

# The SPOT GRADE II: Clinical Validation of a New Method for Reproducibly Quantifying Surgical Wound Bleeding

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## Research article

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# Abstract

**Background:** The SPOT GRADE (SG), a surface bleeding severity scale (SBSS), is a unique visual method for assessing bleeding severity based on quantitative determinations of blood flow. This study assessed the reliability of the SG scale in a clinical setting and collected initial data on the safety and efficacy of HEMOBLAST Bellows (HB), a hemostatic agent, in abdominal and orthopedic operations.

**Methods:** Twenty-seven (27) subjects were enrolled across three (3) centers and received the investigational device. Bleeding severity and hemostasis were independently assessed by two (2) surgical investigators at baseline and at 3, 6, and 10 minutes after application of HB and compared for agreement.

**Results:** The mean paired Kappa statistic for assignment of SG scores was 0.7754. The mean paired Kappa statistics for determining eligibility for participation in the trial based on bleeding severity and the mean paired Kappa statistics determining the presence of hemostasis were 0.9301 and 0.9301, respectively. The proportion of subjects achieving hemostasis within 3, 6, and 10 minutes of HB application were 50.0%, 79.2%, and 91.7%, respectively. There were no unanticipated adverse device effects (UADEs) and one possible serious adverse device effect (SADE), as determined by the Independent Data Monitoring Committee (IDMC).

**Conclusions:** The reliability of the SG scale was validated in a clinical setting. Initial data on the safety and efficacy of HB in abdominal and orthopedic operations were collected and there were no concerns raised by the Investigators or the IDMC.

## Background

Hemorrhage in surgical procedures has been shown to be related to 55% of peri-operative complications and 27% of deaths.[1] The development of hemostatic agents aims to help reduce surgical blood loss and associated morbidity and mortality. Evaluation of hemostatic agents has been performed in prospective, controlled clinical trials.[2-28] However, these clinical trials have utilized subjective, non-clinically validated assessments for bleeding severity and hemostasis or no assessments at all. Use of a subjective assessment for determining bleeding severity in a specific treatment population (a subset of all bleeding severities) as well as for determining hemostasis (success) or the absence of such assessments can result in ambiguous and incomparable efficacy data. Therefore, these published multi-investigator, clinical studies may not be able to reliably and consistently evaluate the comparative performance of hemostatic agents.

Previous work has been performed to develop objective bleeding scales; however, they have not been validated in controlled clinical settings.[29,30] The SPOT GRADE (SG) is a clinically validated surface bleeding severity scale (SBSS) that was developed for the quantitative assessment of target bleeding site (TBS) blood loss (Figure 1) and meets regulatory agency requirements for use. [31,32,33]

In addition to providing a consistent and reliable method for evaluating hemostatic agent performance, another potential benefit of the SG scale in surgery is to serve as an indicator of severity and volume of blood loss prior to systemic blood pressure changes and reductions in hematocrit. Having a consistent, uniform scale for bleeding severity may allow further definition and delineation of appropriate actions to minimize intraoperative bleeding at each level of severity and help avoid the need for transfusion of blood products. Another major advantage of using the SG scale is that multiple bleeding sites can each be independently characterized and treated according to methods appropriate for the bleeding severity of each site. In addition, consistent calibration of assessments of bleeding severity amongst health professionals in a specific patient may also be facilitated leading to more efficient and higher quality care. Thus, training of health professionals on such a scale may potentially enhance patient care.

The SG scale has been previously described based on an in vitro model of surface bleeding severity.[31] The current study was executed to validate the use of the SG scale in a clinical setting to support employment of the scale in large multicenter randomized trials [33] as well as to provide an initial evaluation for the safety and efficacy of a local hemostat, HEMOBLAST Bellows (HB).

## Methods

A prospective, multi-center, multi-specialty, single-arm clinical study was performed to evaluate the SG scale and the safety and efficacy of a hemostatic device, HEMOBLAST Bellows (HB) (Biom'up, SA, Lyon, France). The study was performed in abdominal and orthopedic operations under an FDA-approved Investigational Device Exemption and was registered on ClinicalTrials.gov (NCT02502019). Institutional Review Board (IRB) approvals were obtained prior to any study-specific activities being performed and the study was conducted in accordance with applicable regulations and the Declaration of Helsinki.

HB was supplied as a bellows applicator pre-loaded with 1.65 g of hemostatic powder consisting of porcine collagen, bovine chondroitin sulfate, and human derived thrombin (1500 IU).

