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Safety and Efficacy of a Novel Fibrin Dressing on Bleeding Cancellous Bone

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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, sequelae 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, aPT and INR.

	PT (sec)		aPTT (sec)		INR	
	Baseline	**6-Week Follow-up**	**Baseline**	**6-Week Follow-up**	**Baseline**	**6-Week Follow-up**
n	34	32	39	37	40	38
Mean ± SD	11.7 ± 0.9	11.7 ± 0.9	30.6 ± 4.2	32.9 ± 7.7	1.0 ± 0.1	1.0 ± 0.1
Median	11.5	11.5	31.5	31.7	1.0	1.0
Range	10-14.4	10-15	18.5-39	25-73	0.9-1.22	0.9-1.2

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)**.

Adverse events (AE) considered by the Clinical Review Committee (CEC) to be "possibly device-related" occurred in 2 patients (10%). These included elevated ESR and eosinophilia in 1 patient, monocytosis in 1 patient, neutrophilia and monocytosis in 1 patient, and wound infection in 1 patient.

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

Table 2. Characteristics determined by the surgeons.

Characteristics	**All Subjects % (n/N)**
How easy is product to use?	
Very easy	72.5% (29/40)
Easy	27.5% (11/40)
No opinion	0.0% (0/40)
Difficult	0.0% (0/40)
Very difficult	0.0% (0/40)

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

1. **Norway:** REK (Regionale Komiteer for Medicinisk of Helsefaglig Forskningsetikk) 2015-1382-16.

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

3. **India:** STAR Hospitals Institutional Ethics Committee SH/EC/AX2/SOP02/V1.

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