A novel technology in the management of hemostasis and dural repair

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Bleeding in Adult Spinal Surgery

- 1-3 level posterior lumbar fusion 674 – 1,257cc (Cha et al)
- Posterior fusion for spondyloolisthesis 800 – 1,500cc (Müller et al)
- Adult deformity surgery 1,000 – 3,000cc
- Deformity surgery with osteotomy 325 – 4,700cc
- Longer operative time
- Transfusion
- Infection
- Cost
- Coagulopathy
- Multiple system involvement


Bleeding in Spinal Reconstruction Surgery

Current Strategies

- Blood salvage, auto transfusion
- Packed cotton gauze sponges, pediatric laparotomy sponges
- Bone wax
- Electrocautery, Transcollation radiofrequency
- Collagen sponges
- Oxidized cellulose
- Collagen matrix
- Fibrin spray
- Tranexamic acid, Epsilon amino-caproic acid
Methods Of Decreasing Bleeding

- HEMODYNAMIC
  - Controlled hypotension
  - Local vasoconstrictors
  - Epidural blockade

- CHEMICAL/BIOLOGICAL
  - Systemic
    - Desmopressin
    - Aprotinin
    - Tranexamic acid
    - Epsilon aminocaproic acid
    - Estrogens
    - Other
  - Local
    - Bone wax
    - Hemostatic sponges (gelatin, collagen, cellulose)
    - Fibrin sealants

Spalski, Gaudern,Sztern Eur Spine J (2004)

Anatomy of the Active Haemostatic Sealant

Clotting Proteins
1. Typically Thrombin or Thrombin/Fibrinogen
2. Must be stable in the carrier
3. Must be active once released from the carrier

Carrier
1. Must be durable and conform to wound site
2. Must dissolve quickly to release proteins
3. Must be biocompatible and resorbable

Haemostatic Sealant
1. Proteins react quickly to form fibrin clot
2. Rapid haemostasis is achieved
3. No visible Carrier remains

Product Comparison

<table>
<thead>
<tr>
<th>Bone Wax</th>
<th>FloSeal</th>
<th>Surgifoam Plus</th>
<th>SurgiClot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>J&amp;J/others</td>
<td>Baxter</td>
<td>J&amp;J</td>
</tr>
<tr>
<td>Clotting Protein</td>
<td>None</td>
<td>Human Thrombin</td>
<td>Human Thrombin</td>
</tr>
<tr>
<td>Protein Carrier</td>
<td>NA</td>
<td>Bovine Collagen</td>
<td>Porcine Collagen</td>
</tr>
<tr>
<td>No Visual Signs of Carrier</td>
<td>Absorbable</td>
<td>6 to 8 weeks</td>
<td>6 to 8 weeks</td>
</tr>
<tr>
<td>Expands/Juvenile</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Use for bone bleeding</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Hemostatic Sponges

- Gelatin based
- Gelfoam, Surgifoam and others
- Bovine porcine or equine origin
- Often used with thrombin
- Mechanism of action unclear but appears to be more physical rather than any action on the clotting mechanism
- Widely used in spine surgery

Hemostatic Sponges

- Several publications have reported severe neurologic complications including cauda equina syndrome due to swelling and migration
- Can cause allergy

Fibrin Sealants

- Bi-component Fibrin Sealant
  - Tisseel
  - Beriplast
  - Hemaseel
  - other
- Fibrin sealant using wound fibrinogen
  - Floseal
Fibrin Sealants

- Bi-component fibrin sealant
  - mix fibrinogen with thrombin to form a clot
  - applied with a syringe
  - adhere poorly on wet surfaces
  - some formulations are neurotoxic (tranexamic acid)
  - swelling can cause neurologic injury
- Fibrin sealant using wound fibrinogen
  - contains thrombin and relies on wound’s fibrinogen
  - collagen/thrombin component and a gelatin matrix
  - swelling of gelatin granules restricts bleeding through tamponing mechanism
  - swelling can cause neurologic injury

Electrospun Dextran

- Polysaccharide that dissolves quickly when exposed to liquids
- Recognized by the body as a natural material
- Biocompatible and biodegradable
- Degradation products easily handled by the body

Mechanism of Action

SurgiClot accelerates the clotting cascade by delivering a bolus of Fibrinogen and Thrombin to the wound site, promoting a fast, strong, natural clot.