The primary objective of the study was to assess the reliability of the SG scale in a clinical setting. Secondary objectives were to collect initial data on the safety and efficacy of HB.

Twenty-seven subjects were enrolled across 3 institutions. Patients over the age of 21 undergoing non-emergent operations were evaluated for eligibility after giving written informed consent.

Patients were excluded if they met the following criteria: undergoing laparoscopic, thoracoscopic, robotic, spinal, neurologic, or emergency surgical procedures; pregnant, planning on becoming pregnant during the follow-up period, or actively breast-feeding; clinically significant coagulation disorder/disease (platelet count <100,000 per microliter and/or international normalized ratio [INR] > 1.5) within 4 weeks of surgery; chronic corticosteroid use within 2 weeks before surgery; received intravenous heparin or oral warfarin within 24 hours of surgery; active or suspected infection at the surgical site; had or planned to receive organ transplantation; known sensitivity, allergy, or religious objections to any component(s) of HB; American Society of Anesthesiologists classification of > 4; life expectancy of < 3 months; known

psychiatric disorder which would preclude the subject from completing the study; severe congenital or acquired immunodeficiency; HB would be used at the site of a porous coated joint implant; participation in another investigational study within the past 30 days; and not appropriate for inclusion per the medical opinion of the Investigator.

Eligibility was also assessed intraoperatively to confirm identification of a TBS with SG scale scores of 1 (minimal), 2 (mild), or 3 (moderate) bleeding [31] for which conventional means for hemostasis were ineffective or impractical based on the indications for HB. Subjects were evaluated preoperatively, intraoperatively, postoperatively, and at  $6 \pm 2$  weeks.

The first subject for each investigational site was treated as a lead-in subject; lead-in subjects were considered part of the safety population, but not part of the efficacy analysis population.

Clinical investigators underwent proprietary training and were qualified by testing on the SG scale prior to the enrollment of any subjects.[31] Baseline SG scores for the TBS of each subject were independently assigned by 2 investigators. The 2 investigators also independently assigned SG scores for the TBS at 3, 6, and 10 minutes after HB application. Hemostasis was defined as a SG score of 0.

The primary endpoint of the clinical trial was the mean paired Kappa statistic for the assignment of SG scores by 2 Investigators. Success for the clinical trial was defined as: mean paired Kappa statistics for assignment of SG scores  $> 0.61$ ; and mean paired Kappa statistics for determining eligibility and determining hemostasis using SG scores  $> 0.80$ .[34]

The secondary endpoints were: proportion of subjects achieving hemostasis within 6 minutes of HB application; proportion of subjects achieving hemostasis within 10 minutes of HB application; proportion of subjects achieving hemostasis within 3 minutes of HB application; and incidence of adverse events (AEs) through final follow-up. The safety success criterion was no more than one unanticipated adverse device effect (UADE) or serious adverse device effect (SADE) as determined by the Independent Data Monitoring Committee (IDMC).

Gauze weights were also used to collect data on bleeding severity. Pre-weighed stacks of gauze were held against the TBS at baseline and each evaluation time point for 5 seconds and weighed afterwards to calculate the mass of blood loss from the TBS.

To assess agreement between Investigators in rating bleeding severity using the SG scale, pairwise weighted kappa statistics were computed using all possible pairs of Investigator scorings at all available time points. For an overall summary of Investigator agreement, pairwise weighted kappa statistics were averaged over all pairings. Calculations were also performed to assess the correlation between the SG score and blood mass collected on the gauze.

All statistical analyses were completed using SAS System software, Version 9.3 or above.

## Results

A total of 27 subjects were enrolled and received HB including 3 lead-in subjects and were considered the safety analysis population (9 abdominal and 18 orthopedic). Twenty-four subjects were included in the efficacy analysis population (8 abdominal and 16 orthopedic). All subjects completed the study as planned.

The average age for all subjects was 62.8 years, with 51.9% male and 48.1% female. Regarding ethnicity: 22.2% of the subjects were Hispanic; 77.8% of the subjects were Caucasian; and 22.2% were African American (Table 1).

