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Safety and Hemostatic Effectiveness of SURGICEL® Powder in Mild and Moderate Intraoperative Bleeding

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Abstract

This postmarket clinical study evaluated the safety and effectiveness of the novel adjunctive topical hemostat SURGICEL® Powder (SURGICEL®-P), a powdered form of oxidized regenerated cellulose. In a prospective, open-label, single-arm multicenter trial, adult surgical subjects with mild-to-moderate bleeding for which conventional hemostatic methods were impractical/ineffective were treated with SURGICEL®-P. Descriptive analyses included hemostatic success rate at 3, 5, and 10 min, rebleeding and thromboembolic events, SURGICEL®-P-related serious adverse events requiring surgical intervention, and SURGICEL®-P ease of use (questionnaire). In 8 centers, 103 subjects were enrolled with a median (range) age of 64.0 (33.0-88.0) years. Surgeries were open (53.4%) or laparoscopic/thoracoscopic (46.6%) and mostly urological (37.9%) and abdominal (32.0%) procedures. Bleeding sites included various tissue types, with a median (range) surface area of 4 (0.02-72.0) cm^2. Hemostatic success rates were 77.7%, 87.4%, and 92.2% at 3, 5, and 10 min, respectively. In 7 subjects (6.8%), investigators reverted to standard of care. No safety signals were identified. Two deaths occurred with causes unrelated to SURGICEL®-P. Investigators favorably evaluated the ease of use of the SURGICEL®-P device. SURGICEL®-P is safe and effective in controlling mild-to-moderate bleeding in a broad range of surgical procedures. The trial was registered at https://clinicaltrials.gov as NCT03762200.

Keywords

surgery, bleeding, hemostasis, topical hemostat, absorbable topical hemostat, oxidized regenerated cellulose, SURGICEL®, hemostatic powder, patientblood management

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Introduction

Topical hemostatic agents have acquired an important role in the modern surgical management of perioperative bleeding.[1,2] Uncontrolled surgical bleeding is responsible for a substantial clinical and health care resource utilization burden, specifically given population aging and the associated increased prevalence of comorbidities and increased use of anticoagulants.[3–7] By facilitating hemostasis in situations of mild-to-moderate bleeding where conventional hemostatic measures are insufficient or impractical, the adjunctive use of topical hemostatic agents reduces blood loss and the need for systemic hemostatic drugs and blood transfusions. By reducing surgical time and surgical complications, they ultimately optimize patient health and reduce health care costs.[2,8,9] A variety of absorbable topical hemostatic agents are available, which differ in physicochemical properties and mode of action, as well as in ease of use, safety, and cost. The optimal choice of agent depends on the surgical scenario and bleeding

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situation (visibility, anatomy, and access) and on the patient's coagulation and comorbidity status.[1,10] The current armamentarium distinguishes *mechanical topical agents* which provide a structural matrix for hemostasis and are considered the easiest, safest, and most economical to use, *active agents* which rely on human, bovine, or recombinant thrombin, gelatine–thrombin matrix agents generically termed *flowables*, and *sealants* which are based on human fibrinogen or (semi)synthetic compounds.[1]

Oxidized regenerated cellulose (ORC) is a plant-based polymer, consisting of continuous fibers with mechanical hemostatic properties, that was first introduced as a hemostat in 1943 but is now available in various topical hemostatic formulations.[11,12] ORC provides a matrix for clot formation and enhances platelet activation and adhesion. In addition, because it creates a local acidic milieu, ORC produces coagulative necrosis with a tamponade effect and has been demonstrated to have in vitro bactericidal activity as well as antibacterial activity in an animal model of wound healing.[13–15] As absorbable mechanical hemostats, ORC-based agents are suitable for use in patients with an intact coagulation system. They have been shown effective in facilitating hemostasis in randomized controlled trials in various open, laparoscopic, and endoscopic surgery settings and are one of the most frequently used mechanical hemostats.[1,10] SURGICEL® Original and its family of products were developed to aid in controlling continuous surgical oozing in distinct surgical bleeding situations, and their performance and safety profile are supported by clinical studies in a wide spectrum of surgical procedures.[16] The recently marketed powdered delivery form of these products, SURGICEL® Powder (SURGICEL®-P), was designed to aid in mild-to-moderate intensity bleeding in a range of tissue surfaces including broad or raw surfaces and in locations where access or placement of fabric ORC products may be challenging or impractical.[15] Specifically, for capillary, venous, or small arterial bleeding in soft tissues with uneven tissue topography, or nearby critical nerves and blood vessels, or for oozing over diffuse broad areas, conventional methods such as suturing, ligature, or electrocautery may be impractical to use and may therefore be ineffective. Composed of aggregates of ORC fine fibers, SURGICEL®-P has superior in vitro clotting performance compared to the constituent ORC fine fibers because of the more favorable surface energetics and surface area: the clotting efficacy for high-sphericity ORC aggregates and ORC fine fibers was observed to be 95% versus 26%, respectively.[17] In studies with liver punch biopsy and liver abrasion in swine, which are acute experimental models of mild-to-moderate bleeding and mild diffuse oozing, respectively, SURGICEL®-P has shown superior hemostatic efficacy and faster time to hemostasis compared to other commercially available polysaccharide absorbable hemostats.[18] For example, comparison to PerClot® Polysaccharide Hemostatic System (PC) showed effective hemostasis rates of 100% for SURGICEL®-P versus 75% for PC in the liver punch biopsy model and 100% versus 47%, respectively, in the liver abrasion model. Time-to-hemostasis rates in this study were 30 s for SURGICEL®-P versus 423 s for PC in the liver punch biopsy model and 90 s versus 600 s, respectively, in the liver abrasion model.[18] In addition, in the porcine liver abrasion model, SURGICEL®-P provided more effective and sustained hemostasis and faster time to hemostasis than a combination powder hemostat consisting of thrombin, collagen, and chondroitin sulfate.[16] SURGICEL®-P combines the ORC powder formulation with a delivery system suitable for either open or laparoscopic/thoracoscopic approaches, which is particularly useful for large surfaces and difficult-to-access anatomical locations where application of other forms of topical hemostats may be impractical.[15]

Here we present a postmarket clinical study designed to further evaluate the safety and hemostatic effectiveness of SURGICEL®-P in controlling mild or moderate parenchymal or soft-tissue intraoperative bleeding in a clinical practice setting of general, gynecological, urological, and cardiothoracic surgery.