The final step in nature’s coagulation cascade is conversion of fibrinogen to fibrin, which interacts with or without platelets to form the clot (yellow circle). Thrombin is the enzyme that converts fibrinogen to fibrin.
SurgiClot®
Pre-Clinical Evidence

Femoral Arteriotomy

• Standard injury USAISR
  – 10 STF-treated animals
  – 10 control animals (Combat Gauze™)
• 6mm arteriotomy in femoral artery
  – 30 sec free-bleeding
  – 3 min dressing application
  – 2.5 hrs observation
  – Euthanasia if MAP < 20mm Hg

Endpoints

• Time to hemostasis
• Blood loss
• Presence of clot
• Adherence of clot
• Survival
• Simulated walking test
• Angiography
• Histopathology

<table>
<thead>
<tr>
<th>Dressing</th>
<th>Time to Hemostasis min</th>
<th>Blood Loss cc</th>
<th>Survival</th>
<th>Survival Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>40.5 ± 11.2</td>
<td>286 ± 31</td>
<td>80%</td>
<td>104.7 ± 14.9</td>
</tr>
<tr>
<td>STF</td>
<td>26.2 ± 6.5</td>
<td>238 ± 37</td>
<td>90%</td>
<td>145.6 ± 14.2</td>
</tr>
</tbody>
</table>

*p value* 0.27 0.23 0.14 0.005 0.05

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Control</th>
<th>STF</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clot in Wound</td>
<td>20%</td>
<td>100%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clot Adherent to Injury</td>
<td>0%</td>
<td>100%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clot Sealed Injury</td>
<td>0%</td>
<td>80%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distal Blood Flow</td>
<td>2/5</td>
<td>7/9</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Exact test*
The dressing highly effective at controlling arterial bleeding in coagulopathic swine (USAISR model)
- Swine bled 60% of blood volume
- Hypothermia
- Coagulopathic
- 6mm arteriotomy in femoral artery
- Salmon proteins used
• 90% survival (vs. 20% control dressing)
• 78% restoration of blood flow to distal limb

Hepatic Injuries

• 48 hepatic injuries
  – 12 no treatment
  – 18 control (TachoSil®)
  – 18 STF
• 8mm hepatic biopsy punch
  – 20 sec free-bleeding
  – Dressing application & compression
• Hemostasis ≤ 4 min
• Time to Hemostasis
• Histology

Results

• Odds Ratio of achieving hemostasis ≤ 4 min are 4x greater with STF than control (95% CI: 0.94-17.04)
• Time to hemostasis 2.9 min vs. 4.7 min
• 1.8x faster (95% CI: 0.7-2.8)

Does Size Matter?
Dural Tears Not a Problem in MIS?

- Less Dead Space/Tissue Violation
- Muscle Forms Living Barrier
- “I have never seen Pseudomeningocele/Wound Infection After Tubular Disectomy”

MIS Pseudomeningocele

Dural Repair Techniques

- Clips
Dural Tear Study in Swine
Lumbar laminectomy and 3mm durotomy

1. Leakage of CSF confirmed
2. OrthoClot applied with pressure for 1 minute
3. Appearance of OrthoClot clot (3 min)
4. Excess OrthoClot removed (5 min), note that the edge of the laminectomy remains exposed

Efficacy on Dural Lacerations
GLP Study in Goats
- Lumbar laminectomy
- 4mm durotomy
- Application of SurgiClot®
- Valsalva maneuver 40cm water
- Survived goats 30 days
- Examined for pseudomeningocele
- Checked for leak with 200 cm H2O Valsalva
- Histopathology (final report pending)
Durotomy Results – CSF Leak

<table>
<thead>
<tr>
<th>Animal</th>
<th>CSF Leak</th>
<th>Number of Dressings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>YES</td>
<td>N/A - sutured</td>
</tr>
<tr>
<td>3</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>NO</td>
<td>3</td>
</tr>
</tbody>
</table>