Table 1 – Subject Demographic Data by Surgery Type (Safety Analysis Population)

Measure	All	Abdominal	Orthopedic
Age	62.8 ± 8.64 (27) 63.0 [55.0, 68.0]	60.4 ± 10.70 (9) 55.0 [53.0, 66.0]	64.0 ± 7.48 (18) 64.5 [62.0, 68.0]
Gender			
<i>Male</i>	14/27 (51.9%)	6/9 (66.7%)	8/18 (44.4%)
<i>Female</i>	13/27 (48.1%)	3/9 (33.3%)	10/18 (55.6%)
Ethnicity			
<i>Hispanic or Latino</i>	6/27 (22.2%)	6/9 (66.7%)	0/18 (0.0%)
<i>Not Hispanic or Latino</i>	21/27 (77.8%)	3/9 (33.3%)	18/18 (100.0%)
Race			
<i>Caucasian</i>	21/27 (77.8%)	9/9 (100.0%)	12/18 (66.7%)
<i>African American</i>	6/27 (22.2%)	0/9 (0.0%)	6/18 (33.3%)
<i>American Indian or Alaska Native</i>	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
<i>Asian</i>	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
<i>Native Hawaiian or other Pacific Islander</i>	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
<i>Other</i>	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)

The surgical procedures consisted primarily of liver resections and total knee replacements, with the most common indications being metastatic cancers to the liver and osteoarthritis. The TBSs consisted of soft tissue, muscle, parenchyma, and bone. The average dimensions of the TBS were 21.1 ± 75.9 cm<sup>2</sup>, with larger dimensions in the abdominal arm (51.0 ± 131.0 cm<sup>2</sup>) and smaller dimensions in the orthopedic arm (6.1 ± 3.8 cm<sup>2</sup>).

For the primary endpoint, the mean paired Kappa statistic for the assignment of SG scores by 2 Investigators, the pairwise weighted Kappa statistics were 0.7441, 0.7640, and 0.8182 for each Investigator pair; the mean paired Kappa statistic was 0.7754 (Table 2).

Table 2 – Mean paired Kappa statistic for assignment of SPOT GRADE scores

Surgical Investigator Pair	Pairwise Weighted Kappa
Investigator Pair 1	0.7441
Investigator Pair 2	0.7640
Investigator Pair 3	0.8182
<b>Mean</b>	<b>0.7754</b>

The inter-rater agreement was also assessed for determining eligibility (SG score of 1, 2, or 3 [eligible] vs SG score of 0, 4, or 5 [ineligible]) and determining hemostasis (SG score of 0 vs SG score > 0). The mean paired Kappa for determining eligibility and hemostasis were both 0.9301. The pairwise simple Kappa statistics for the investigator pairs along with the mean paired Kappa are provided (Table 3).

Table 3 – Mean paired Kappa statistic for determining eligibility and hemostasis

<b>Surgical Investigator Pair</b>	<b>Eligibility - Pairwise Simple Kappa</b>	<b>Hemostasis - Pairwise Simple Kappa</b>
Investigator Pair 1	1.0000	1.0000
Investigator Pair 2	0.8902	0.8902
Investigator Pair 3	0.9000	0.9000
<b>Mean</b>	<b>0.9301</b>	<b>0.9301</b>

Change in gauze weight by SG score was examined. There was no statistically significant correlation between a change in gauze weight and SG scores.

Efficacy of HB was a secondary endpoint of this study. Rates of hemostasis across all study arms at 3, 6, and 10 minutes after HB application were 50.0%, 79.2%, and 91.7%, respectively (Table 4). Rates of hemostasis for the abdominal arm of the study at these time points were 25.0%, 50.0%, and 75.0% (Table 4). Rates of hemostasis for the orthopedic arm of the study at 3, 6, and 10 minutes after HB application were 62.5%, 93.8%, and 100.0%, respectively (Table 4).

Table 4 – Proportion of subjects achieving hemostasis at 3, 6, and 10 minutes

<b>Time</b>	<b>All</b>	<b>Abdominal</b>	<b>Orthopedic</b>
3 minutes	12/24 50.0% (31.4%, 68.6%)	2/8 25.0% (7.1%, 59.1%)	10/16 62.5% (38.6%, 81.5%)
6 minutes	19/24 79.2% (59.5%, 90.8%)	4/8 50.0% (21.5%, 78.5%)	15/16 93.8% (71.7%, 98.9%)
10 minutes	22/24 91.7% (74.2%, 97.7%)	6/8 75.0% (40.9%, 92.9%)	16/16 100.0% (80.6%, 100.0%)

Numbers are n/N percent (95% CI). Wilson confidence limits (score based) are used in the table. Cumulative numbers of subjects achieving hemostasis at each time are counted.

