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Original Article

A Study of Safety and Effectiveness of Evicel Fibrin Sealant as an Adjunctive Hemostat in Pediatric Surgery

Simon Kenny[1] Hany Gabra[2] Nigel J. Hall[3] Helene Flageole[4] Bogdan Illie[5] Ellie Barnett[6] Richard Kocharian[5] Khalid Sharif[7]

[1] Department of Paediatric Surgery, Alder Hey Children's Hospital, Liverpool, Merseyside, United Kingdom of Great Britain and Northern Ireland
[2] Department of Children's Surgery, Great North Children's Hospital, Newcastle Upon Tyne, United Kingdom of Great Britain and Northern Ireland
[3] Department of Neonatal and Paediatric Surgery, Southampton Children's Hospital, Southampton
[4] United Kingdom of Great Britain and Northern Ireland
[5] Department of Pediatric Surgery, McMaster Children's Hospital, Hamilton, Ontario, Canada

Address for correspondence Simon Kenny, OBE, BSc, MB ChB (Hons), FRCS (Paed), MD, Alder Hey Children's Hospital NHS Foundation Trust & University of Liverpool, East Prescot Rd, Liverpool, L2 2AB, United Kingdom (e-mail: simon.kenny1@nhs.net).

[6] Department of Scientific Affairs, Ethicon Inc, Raritan, New Jersey, United States
[7] Department of Scientific Affairs, Ethicon UK, Livingston, United Kingdom of Great Britain and Northern Ireland
[8] Department of Paediatric Surgery, Birmingham Children's Hospital NHS Foundation Trust, Birmingham, United Kingdom of Great Britain and Northern Ireland

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Abstract

Introduction Data on the use of fibrin sealants to control intraoperative bleeding in children are scarce. Evicel Fibrin Sealant (Ethicon Inc., Raritan, New Jersey, United States) was found safe and effective in clinical trials of adults undergoing various surgery types. We evaluated the safety and efficacy of Evicel versus Surgicel Absorbable Hemostat (Ethicon Inc.) as adjunctive topical hemostats for mild/moderate raw-surface bleeding in pediatric surgery.

Methods A phase III randomized clinical trial was designed as required by the European Medicines Agency's Evicel Pediatric Investigation Plan: 40 pediatric subjects undergoing abdominal, retroperitoneal, pelvic, or thoracic surgery were randomized to Evicel or Surgicel, to treat intraoperative mild-to-moderate bleeding. Descriptive analyses included time-to-hemostasis and rates of treatment success (4, 7, 10 minutes), intraoperative treatment failure, rebleeding, and thromboembolic events.

Results Forty of 130 screened subjects aged 0.9 to 17 years were randomized 1:1 to Evicel or Surgicel. Surgeries were predominantly open abdominal procedures. The median bleeding area was 4.0 cm^2 for Evicel and 1.0 cm^2 for Surgicel. The median time-to-hemostasis was 4.0 minutes for both groups. The 4-, 7-, and 10-minute treatment success rates were 80.0% versus 65.0%, 100.0% versus 80.0%, and 95.0% versus 90.0%, whereas treatment failure rates were 5.0% versus 25.0%, for Evicel and Surgicel, respectively. No deaths or thrombotic events occurred. Re-bleeding occurred in 5.0% of Evicel and 10.0% of Surgicel subjects.

Conclusions In accordance with adult clinical trials, this randomized study supports the safety and efficacy of Evicel for controlling mild-to-moderate surgical bleeding in a broad range of pediatric surgical procedures.

