Safety and Efficacy of a Fibrin on Bleeding Bone

Birender Balain1, Niall Craig2, Kanna Gnanalingham3, Sanjeev Madan4, Hemant Sharma5, Guy Wynne-Jones6, John Hoseth7, Lian Øysyein7, Vidar Punsvik7, Sukumar Sura8, Rodolfo Padua9 and Timo Floyd thy9*

1Department of Orthopaedic Surgery, Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, England, UK
2Woodend Hospital & BMI Albyn Hospital, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK
3Department of Neurosurgery, Salford Royal Foundation Trust, Manchester, England, UK
4Department of Orthopaedic Surgery, Doncaster and Bassetlaw Foundation Trust, Doncaster, England, UK
5Department of Orthopaedic Surgery, Spire Hull and East Riding Hospital, Hull, England, UK
6Department of Neurosurgery, Spire Washington Hospital, Newcastle, England, UK
7Department of Orthopaedic Surgery, Helse Møre og Romsdal HF, Kristiansund, Norway
8Department of Neurosurgery, Star Hospitals, Hyderabad, India
9Scientific Advisory Board, St. Teresa Medical, Inc., Eagan, MN, USA

*Corresponding author: Timothy Floyd, MD, FACS, Chief Scientific Officer, Chairman, Scientific Advisory Board, St. Teresa Medical, Inc., Eagan, MN, USA. Tel: 001 208 841 2646; Fax: 001 208 367 7507; E-mail: t.floyd@steresamedical.com

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Abstract

**Background:** Cancellous bone bleeding (CBB) is a significant source of blood loss in spine and pelvis surgery. Current hemostatic methods are either ineffective or interfere with bone healing. A novel fibrin dressing (NFD) controls arterial, solid organ, and CBB in various species. The purpose of this clinical study was to determine the safety and performance of the NFD at controlling CBB.

**Methods:** Forty patients were enrolled at 9 centers in the UK, Norway and India. In each country Ethics Committee approvals were obtained prior to the study. This was a Level IV single-arm study of patients who met the inclusion eligibility criteria. The follow-up period was 6 weeks. The primary endpoint was control of bleeding at 3 min. Secondary endpoints were control of bleeding at 6 min, as well as clinical and laboratory criteria. Anatomical sites (AS) included posterior spinal fusion (PSF), iliac crest graft (ICG), and pelvic osteotomy (PO). Intraoperatively, the surgeon assessed the severity of CBB (pulsatile, flowing, oozing or none) and applied the dressing for 3 min. Bleeding was then assessed again and if it was not controlled (oozing or none) a second dressing was applied for an additional 3 min. For bleeding not controlled after the second dressing application the surgeon used an alternative method. Patients were assessed at 24 h and 6 weeks clinically (for hematoma, allergic reaction, etc.) and with lab analysis, including CBC, PT, aPTT and INR.

**Results:** All 40 patients completed the 6 week follow up. Twenty-three patients had PSF, 14 ICG and 3 PO. The dressing was used on a second AS in 11 of these patients for a total of 51 AS tested. Of the 51 treated AS, bleeding was controlled at 3 min in 41/51 (80.4%) and 6 min in 48/51 (94.1%). Three patients required alternative treatment. Bleeding in all 3 of the PO patients, the most vigorous bleeding, was controlled with the dressing. Adverse events (AE) considered to be “possibly device-related” occurred in 4 patients (13.3%).

**Conclusions:** This Phase I clinical trial demonstrated the safety and efficacy of this novel fibrin dressing, SurgiClot in cancellous bone bleeding. A randomized, controlled FDA trial currently is underway.

**Introduction**

Cancellous bone bleeding (CBB) is a significant source of blood loss in orthopedic and other surgery involving bone. Large blood loss in orthopedic surgery has been associated with transfusion risk, sequela of shock, coagulopathy, electrolyte abnormalities, disseminated intravascular coagulation, infection, hematoma and neurologic injury [1-8]. Current hemostatic methods either are ineffective or interfere with bone healing [9-14]. Commonly used xenograft gelatin-based hemostatic agents swell, which can cause neurologic injury, anaphylaxis or intravascular thrombosis [15-17]. Other agents utilizing gelatin or cellulose have been useful in vascular surgery [18].
A novel fibrin dressing (trade name SurgiClot) controls bleeding in a variety of tissues in preclinical animal studies, including arterial and bone bleeding [19-21]. We conducted a single-arm clinical study to determine its safety and efficacy on CBB in humans as a Phase I prelude to a Phase III controlled trial. This is a report of our findings.

Materials and Methods

This was a Level IV single-arm study of patients who met the inclusion eligibility criteria. Enrollment was consecutive and was conducted in 9 centers in the UK, Norway and India. The follow-up period was 6 weeks. Forty patients were enrolled in this study.

When confronted intraoperatively with significant cancellous bone bleeding, the surgeon identified the site as appropriate for testing the NFD. Severity of CBB was graded according to a standardized system developed by Renkens. Bleeding was graded as either pulsatile, flowing, oozing or none. The surgeon then applied the dressing directly to the bleeding site and applied slight manual pressure using a standard gauze sponge. After 3 min the gauze sponge was removed and the bleeding site was assessed for the presence of residual bleeding which was assessed using the same criteria. If bleeding persisted, a second dressing was applied for another 3 min and then the site was reassessed. If significant bleeding persisted the surgeon then used other means to control the bleeding and the dressing was considered a failure.