Results at 30 Days

- No pseudomeningocele
- No leakage with 200 cm H2O
- Minimal focal inflammation in 3 of 15 sections
- Minimum focal fibrosis in 6 of 15 sections
- No histopathological findings
Discussion
The dressing shows promise in sealing dural lacerations
• 80% successful at complete closure in goats without suture
• Starting a clinical trial in India in 2016

Spine Corpectomy Model - Bone
Comparing OrthoClot™ to Gelfoam®

• Endpoints
  – 36 spine injuries
    • 19 control (Gelfoam®)
    • 17 OrthoClot™ (human T/F)
  – Hemostasis ≤ 4 min
  – Time to Hemostasis
  – Histology

Materials and Methods
• 10 dairy bred goats
• 35 – 58 kgs
• 14 – 29 mos
• GLP study
• Decorticated 2 laminae
• Decorticated both iliac crests
• Dressing applied 4 minutes
• Second dressing if necessary
Grading of Bleeding

*Pulsatile*
*Flowing*
*Oozing*
*Stopped*


Endpoints

- Control of bleeding within 4 minutes
- Blood loss (weighed sponges)
- Need for dressing re-application
- 4 data points from each animal
  - R L4 lamina
  - L L5 lamina
  - Both iliac crests
- Each animal was survived for 28 days
- Euthanized and histopathology
- Coagulation studies beginning and end of study
- 20 data points for control animals
- 20 data points for test animals

Results

All animals survived
3 of 5 control animals developed wound complications
\( p = 0.05 \)

12 oozing and 8 flowing
Complete hemostasis at 4 minutes at all test article injury sites

12 oozing and 8 flowing
Complete hemostasis at 4 minutes in at 1 control injury site

\( p < 0.001 \)
Results

Control Article
19 injury sites required dressing re-application
Hemostasis achieved in 5 animals after second dressing application
Injury sites sealed with bone wax

Blood Loss
Test animals: $1.1 \pm 0.77 \text{ g}$
Control animals: $2.4 \pm 1.05 \text{ g}$
$p = 0.00031$

Results

Coagulation Studies
No difference between test and control groups
PT, aPTT, fibrinogen levels

Results - Histopathology

Test article, vertebra, HE stain 20X
Control article, vertebra, HE stain 20X
Discussion

• The new DFD is more efficacious than standard gauze sponges at providing hemostasis on decorticated bleeding cancellous bone in a spine surgery model.
• A single application of the DFD stopped blood flow at 4 min 100% of the time.
• The new DFD resulted in significantly less blood loss.
• Associated with fewer wound complications in this study.
• The new DFD is safe with respect to histopathological findings and immunological reaction.

Cancellous Bleeding Human Trial

UK

Anatomic Sites*

- Pelvic Osteotomy (3)
- ICBG (14)
- Spinal Fusion (8)
- Spinal Decompression (1)

Bleeding Grade

- Pulsatile
- Flowing
- Oozing
- Stopped

*22 patients to date

Hemostasis at 26 sites

<table>
<thead>
<tr>
<th>Controlled within 3 minutes</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled within 6 minutes</td>
<td>7</td>
</tr>
<tr>
<td>Bleeding decreased to oozing within 6 minutes</td>
<td>1</td>
</tr>
<tr>
<td>No hemostasis</td>
<td>0</td>
</tr>
</tbody>
</table>
Discussion

• Safety studies in our lab have shown the dressing is completely dissolved and resorbed
• No residual animal collagen to elicit inflammation or fibrosis

• Mechanism of action
  – Initial tamponade by the dextran matrix
  – Dissolution of matrix allows proteins to solubilize
  – Fibrin clot is quickly formed

Discussion

Currently undergoing clinical trials in UK and Norway
Periacetabular osteotomy, posterior spine fusion, ICBG
Similar results to this GLP pre-clinical study
Dressing may result in:
  ✓ Reduction of surgical bleeding
  ✓ Reduction of surgical time, morbidity and mortality
  ✓ Reduction in transfusions
  ✓ Reduction of costs
  ✓ Reduction of time in hospital