Methods

Study Design

This was a prospective, single-arm, multicenter trial on the adjunctive use of SURGICEL®-P to control surgical hemorrhage (capillary, venous, or small arterial) for which conventional hemostatic methods (such as sutures, ligature, or electrocautery) were impractical or ineffective because of the anatomy or the tissue characteristics at the bleeding site (eg soft tissues with uneven tissue topography, nearby critical nerves and blood vessels, or oozing over diffuse broad areas). The trial was designed as a postmarketing study across multiple surgical subspecialties and across open, laparoscopic, or thoracoscopic procedures in adult subjects with a mild-to-moderate "target bleeding site" (TBS). The TBS was defined as the first active bleeding site that was identified during surgical dissection, that was related to the operative procedure, and that required an adjunctive hemostat. In accordance with SURGICEL®-P clinical indication,[15] subjects were included with a mild bleeding TBS, defined as a small area of capillary, arteriole, or venule oozing; or a moderate bleeding TBS, defined as a larger area of capillary, arteriole, or venule oozing that presented a significant challenge because of the larger area involved (increasing the volume of blood loss), or as an area with bleeding that was more pronounced than oozing, that could also come from a small artery or vein, but that was not massive, pulsatile, or flowing. This postmarket study was conducted as a regulatory requirement to obtain European CE mark for SURGICEL®-P. The regulatory authorities approved the single-arm study design with a minimum of 100 evaluable subjects, as a means to establish further evidence on the safety and hemostatic effectiveness of SURGICEL®-P in mild and moderate parenchymal or soft-tissue intraoperative bleeding in various clinical surgery settings. Subjects were recruited from 8 investigational sites (up to 20 subjects per site) in the United Kingdom and Belgium. The study was performed in accordance with the International Conference on Harmonization (ICH) tripartite guideline for Good Clinical

Practice (2016) and the Declaration of Helsinki (2013). Protocols and informed consent forms were approved by institutional review boards at participating sites (West of Scotland Research Ethics Service [WoSRES], Paisley, United Kingdom), Commissie Voor Medische Ethiek (Gent, Belgium), and Ziekenhuis Oost Limburg Ethisch comité (Genk, Belgium). The trial was registered at https://clinicaltrials.gov as NCT03762200.

Study Subjects and Procedure

Patients aged 18 years or older who required a nonemergent, open or endoscopic, and general, gynecological, hepatopancreatobiliary, cardiothoracic, or urological surgical procedure were considered for enrollment if informed consent was obtained and an international normalized ratio (INR) < 1.5 was documented within 24 h of starting surgery. Subjects were included in the study if an appropriate TBS was identified intraoperatively and if none of the exclusion criteria were met. Exclusion criteria were as follows: subjects who were pregnant or nursing; subjects taking anticoagulant medication unless washout periods were observed per the product instructions for use (IFU); subjects on antiplatelet/P2Y12 inhibitor medications unless washout periods and platelet recovery times were observed; subjects participating or planning to participate in any other investigational device or drug study without prior approval from the sponsor; subjects who were known current alcohol and/or drug abusers; subjects with any preoperative or intraoperative findings identified by the surgeon that may preclude the use of study product; TBS in an actively infected field (Class III Contaminated or Class IV Dirty or Infected); TBS on arteries or veins where application of SURGICEL®-P would present a risk of introducing the study product into an open blood vessel; major arterial or venous bleeding or major defects in arteries and veins; TBS where silver nitrate or any other escharotic chemicals had been applied; TBS in, around, or in proximity to foramina in bone or areas of bony confine, the spinal cord, or optic nerve and chiasm because the swelling of the product in these areas holds a risk of compressing structures such as arteries and nerves[15]; TBS in urological procedures where plugging (blocking) of the urethra, ureter, or a catheter was possible by the study product.

For each subject, 2 distinct kits of SURGICEL®-P product were available in the operating room, ready to use prior to TBS identification. The SURGICEL®-P single-use applicator and angling tip were used in open procedures and the SURGICEL®-P Endoscopic Applicator in laparoscopic and thoracoscopic procedures. SURGICEL®-P was applied according to the manufacturer's IFU. Per these IFU, manual compression could be performed, as this prevents the powdered product from being washed away by oozing or moderately flowing blood. The TBS was assessed for hemostasis at 3, 5, and 10 min after the SURGICEL®-P application and again just prior to initiating fascial closure in open procedures or just prior to port-site closure in laparoscopic and thoracoscopic procedures. During this 10-min assessment, more than 1 layer of SURGICEL®-P could be applied to the TBS, as per the product's IFU. The SURGICEL®-P was left in situ, but also per the product IFU, it was advised to remove excess powder with irrigation and aspiration once hemostasis was achieved, without disturbing the clot. Moreover, if hemostasis could not be achieved and the surgeon felt it necessary—within the 10-min window—to revert to the standard of care to control the bleeding, hemostatic measures other than SURGICEL®-P could be used (treatment failure). Postoperatively, subjects were followed until hospital discharge and evaluated for adverse events (AEs) at 30 (+14) days (clinically), and for serious adverse events (SAE) that were related to SURGICEL®-P and required surgical intervention at 6 months (±30 days) (clinically or by voice call).

Each investigator was asked to complete an ease-of-use survey for their first 2 open and first 2 endoscopic procedures performed within the study. Questionnaires were to be completed as soon as possible but within approximately 72 h.