The primary endpoint was control of bleeding at 3 min. Secondary endpoints included control of bleeding at 6 min, as well as clinical and laboratory criteria. Treatment sites included posterior spinal fusion (PSF), iliac crest graft (ICG), and pelvic osteotomy (PO).

Patients were assessed clinically at 24 h and 6 weeks (for hematoma, allergic reaction, etc.) and with lab analysis, including complete blood count (CBC), pro-time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR). Surgeons completed a questionnaire regarding handling properties of the dressing.

Results

Thirty-eight of 40 patients completed the 6 week follow-up. Thirty-two PSF treatment sites were tested in 23 patients. Sixteen ICG treatment sites were tested in 14 patients. Three PO treatment sites were tested in 3 patients. The dressing was used at 2 anatomic sites in 11 of the 40 patients for a total of 51 treatment sites.

Of the 51 treatment sites, bleeding was controlled at 3 min in 41 (80.4%) and 6 min in 48 (94.1%). Nine of the 51 treatment sites required a second dressing application (17.6%) and a surgeon deviated from protocol on one patient who required a third application (2.0%) which controlled the bleeding. The second dressing application achieved hemostasis in 7 of the 9 sites (77.8%). Two sites required alternative treatment, but in total 49 of 51 (96%) bleeding sites were controlled with one or two dressing applications.

Table 1. Analysis of pre-op and post-op PT, aPTT and INR.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PT (sec)</th>
<th>aPTT (sec)</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6-Week Follow-up</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>34</td>
<td>32</td>
<td>39</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>11.7 ± 0.9</td>
<td>11.7 ± 0.9</td>
<td>30.6 ± 4.2</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>11.5</td>
<td>11.5</td>
<td>31.5</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>10-14.4</td>
<td>10-15</td>
<td>18.5-39</td>
</tr>
</tbody>
</table>

Interestingly, 100% of the secondary treatments sites (11/11) achieved hemostasis with a single dressing application at 3 min. Bleeding in all 3 of the PO patients, the most vigorous bleeding, was controlled with the dressing.

We saw no difference between pre-op and post-op protime (PT), activated partial thromboplastin time (aPTT) or international normalized ratio (INR) (Table 1).

A further secondary endpoint was handling characteristics determined by the surgeons (Table 2).

Table 2. Characteristics determined by the surgeons.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>How easy is product to use?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very easy</td>
<td>72.5% (29/40)</td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>27.5% (11/40)</td>
<td></td>
</tr>
<tr>
<td>No opinion</td>
<td>0.0% (0/40)</td>
<td></td>
</tr>
<tr>
<td>Difficult</td>
<td>0.0% (0/40)</td>
<td></td>
</tr>
<tr>
<td>Very difficult</td>
<td>0.0% (0/40)</td>
<td></td>
</tr>
</tbody>
</table>
How easy is product to apply to the bleeding site?
- Very easy: 65.0% (26/40)
- Easy: 35.0% (14/40)
- No opinion: 0.0% (0/40)
- Difficult: 0.0% (0/40)
- Very difficult: 0.0% (0/40)

How well did material conform to tissue surface?
- Material conformed very well to tissue: 60.0% (24/40)
- Material conformed well to tissue: 27.5% (11/40)
- No opinion: 5.0% (2/40)
- Material conformed poorly to tissue: 7.5% (3/40)
- Material conformed very poorly to tissue: 0.0% (0/40)

How well did the product dissolve?
- Material dissolved very well: 80.0% (32/40)
- Material dissolved well: 17.5% (7/40)
- No opinion: 2.5% (1/40)
- Material dissolved poorly: 0.0% (0/40)
- Material dissolved very poorly: 0.0% (0/40)

How effective was SURGICLOT at controlling bleeding compared to other topical haemostatic agents?
- Much more effective: 47.5% (19/40)
- More effective: 32.5% (13/40)
- About as effective: 20.0% (8/40)
- Less effective: 0.0% (0/40)
- Much less effective: 0.0% (0/40)

Discussion

This feasibility study successfully demonstrated the efficacy and safety of this novel fibrin dressing.

We have shown it to be superior to a standard U.S. Army dressing in achieving hemostasis in arterial injuries in hypothermic, coagulopathic swine and it easily controlled bleeding cancellous bone in goats [19,20].

The surgeons participating in the present study were naive to the dressing yet were able to achieve 3 min hemostasis with one dressing application 80.4% of the time. They were able to achieve 3 min hemostasis 100% of the time upon treatment of subsequent different anatomic sites. Therefore, the learning curve is very short. Surgeons universally graded the dressing as either “as easy to use” or “easier to use” than currently available hemostatic products.

We believe it will have wide application in all surgical procedures involving bone and will help mitigate some of the complications and costs associated with blood loss in surgery where bone is cut, such as orthopedic surgery, spine surgery, cardiovascular surgery and head/neck surgery.

Since the dextran component quickly dissolves this dressing has the added advantage of leaving no residual foreign material. Pre-clinical safety studies have demonstrated inflammatory response comparable to controls with minimal foreign body reaction.

Conclusions

SurgiClot® is efficacious and safe at controlling CBB in spine and pelvis procedures (PSF, ICG, PO). A global randomized, controlled FDA trial of the dressing on bleeding cancellous bone currently is underway.

Ethics Committee Approvals

2. United Kingdom: WoSRES (West of Scotland Research Ethics Service) 14/WS/1153.

References


