adventure Enthusiasts – Particularly Those Who Venture Far From Medical Attention

Latest Lifesaving Blood Clotting Technologies Result from Z-Medica Collaboration with United States Navy & Prof Galen Stucky at University of California, Santa Barbara

In use in Middle East by Navy, Army and Marines

Cool Formulation - New for First Responders, Environmental Health & Safety Teams, Industrial Nurses
Tunable Heat Response and Hydration Capacity

Increasing Hydration

In Vitro Heat Release with Hydration Level

Decreasing Heat Release

April Sawvel
Two effective ways to tune heat release

Increasing Pre-Hydration

0%  10%  20%  40%  80%  100%

0.37% Ag-Exchanged QuikClot™

Optimal Pre-Hydration Range

96.9 °C  68.4 °C  29.2 °C  24.0 °C  19.5 °C  19.2 °C
Clotting Quotient (CQ) = \frac{R \text{ Time with Agent}}{R \text{ Time without Agent}}

CQ for Native Blood = 1

Values < 1 represent accelerated clotting

Values > 1 represent prolonged clotting

Haemoscope Thrombelastograph™
In Vivo Simulated Traumatic Swine Injury Testing

Selection Criteria for New Hemostatic Agents: 
In Vitro Parameters and In Vivo Performance

--

Sample | R (minutes) | α (degrees) | MA (mm Displacement)
---|---|---|---
Blood Alone | 10 | 53.4 | 72.7
Dry QuikClot | 1.4 | 74.0 | 71.4
Hydrated QuikClot | 2.8 | 65.4 | 70.3

Hydrated QuikClot™ still accelerates blood clotting!
A little bit of heat is good!
Blood Clotting Cascade

**Intrinsic Pathway**

- Factor XI
- Factor X
- Factor IX
- Factor VII
- Tissue Factor
- Ca$^{2+}$
- Thrombin
- Factor Xa

**Extrinsic Pathway**

- Vascular Injury
- Tissue Factor
- Factor VII
- Ca$^{2+}$
- Thrombin
- Factor Xa

**Ten-ase complex**

- Factor XIII
- Factor XIIIa
- Fibrin
- Ca$^{2+}$
- Fibrinogen
- Fibrinogen
- Fibrin (crosslinked)

*Davie et. al. Biochemistry, Vol. 30, No. 43, 1991, 10363*
Zone of No Growth Surface Area: Pellet Geometric Surface Area after 24 hours ~ 2.2 for Ag-exchanged LTA-5A
Antibiotic Activity $f(\text{Ag content})$

**Ion Exchange**

- Zone of Clearing / Ag-Zeo Pellet
- No reduced activity
- But even this could still be sufficient for protecting some wounds.

**Solid-State Mixing**

- Zone of Clearing / Ag-Zeo Pellet
- No reduced activity

Onset of Coagulation / Isoelectric Point

In Vitro Sheep’s Blood Results with Different Oxides

Ostomel et al. 2006
**MBG: Mesoporous Bioactive Glass**

- Homogeneous Composition
- High Surface Area

**BG: Bioglass**

- Phase Separation Problems
- Lower Surface Area


Clot Strength for Bioglasses

- MBG 90
- CaO
- Spherical MBG 80
- Hydroxyapatite
- SBA 15
- Sheep Blood
- No Agent Added
- Non-porous BG 6

Viscoelastic Clot Strength

Time (5 min/div)
Hemostasis vs Bone-Forming

Hydroxyapatite \((\text{CaO})_{10}(\text{P}_2\text{O}_5)_3(\text{OH})_2\) (Ca:P 3.3:1)
Synthetic analog of the inorganic oxide found in bone……Antithrombotic

Bioactive glass 60, \((\text{SiO}_2)_{6.7}(\text{CaO})_4(\text{P}_2\text{O}_5)\) (Ca:P 4:1)
Fastest rate of hydroxyapatite deposition…..least hemostatically active

Bioactive glass 80, \((\text{SiO}_2)_{20}(\text{CaO})_4(\text{P}_2\text{O}_5)\) (Ca:P 4:1)
Slowest rate of hydroxyapatite deposition….most hemostatically active
Remove Ca$^{2+}$

Dehydration of layered clay does not improve effectiveness

Kaolin vs QuikClot

Thrombelastograph comparison between kaolin and QuikClot

Clotting Time versus Dosage Kaolin and QuikClot

Additionally, kaolin is:
~non-toxic
~inexpensive

Kaolin is as effective as QuikClot per unit weight and does not generate heat upon contact with water

QUIKCLOT® COMBAT GAUZE™

100 % *in vivo* test survivability

How did we get there?
**Conclusions: Kaolin**

- **rapid response**
- *In vivo* testing confirms positive *in vitro* results
- lightweight
- non-toxic
- time- and temperature-stable
- active in presence of anticoagulants
- dirt cheap --very cost effective

> Clays have appropriate surface chemistry/charge and protein-accessible surface area to be as effective as QuikClot without the drawback of tissue injury

> QuikClot can be improved by increasing protein-accessible surface area

> Clays are versatile starting point for more complex materials: polymer composites, ion-loaded materials, protein-loaded materials
**Giacomo Basadonna**

- Kaolin-coated gauze in a swine model

- Severe bleeding injuries
  - liver \((n = 15)\)(3.5 x 0.5 cm injury within segments V-VIII)
  - spleen lacerations \((n = 13)\)(3.5 x 0.5 cm longitudinal injury)
  - mesenteric injury \((n = 11)\)(3 cm)
  - femoral artery and vein transection \((n = 7)\)

- Regular surgical gauze \((n = 11)\) was used as control and complete clotting within 5 minutes was compared
In vitro Testing: Kaolin

(Basadonna - Tilt tube)

<table>
<thead>
<tr>
<th>Material</th>
<th>Time (minutes ± Standard Deviation)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaolin alone</td>
<td>2.76 ± 0.11 vs. 10.92 ± 0.30</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Kaolin gauze</td>
<td>1.88 ± 0.15 vs. 10.92 ± 0.30</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QuikClot</td>
<td>2.92 ± 0.2 vs. 10.92 ± 0.30</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

No significant difference was noticed when QuikClot was compared to kaolin alone or kaolin-coated gauze.
In vivo Testing: Kaolin

(Basadonna)

• In-vivo studies show that the kaolin-coated gauze was successful in controlling bleeding in 100% injuries (liver, spleen, mesentery and femoral vessels) within 1-5 minutes from its application.

• The gauze(s) did not become saturated with blood and no other intervention was necessary.

• Control surgical gauze failed to control bleeding in all cases within 5 minutes from application.

• In several cases, because of persistent bleeding the control gauze was removed and kaolin-coated gauzes were successfully used to control hemorrhage.
Besides the hemostatic properties, the novel product offers all the advantages of a regular surgical sponge: easy to use without requiring complicated training; pliable and can be introduced in deep cavities even through small orifices, easily reaching distant bleeding points.

The kaolin-coated gauze represents an exciting and promising new treatment choice for acute traumatic bleeding in both the military and civilian theater.

www.newscientist.com/article/mg18925435.800-saved-by-sand-poured-into-the-wounds.html

“Life Saving Sand”, Convergence (Magazine of Engineering and Sciences at UCSB)
Volume 8, Summer 2007

www.engineering.ucsb.edu/convergence/

www.chem.ucsb.edu/~stuckygroup/stuckygroup
Future Directions

- Internal Bleeding
- Wound Healing
- Nerve and Tissue Regeneration
- A Predictive Systems Model of the Blood Clotting Cascade
- System Integration with other Cardiovascular Processes