Study Endpoints

The study outcome was binary (presence or absence of hemostatic success). The primary endpoint was the proportion of subjects achieving hemostatic success at 5 min following the application of SURGICEL®-P, without reoccurrence of bleeding needing other hemostatic treatment until the initiation of fascial closure. Per the SURGICEL®-P IFU, reapplication of several layers of SURGICEL®-P was allowed, and in this study this did not affect subsequent effectiveness endpoints. The secondary effectiveness endpoints were the proportions of subjects achieving this criterium at 3 and 10 min following the initial SURGICEL®-P application. The 5-min primary endpoint has conventionally been employed in similar studies, and the secondary 3- and 10-min endpoints were included for comparison with broader preclinical and clinical experience with topical hemostats.[16,18–21] The investigators' evaluation of the ease of use of the SURGICEL®-P delivery system was investigated using a questionnaire survey.

Safety Monitoring

Investigators monitored AEs from the time of SURGICEL®-P application through the 30-day and 6-month follow-up points, and adjudicated all AEs for their relationship with study product and procedure. Specific safety endpoints were the incidence of thromboembolic events and the incidence of TBS rebleeding events requiring medical/surgical intervention through Day 30, and SAEs requiring surgical intervention through Month 6, which were considered to have an unlikely, possible, probable, or causal relationship to the study treatment. An internal independent safety committee reviewed cumulative safety data and adjudicated all events for the specific safety endpoints.

Statistical Analysis

Primary and secondary efficacy endpoints were analyzed using the intent-to-treat (ITT) set, which consisted of all subjects for whom a TBS was identified (subjects who do not complete the procedure after TBS identification are included in the ITT) and summarized descriptively (frequency count and percentage with 2-sided Clopper–Pearson 95% confidence interval [CI]); missing data were considered as failures. Analyses on the per-protocol (PP) set (evaluable set) were considered supportive. Effectiveness endpoints were also stratified by bleeding severity (mild or moderate) and surgical approach (open vs endoscopy). The primary endpoint was compared between surgical approaches using the chi-square test. Ease-of-use questionnaire data were summarized descriptively. Safety endpoints were analyzed using the safety set, which consisted of all subjects who received study product, and summarized descriptively (frequency count and percentage); missing safety data were not imputed. Software SAS® version 9.4 or later was used.

Results

Subjects and Surgical Procedures

Between November 26, 2018, and January 10, 2020, 132 subjects provided informed consent. Of these, 29 subjects were screen failures for either intraoperative findings precluding study treatment (16 subjects), for failing in- or exclusion criteria (12 subjects), or for patient withdrawal prior to surgery (1 subject) (Figure 1). As a result, 103 subjects were included in the ITT set. A total of 100 subjects completed the study as planned, while 2 subjects died, and 1 subject was lost to follow-up prior to the 6-month visit. One subject, although treated, had a major protocol deviation due to failing an inclusion criterion and was excluded from the PP set, which resulted in 102 evaluable subjects included in the PP set. There were 8 investigative sites, each having enrolled 2 to 20 evaluable subjects.

The median (range) age of the study population was 64.0 (33.0-88.0) years, the male/female gender distribution was approximately equal, and subjects were predominantly Caucasian (Table 1). The distribution of operative procedures showed predominantly urological, followed by abdominal, gynecological, cardiothoracic, and pelvic procedures; open surgery was slightly more frequent than laparoscopic/thoracoscopic surgery (including 7 robotic and 2 thoracoscopic procedures). The TBS tissue types included parenchymatous tissue (with the majority [19/20 TBS] being liver), connective tissue, a separate category of loose areolar tissue, as well as a small number of other TBS (Table 1). The median (range) surface area of the TBS was 4.00 cm^2 (0.02-72.00);bleeding was considered mild in approximately two-thirds of subjects and moderate in the remaining one-third (Table 1).

In 100/103 subjects (97.1%), 1 single SURGICEL®-P applicator was used, and sufficient coverage was obtained in all subjects (100%). At initial SURGICEL®-P application, manual compression, which—according to the SURGICEL-P IFU—is optional after application, was applied in 28/102 procedures (27.5%, $n = 1$ data unavailable) (Figure 2). During longitudinal assessment of hemostasis, this rate declined progressively to 2/102 procedures at fascial closure (2%, $n = 1$ data unavailable), while the percentage of bleeding sites showing hemostasis increased from 89/103 procedures (86.4%) at 3 min to 96/101 procedures (95.0%) at fascial closure (Figure 2). In 18 subjects (17.5%), additional SURGICEL®-P treatment, manual compression or observation (or a combination of these) was administered, whereas in 7 subjects (6.8%), investigators reverted to standard of care using other hemostatic methods including cautery, suture, SURGICEL®-SNoW (Structured Non-Woven), or TachoSil® (Figure 2).

The median total surgical procedure duration was 197 min (range 32-895 min), median total time in the operating room was 244 min (range 81-995 min), and median total postoperative hospital stay was 5 nights (range 0-76 nights, data unavailable for $n = 1$). The maximal procedure time of 895 min and hospital length of stay of 76 days were observed in a single patient who underwent a Whipple pancreaticoduodenectomy and whose TBS was a mildly bleeding area of the liver parenchyma that showed effective hemostasis at all primary and secondary endpoints. The median estimated total intraoperative blood loss amounted to 150 mL (range 5-4000 mL), and blood or blood product transfusions were given in 13/103 subjects (12.6%). The maximal blood loss of 4000 mL was observed in a subject who underwent a laparotomy for a retroperitoneal tumor resection and was unrelated to the TBS, a moderate bleeding site on the mesentery that showed 5-min hemostatic success with no rebleeding requiring additional treatment.