The median hospital stay was 4 days; no subjects were noted to have any clinical signs or symptoms of post-operative bleeding and there were no re-operations for bleeding. A total of 10 subjects (37.0%) experienced post-operative complications or adverse events (AEs). Forty-one AEs were reported, with 8 deemed as severe adverse events (SAEs). The IDMC reviewed and adjudicated each SAE and identified one as a possible severe adverse device event (SADE) – the development of non-occlusive thrombi in the portal and superior mesenteric veins. This study subject underwent a liver resection for metastatic rectal cancer. Prior to initiation of the hepatic transection, the portal pedicle was clamped (Pringle maneuver) for 30 minutes without heparinization. HB was applied to segment 2 liver parenchyma. The subject

presented with development of thrombi 6 days postoperatively, which resolved with heparin administration. Right hepatectomy, cancer, and longer duration of Pringle maneuver are shown to be independent significant risk factors for portal vein thrombosis.[,] All other SAEs were determined by study Investigators to be unrelated to HB.

All pre-defined conditions of study success were met (Table 5).

Table 5 – Conditions of study success

Parameter	Threshold for Success	Study Results	Meets Threshold
Mean paired Kappa statistic	> 0.61	0.7754	Yes
Mean paired Kappa statistic for determining eligibility	> 0.80	0.9301	Yes
Mean paired Kappa statistic for determining hemostasis	> 0.80	0.9301	Yes
No more than one UADE or SADE as determined by the IDMC	≤ 1 UADE or SADE	1 possible SADE	Yes

## Discussion

The SG is a visual scale based on quantitative determinations of blood flow and is used to assess bleeding severity and hemostasis. The scale has been shown to be reproducible and reliable.[31] This clinical study was performed to validate utility of the SG scale in a clinical setting, as investigators were able to simultaneously visualize and independently score bleeding.

The mean paired Kappa statistic for independent Investigator assignment of SG scores was 0.7754, indicating substantial agreement.[34] The mean paired kappa for determining eligibility and hemostasis were both 0.9301, indicative of almost perfect agreement. These results confirm the validity of the SG scale when used clinically.

This study found that there was no correlation between the mass collected on the gauzes and SG score. The gauze weight method has multiple possible inherent flaws: 1) other fluids in the vicinity of the TBS may be soaked up by the gauze (irrigation fluid, other bleeding sites, lymph, bile etc.); 2) variable amounts of pressure applied and imprecise timing of holding the gauze against the TBS; 3) requirement for maintenance of sterility when pre-weighing the gauze; 4) TBS assessment gauze may be mixed up with gauzes in the field; and 5) additional time and resources required to execute the measurements that are not practical during routine use of hemostats when determining eligibility for treatment of a TBS.

The SG scale is a visual assessment tool and requires no additional materials or time in the operating room to evaluate bleeding severity. The SG scale has been previously shown to be an effective method of training surgeons to assess intraoperative TBS bleeding severity.[31,33] The results of this study now validate the reproducibility and reliability of the scale when used clinically. Use of this scale may be the new standard for consistently and objectively assessing bleeding severity and hemostasis. This is especially important in randomized and controlled clinical investigations evaluating the performance of

hemostatic agents.[32,33] Previous clinical investigations have often relied on subjective assessments for bleeding severity or no assessments at all; therefore, the treatment of the same levels of bleeding between different treatment arms or different investigations cannot be precisely determined and validated. In addition, the assessment of hemostasis – usually the efficacy endpoint of these clinical investigations – can also be considered subjective.[29,30]

This clinical study demonstrates that surgeons who have undergone SG scale training and testing have substantial agreement on the assignment of scale scores and almost perfect agreement in the identification of eligible bleeding severities and hemostasis.

As noted previously, blood loss estimates in surgical procedures can be imprecise.[31] The ability to more accurately assess blood loss during orthopedic procedures is valuable as it may help surgeons and anesthesiologists improve understanding of intraoperative hemorrhage, leading to improved patient blood management. Better assessment of TBS bleeding rates may allow for improved management in terms of surgical techniques as well as blood product use. Rapid and precise assessments may also enhance communications between health care professionals leading to improved intraoperative, postoperative, and emergency care.