Effectiveness Endpoints

The primary endpoint analysis (Figure 3) in the ITT set showed the proportion of subjects achieving hemostatic success at 5 min to be 90/103 subjects (87.4%; 95% CI [79.4%, 93.1%]). The primary endpoint success rate according to bleeding intensity was 67/72 subjects with mild bleeding (93.1%; 95% CI [84.5%, 97.7%]) versus 23/31 subjects with moderate bleeding (74.2%; 95% CI [55.4%, 88.1%]). According to surgical approach, the success rate was 50/55 subjects (90.9%; 95% CI [80.0%, 97.0%]) for the open procedure group and 40/48 subjects (83.3%; 95% CI [69.8%, 92.5%]) for the laparoscopic/thoracoscopic procedure group ($P = 0.25$, chi-square test). Endpoint analysis results in the PP set were similar (not shown).

The secondary endpoint analysis (Figure 3) in the overall group showed hemostatic success in 80/103 subjects (77.7%; 95% CI [68.4%, 85.3%]) at 3 min and in 95/103 subjects (92.2%; 95% CI [85.3%, 96.6%]) at 10 min. In the subgroup analysis according to surgical approach, hemostatic success for the open procedure group was 44/55 subjects (80.0%; 95% CI [67.0%, 89.6%]) at 3 min and 53/55 subjects (96.4%; 95% CI [87.5%, 99.6%]) at 10 min; for the laparoscopic/thoracoscopic group, hemostatic success was 36/48 subjects (75.0%;

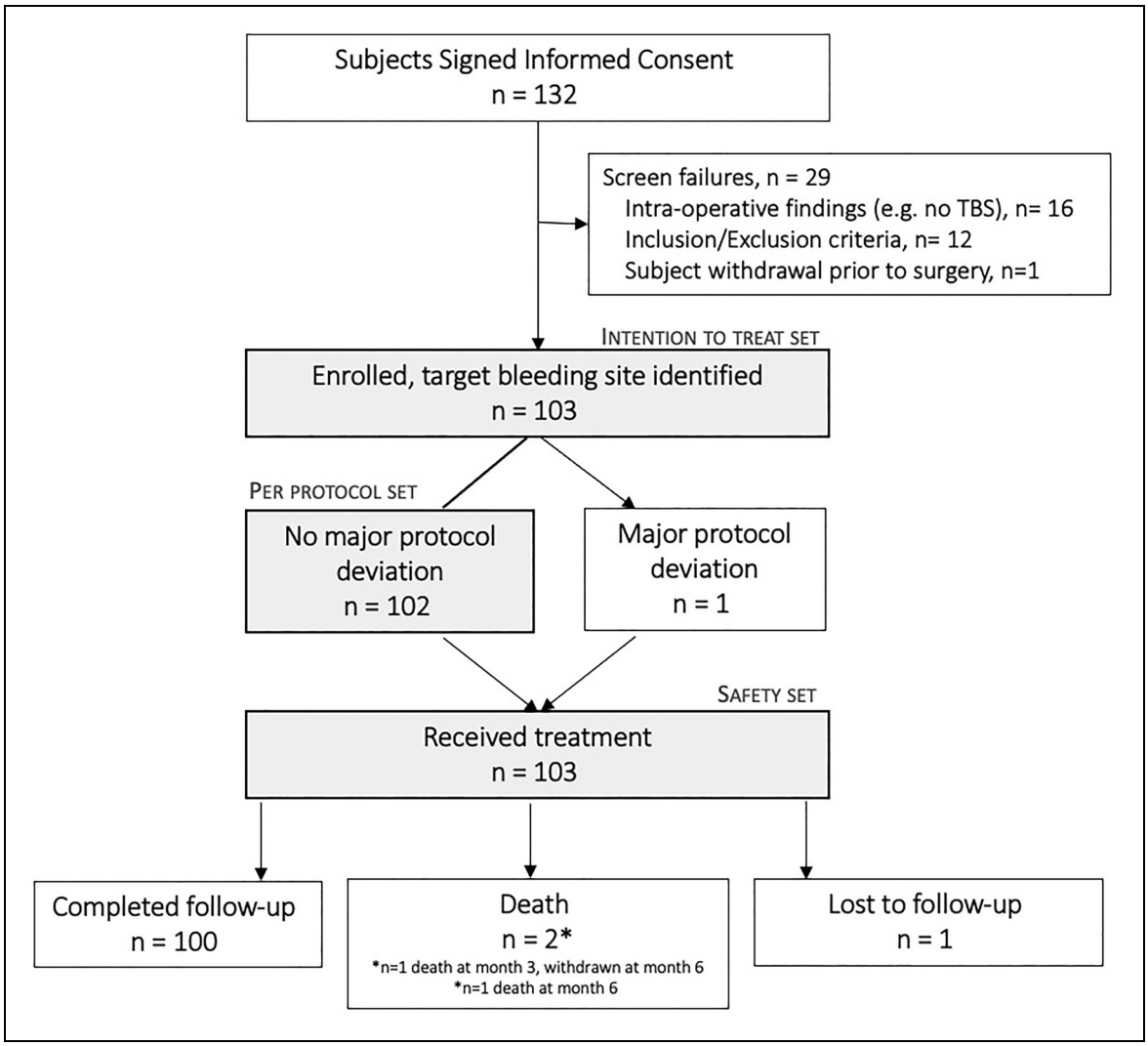

Figure 1. CONSORT flow diagram: disposition of study subjects and analysis sets. Abbreviation: TBS, target bleeding site.

95% CI [60.4%, 86.4%]) at 3 min and 42/48 subjects (87.5%, 95% CI [74.8%, 95.3%]) at 10 min. In the subgroup analysis according to bleeding severity, hemostatic success for mild bleeding was 61/72 subjects (84.7%; 95% CI [74.3%, 92.1%] at 3 min and 69/72 subjects (95.8%; 95% CI [88.3%, 99.1%]) at 10 min; for moderate bleeding, hemostatic success was 19/31 subjects (61.3%; 95% CI [42.2%, 78.2%]) at 3 min and 26/31 subjects (83.9%, 95% CI [66.3%, 94.6%]) at 10 min.

Of note, for 2 subjects, the 10-min hemostasis assessment was not performed as the fascia was closed at 5 min and 8 min; these subjects were considered as successes given the specific clinical bleeding scenarios with hemostatic success at 3 and 5 min without rebleeding or the subsequent need for additional treatment.

Safety

Over the 6-month follow-up, a total of 257 AEs occurred in 70/103 subjects (68.0%) (safety set), which included 33 SAE in 24 subjects (23.3%) and 23 severe AEs in 15 subjects (14.6%) (Table 2). There were no AEs or SAEs, specifically, no postoperative TBS-rebleeding or thromboembolic events, considered by the investigator to be unlikely, possibly, probably, or causally related to SURGICEL®-P. A total of 64 subjects (62.1%) experienced at least 1 AE that was categorized as unlikely, possibly, probably, or causally related to the study procedure. Seven subjects experienced AEs of ileus, which were considered anticipated for their procedure. All cases of ileus were dynamic/functional and resolved with nonsurgical treatment and without sequelae. The AE and SAE occurred most frequently within the system classes of gastrointestinal disorders (43/103 subjects [41.7%]) and infections and infestations (27/103 subjects [26.2%]). Two subjects (1.9%), both known with pancreatic cancer, died between Day 30 and Month 6 visits: 1 subject died at 3 months from an undetermined cause, and 1 subject died at 6 months due to pulmonary embolism after chemotherapy.

Surgeon Ease-of-Use Questionnaire

Data were collected for a total of 43 procedures, including 19 open, 22 laparoscopic, and 2 thoracoscopic procedures. For the majority of procedures, investigators either "agreed" or "strongly

Table 1. Subject Demographics, Surgical Procedure and Target Bleeding Site Characteristics.

	Overall group ($N = 103$)
Patient characteristics	
Age at consent, years	
Mean (SD)	61.0 (12.8)
Median (range)	64.0 (33.0, 88.0)
Gender, n (%)	
Male	52 (50.5)
Female	51 (49.5)
Race, n (%)	
Caucasian	93 (90.3)
Asian	2 (1.9)
Not reported	8 (7.8)
Prior/concomitant medical conditions, n (%)	103 (100.0)
Relevant surgical history, n (%)	86 (83.5)
Surgical procedure characteristics	
Surgical approach, n (%)	
Open	55 (53.4)
Laparoscopic/thoracoscopic	48 (46.6)
Surgical procedure, n (%)	
Cardiothoracic[a]	14 (13.6)
Abdominal[b]	33 (32.0)
Gynecological[c]	17 (16.5)
Urological[d]	39 (37.9)
Target bleeding site characteristics	
Primary method for hemostasis, n (%)	
None (other methods impractical)	80 (77.7)
Suture	1 (1.0)
Ligation	1 (1.0)
Cautery	19 (18.4)
Other	2 (1.9)
Type of bleeding, n (%)	
Mild	72 (69.9)
Moderate	31 (30.1)
Tissue type, n (%)	
Connective tissue	47 (45.6)
Loose areolar tissue	28 (27.2)
Parenchyma	20 (19.4)
Other[e]	8 (7.8)
Size (area), cm^2	
Mean (SD)	7.58 (10.06)
Median (range)	4.00 (0.02, 72.00)

[a] $n = 8$ coronary artery bypass graft, $n = 4$ aortic valve replacement, and $n = 2$ lobectomy.
[b] $n = 16$ hepatectomy (± cholecystectomy), $n = 10$ Whipple, $n = 2$ pancreatectomy, $n = 1$ pancreatectomy + splenectomy, $n = 3$ abdominal wall hernia repair, and $n = 1$ tumor resection.
[c] $n = 9$ hysterectomy, $n = 2$ endometriosis resection, $n = 2$ hysterectomy + endometriosis resection, $n = 1$ debulking, $n = 1$ myoma resection, $n = 1$ hysterectomy + adnexectomy, and $n = 1$ adnexectomy.
[d] $n = 34$ nephrectomy (± ureterectomy), and $n = 5$ prostatectomy.
[e] Superior vena cava needle holes ($n = 1$), perivascular tissue ($n = 1$), right atrium needle holes ($n = 1$), epicardial dissection on left ventricle ($n = 1$), peri-adrenal tissue ($n = 3$), and periprostatic tissue ($n = 1$).

agreed" that SURGICEL®-P was easy and quick to prepare for application (41/43 [95.3%]) and could be easily applied to the TBS (39/43 [90.7%]), that the investigator could exactly control the amount of SURGICEL®-P applied to the TBS (30/43 [69.8%]) and could adequately cover a broad area of bleeding (40/43 [93.0%]), and that excess SURGICEL®-P was easy to irrigate/aspirate out of surgical site without disturbing the clot at the TBS (29/36 [80.5%]). Similarly, for the majority of procedures, the investigators "agreed" or "strongly agreed" feeling confident about the ability of the product to achieve and maintain hemostasis (37/43 [86.1%] and 37/43 [86.1%], respectively). A subgroup analysis according to surgical approach (Figure 4) showed a similar response pattern for open and laparoscopic/thoracoscopic procedures; across the different survey items, the proportion of surgeons who "strongly agreed" varied between 42.1% and 84.2% for the open approach (median 63.2%) and between 28.6% and 54.2% for the laparoscopic/thoracoscopic approach (median 45.8%) (Figure 4).