The safety and efficacy of HB initially demonstrated in this study have since been confirmed in a previous, large, prospective, randomized, multi-center study evaluating HB against a standard of care hemostat in cardiothoracic, abdominal, and orthopedic surgical procedures utilizing the SG scale.[33] In this current SG scale validation study, the scale was used to assess both eligibility of TBSs as well as successful hemostasis in both treatment arms. The SG scale may be usable as a standard means of measuring bleeding severity in future clinical trials designed in different specialties to evaluate the efficacy of a wide variety of hemostatic interventions.

## **Conclusion**

This study supports the clinical validity of the SG scale as a reliable means of assessing bleeding severity. Thus, the SG scale is believed to be a useful tool as a now clinically validated, quantitative scale available to surgeons for assignment of bleeding severity during surgical operations. Given the promising clinical results of HB in both soft tissue and boney bleeding seen in this and other randomized clinical trials, further prospective, investigations in other specialties evaluating the use of HB may be warranted.

## **Declarations**

### **Ethics Approval and Consent to Participate**

Institutional Review Board (IRB) approvals were obtained prior to any study-specific activities being performed (Western IRB protocol number 20151964). Written informed consent was obtained from subjects prior to any investigation-specific procedures being performed.

## **Consent for Publication**

Not applicable.

## **Availability of Data and Materials**

The datasets used and/or analyzed for the study are available from the corresponding authors on reasonable request.

## **Competing Interests**

Dr. Del Gaizo, Dr. Hermann, Dr. Genyk, Dr. Gillen, Mr. White, and Mr. Miller have received honoraria from Biom'up. Dr. W. Spotnitz, Ms. Hoffman, Dr. R. Spotnitz, Mr. Schorn, and Dr. Manson were consultants or employees of Biom'up at the time of the study.

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Biom'up provided the funding for the study.

## **Authors' Contributions**

Concept/design: W. Spotnitz, Hoffman, Gillen

Data analysis/interpretation: Hoffman, Gillen

Drafting article: Hoffman

Critical revision of article: W. Spotnitz, R. Spotnitz, Schorn, Manson

Data collection: Del Gaizo, Hermann, Sher, Genyk, White, Miller

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Not applicable.

## **Abbreviations**

AE: Adverse Event

HB: HEMOBLAST Bellows

IDMC: Independent Data Monitoring Committee

INR: International Normalized Ratio

SADE: Serious Adverse Device Effect

SAE: Serious Adverse Event

SBSS: Surface Bleeding Severity Scale

SG: SPOT GRADE

TBS: Target Bleeding Site

UADE: Unanticipated Adverse Device Effect

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## Figures

<b>SBSS Score</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
<b>Verbal Descriptor</b>	None	Minimal	Mild	Moderate	Severe; not immediately life-threatening	Extreme; immediately life-threatening
<b>Visual Descriptor</b>	Dry	Oozing	Pooling	Flowing	Streaming	Gushing
<b>Expected Intervention(s)</b>	None	Manual pressure, cautery, adjuvant hemostat (s)	Manual pressure, cautery, suture, adjuvant hemostat(s)	Manual pressure, cautery, suture, adjuvant hemostat(s)	Manual pressure, cautery, suture, staples, tissue repair	Manual pressure, cautery, suture, staples, tissue repair
<b>Maximum Expected ACS-ATLS Shock Risk Class</b>	1	1	1	2	3	4
<b>Flow Rate (mL/min) Ranges for Target Bleeding Sites (1 cm<sup>2</sup>)</b>	[0]	[0;4.8]	[4.8;12.0]	[12.0;25.3]	[25.3;102.0]	[ <u>102.0</u> ;+∞]
<b>Flow Rate (mL/min) Ranges for Target Bleeding Sites (10 cm<sup>2</sup>)</b>	[0]	[0;9.1]	[9.1;20.0]	[20.0;71.3]	[71.3;147.4]	[ <u>147.4</u> ;+∞]
<b>Flow Rate (mL/min) Ranges for Target Bleeding Sites (50 cm<sup>2</sup>)</b>	[0]	[0;13.5]	[13.5;28.0]	[28.0;117.3]	[117.3;192.7]	[ <u>192.7</u> ;+∞]

Figure 1

Surface Bleeding Severity Scale (SBSS), the SPOT GRADE, including flow rates.\* ACS-ATLS, American College of Surgeons – Advanced Trauma Life Support. \* As modified from Spotnitz WD, Zielske D, Centis

V, et al. The SPOT GRADE: A New Method for Reproducibly Quantifying Surgical Wound Bleeding. *Spine (Phila Pa 1976)* 2018;43(11):E664-E671.