Discussion

This postmarket clinical follow-up study shows that SURGICEL®-P is effective and safe in controlling mild-to-moderate surgical bleeding in adults undergoing major general, gynecological, urological, and cardiothoracic procedures, and in both laparoscopic and thoracoscopic approaches. Surgeons favorably evaluated the use of SURGICEL®-P and the delivery system. These real-world data support the SURGICEL®-P efficacy data from in vivo animal models and confirm its indication within the SURGICEL® group of products for continuous bleeding on raw or broad surfaces or anatomically complex surgical sites.[16,18]

Whereas the 5-min hemostatic success rate exceeded 87%, most bleeding sites were controlled earlier, at 3 min. Manual compression, initially applied in circa one-third of bleeding sites, was almost completely abandoned within 10 min, when hemostatic success exceeded 90%. These data confirm that SURGICEL®-P exhibits equal or superior hemostatic performance to the original SURGICEL® formulation, commonly used as a comparator in randomized clinical trials.[19,20,22] In 2 separate clinical studies, SURGICEL® was reported to achieve 73.3% and 82.3% hemostatic efficacy at 10 min in adults undergoing elective retroperitoneal, abdominal, thoracic, or pelvic surgery; in another study of adults undergoing hepatectomy, 10-min hemostatic efficacy was 89.1%.[19,20,22]

The 5-min hemostatic success rate was lower for moderate (74.2%) than mild (93.1%) bleeding sites. Although the optimal choice of a topical hemostat is primarily dependent on the surgical scenario, type of bleeding, and the agent's mechanism of action, bleeding intensity critically determines time to hemostasis. However, the difference in hemostatic success between mild and moderate bleeding sites declined over time, with both reaching more than 80% at 10 min. This is consistent with findings in preclinical models of liver punch biopsy or liver abrasion.[18] Approximately one-fifth of bleeding sites required additional treatment, but this consisted mostly of repeat application of SURGICEL®-P. Reversion to standard of care was necessary in only 6.8% of procedures, further confirming the efficacy of SURGICEL®-P for the selected indications, as well as its potential to avoid bystander damage from hemostatic measures such as

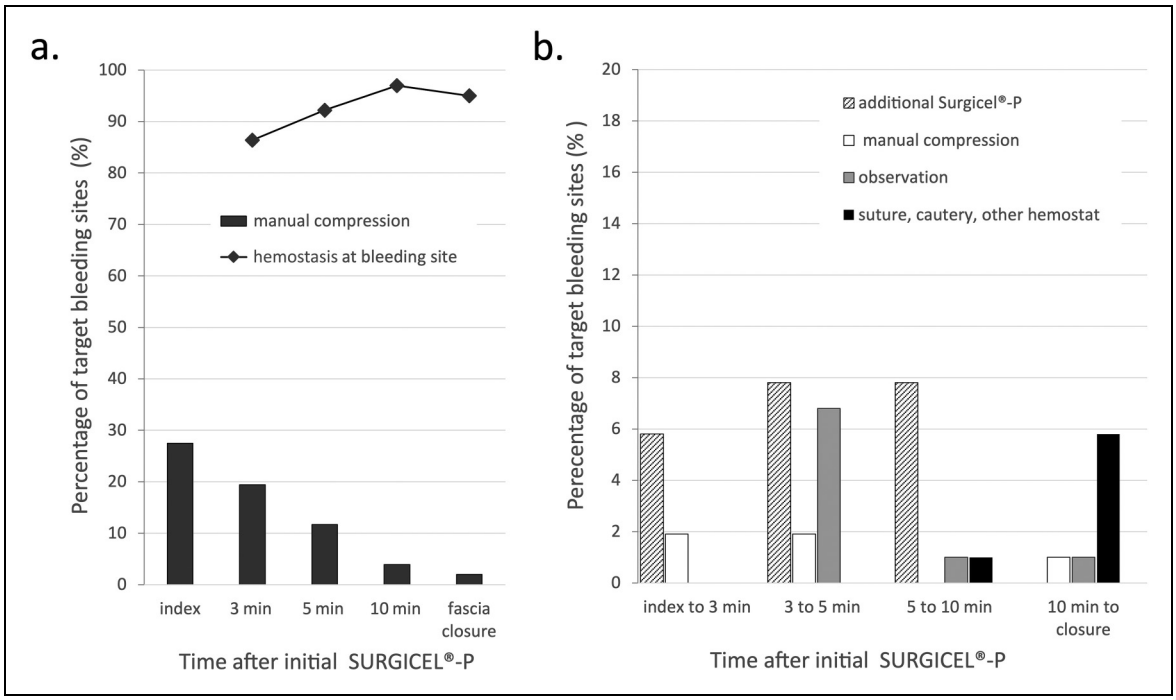

Figure 2. Evaluation of hemostasis and need for additional hemostatic treatment. Shown are (a) the percentage of procedures where manual compression was applied to the target bleeding site at index (along with SURGICEL®-P application) and during evaluation of hemostasis until fascial closure, along with the percentage of target bleeding sites that were considered hemostatic at 3, 5, and 10 min and before fascial closure; (b) the percentage of procedures where additional hemostatic measures were applied to the target bleeding site after the first SURGICEL®-P application at index. Values represent percentages of target bleeding sites.

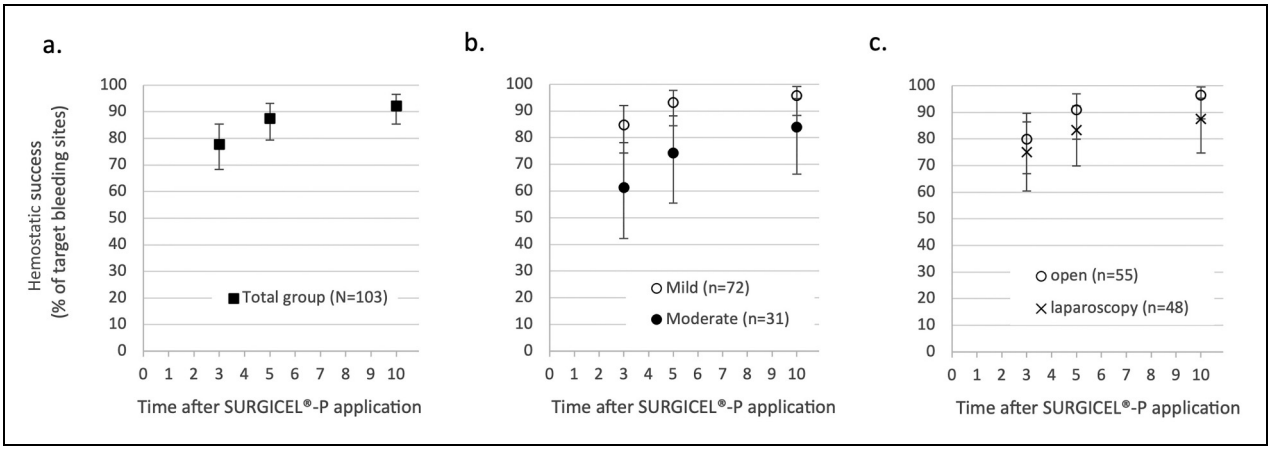

Figure 3. Primary and secondary hemostatic efficacy endpoints (ITT set). Shown are the primary and secondary study endpoints for hemostatic efficacy for (a) the total group and for the subgroups according to (b) bleeding intensity (mild or moderate) and (c) surgical approach (open vs laparoscopic/thoracoscopic surgery). Values indicate percentages (%) of target bleeding sites, with 95% confidence intervals. Abbreviation: ITT, intent to treat.

ligature or cautery. Success rates for laparoscopic/thoracoscopic and open procedures showed no statistically significant difference, and the ease-of-use survey showed similar agreement profiles for both approaches.

Procedure time and procedural blood loss were captured for the entire surgical procedure. Although median values were consistent with the nature of the procedures, these parameters, along with hospital length of stay, showed a high upper end-of-range value due to 2 subjects who experienced surgical complications unrelated to the TBS.

For the large majority of procedures, surgeons indicated in the ease-of-use survey that they agreed, or strongly agreed, that SURGICEL®-P was easy and quick to prepare and could adequately cover a broad area of bleeding, and that they felt

confident in the ability of the product to achieve and maintain hemostasis at the TBS. Similar to its fabric forms, the powdered SURGICEL®-P is resorbable, but it is recommended to apply the least amount necessary and to remove any excess powder when bleeding is controlled. In 97.1% of the procedures, a single applicator was used while most surgeons agreed that this allowed adequate coverage of the bleeding site and that excess product could be easily removed. Considering that two-thirds of bleeding sites were mild and one-third were moderate, this real-world data confirm that the SURGICEL®-P applicator is adequately dosed for its clinical indication.

Table 2. Adverse Events.

	SURGICEL®-P $N = 103$
Total number of adverse events	257
Total number of serious adverse events	33
Number (%) of subjects with ≥1 event in category	
AE	70 (68.0)
Serious AE	24 (23.3)
Severe AE	15 (14.6)
AE related* to SURGICEL®-P	0 (0.0)
SAE related* to SURGICEL®-P	0 (0.0)
AE related* to study procedure	64 (62.1)
AE expected/anticipated	55 (53.4)
Number (%) of subject deaths	2 (1.9)

*Unlikely related, possibly related, probably related, or related.

Whereas appropriately dosed SURGICEL®-P product is essentially resorbed within 2 to 5 weeks, follow-up in this postmarket study was extended to 6 months to monitor longer-term complications. Although infrequent, complications of ORC use have been reported. Most concern inflammatory foreign body reactions with granuloma or pseudotumor formation, thought to be related to the characteristic acidic environment created by ORC, particularly if excess product is present.[10,23] In addition, mass effect complications have been described due to ORC swelling, resulting, for example, in neural compression syndromes.[10,24] As per the manufacturer's instructions, in this study, investigators were advised to irrigate or aspirate excess powder once hemostasis was achieved,

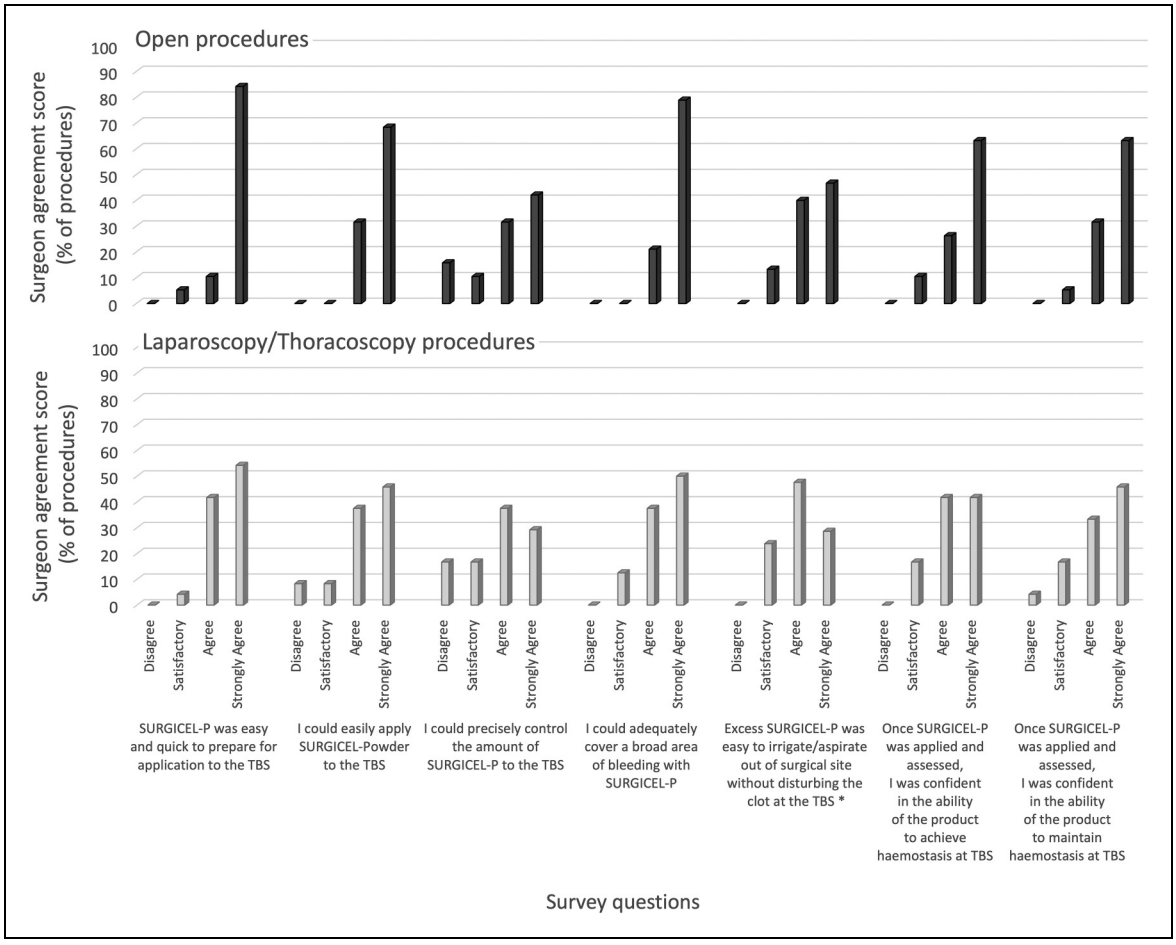

Figure 4. Ease-of-use survey. Shown is the surgeons' agreement score to the 7-item ease-of-use questionnaire, as reported by surgeons for their first 2 open and first 2 laparoscopic/thoracoscopic procedures performed within this study. Values represent the percentage of procedures for which a survey was completed and for which the indicated agreement score was reported. Results are shown according to surgical approach (open [top panel, $n = 19$] vs laparoscopic/thoracoscopic procedure [lower panel, $n = 24$]). *$n = 15$ for open procedures and $n = 21$ for laparoscopy/thoracoscopy procedure. Abbreviation: TBS, target bleeding site.

while not disturbing the clot. During the 6-month follow-up, no safety signals were identified, supporting the safety of the adjunctive use of SURGICEL®-P. The AEs and SAEs reported were those anticipated following the distinct major surgical procedures in the study, in an adult population with high rates of pre-existing medical and surgical histories. While several AEs were considered to have a possible relationship with the procedure, such was not the case for a relationship with the SURGICEL®-P device. Specifically, there were no SAEs, postoperative rebleeding or thromboembolic events assessed as having a causal relationship (including unlikely or at least possible) to SURGICEL®-P.

The single-arm design of this postmarket study precludes comparative evaluation with alternative hemostatic agents; however, we mitigated this limitation by comparing efficacy and safety with other SURGICEL® formulations that are accepted comparators in clinical trials of adjunctive topical hemostats in various surgical specialties.[19,20,22] Consistent with the clinical product indication of SURGICEL®-P, we used qualitative parameters to define the TBS. Despite the variability in tissue types and surgical approaches, and despite the wide range in bleeding surface area, hemostatic success rates were high in both mild and moderate bleeding sites, supporting the efficacy of SURGICEL®-P for its indication in true clinical practice. The longitudinal assessment of hemostasis, the prospective 6-month clinical follow-up, the sizeable patient sample within this area of clinical research,[22,25] and the broad range of major, open, and laparoscopic/thoracoscopic approaches provide a robust set of real-world data that support the efficacy and safety of the powder form of the ORC product.

The ORC hemostats are particularly useful for continuous bleeding from broad or raw surfaces that is unlikely to stop with conventional methods. Retrospective studies have shown that appropriate use of ORC is associated with reduced hemostatic agent use and spending relative to the use of other hemostats, while leaving clinical outcome unaffected.[26] Within the SURGICEL® family of products, the use of the advanced fibrillar and SNoW forms was associated with a shorter length of stay and lower all-cause cost than the original sheer-woven SURGICEL® product.[27] While these advanced SURGICEL®-P products share a superior hemostasis performance, the powder structure of SURGICEL®-P also offers improved conformability and adherence to broad surfaces and anatomically complex wound geometry. A recent study in porcine liver and spleen bleeding models showed both powder and sponge gelatine-based mechanical hemostats to be effective for parenchymal surgical bleeding but powder to be more suitable for mild diffuse bleeding.[28]

Conclusions

The findings of this postmarket clinical follow-up study support the safety and efficacy of the new powder form of ORC, SURGICEL®-P in controlling mild-to-moderate parenchymal surgical bleeding in a broad range of surgical procedures. The design of SURGICEL®-P applicators is intuitive and easy to use, offering a controlled and consistent expression of powder regardless of device orientation.

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Author Contribution

NA, ED, RK, IB, EB, and FB: conceptualization and methodology. NA, FB, and ED: investigation. ED, RK, and IB: funding acquisition, resources, and project administration. NA, ED, RK, IB, EB, and FB: formal analysis. NA, ED, RK, IB, EB, and FB: writing – review & editing.

Availability of Data and Materials

The study protocol including analysis plan was registered at https://clinicaltrials.gov at study start on November 26, 2018 and first posted on December 3, 2018 at https://clinicaltrials.gov/ct2/show/results/NCT03762200. All data underlying the results are available as part of the article and at https://clinicaltrials.gov/ct2/show/results/NCT03762200, and no additional source data are required.

Disclosure

This article is original work; it has not been published in peer-reviewed literature or presented at scientific meetings. The article is currently not being considered for publication elsewhere, but during a prior submission, it was posted as preprint before peer review (https://doi.org/10.21203/rs.3.rs-1185642/v1). All authors confirm they had complete access to the data that support the publication.

Declaration of Conflicting Interests

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Research Ethics

The study was performed in accordance with the ICH tripartite guideline for Good Clinical Practice (2016) and the Declaration of Helsinki (2013). Protocols and informed consent forms were approved by the institutional review boards at participating sites (WoSRES [West of Scotland Research Ethics Service], Paisley, United Kingdom,

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