Keywords
- pediatric surgery
- bleeding
- hemostasis
- topical hemostat
- fibrin sealant

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Introduction

Achieving timely hemostasis during surgery is critical to ensure wound healing and minimize blood loss. Complications from perioperative bleeding and associated transfused blood products account for substantial clinical morbidity and economic burden.[1–3] Innovation in surgical techniques has included the development of various topical hemostatic agents (THA) that are used as adjuncts when conventional techniques such as ligature, sutures, or electrocautery are insufficient or impractical.[4,5] THA are known to improve patient outcome and reduce health care cost.[6–8] Classified by mechanism of action, they include mechanical agents that provide a structural matrix, active agents that contain thrombin, flowable consisting of gelatin matrix with/without thrombin, and fibrin sealants (FSs) that are based on fibrinogen and thrombin.[4,5]

FSs have emerged as effective and safe adjuncts for controlling perioperative bleeding in a wide range of open and endoscopic surgical scenarios.[9] Upon mixing, the dual-component thrombin/fibrinogen system mimics the final step in the natural coagulation pathway, forming a stable physiological fibrin clot that assists in tissue healing. Rapid hemostatic action occurs regardless of the patient's coagulation status, whereas the biocompatible clot is absorbed through physiological fibrinolysis. Evicel Fibrin Sealant (Ethicon Inc., Raritan, New Jersey, United States) consists of a human fibrinogen/fibronectin concentrate and human thrombin. The hemostatic effectiveness of Evicel was demonstrated in adult clinical trials of retroperitoneal, intra-abdominal, orthopaedic, vascular, and neurosurgery, and no safety concerns emerged.[10–13] In the United States and European Union (EU), Evicel is indicated as adjunct to surgical hemostasis when standard surgical techniques are ineffective or impractical.[14,15] In EU, Evicel is also indicated as suture support in vascular surgery and for suture line sealing in dura mater closure; however, it is not yet approved in children.[15]

Observational data have supported the efficacy of FSs as sealants/adhesives in children treated for dural puncture leakage,[16,17] peritoneal catheter cuff leakage,[18–20] and other conditions,[21–26] and these studies did not raise any safety concerns. A shortage of clinical data exists, however, on the use of FSs to control intraoperative bleeding in pediatric patients. FSs were shown to be safe and effective as adjunctive hemostats in children undergoing hepatectomy and tonsillectomy[27–29] and to reduce the transfusion need and intensive care hospitalization time after cardiovascular surgery.[30] For other surgical indications, however, studies are scarce. Here, we present a multicenter randomized, controlled clinical trial evaluating the safety and efficacy of Evicel versus Surgicel as adjuncts to surgical hemostasis in children undergoing abdominal, retroperitoneal, pelvic, or thoracic surgery.

Patients and Methods

Study Design

This was a multicenter, prospective, randomized controlled study across pediatric surgery centers in the United Kingdom, Canada, and Belgium, evaluating Evicel versus Surgicel (Ethicon, Inc., Raritan, New Jersey, United States) as adjunctive hemostats for mild-to-moderate intraoperative bleeding in children undergoing open or laparoscopic procedures in multiple surgical subspecialties. The "target bleeding site" (TBS) was defined as "the first active bleeding site identified during soft tissue or parenchymal organ dissection (kidney, liver, spleen, pancreas) that was related to the operative procedure and required the use of an adjunctive hemostat because conventional hemostatic methods were considered ineffective or impractical to use." Concurrent with prior hemostasis trials in adults, mild bleeding was defined as a "small area of capillary, arteriole, or venule oozing," and moderate bleeding as "bleeding that was considered challenging because of a larger area of capillary, arteriolar, or venular oozing, or bleeding that was more pronounced than oozing, possibly originating from a small artery or vein, but not massive, pulsatile, or flowing." As required by the European Medicines Agency Pediatric Investigation Plan for Evicel, a descriptive analysis on a randomized sample of 40 subjects ($\geq$20 subjects per arm) was needed to demonstrate safety of the product in pediatric population. In alignment with EU Guidance on the clinical investigation of plasma-derived FSs,[31] control subjects received standard treatment without FS, and the clinical situations represented those encountered in actual clinical practice. The performance and safety profile of the Surgicel family of products are supported by clinical studies in a wide spectrum of surgical procedures.[32] As a widely available product, Surgicel is considered a reasonable and acceptable international standard of care. This study was performed in accordance with the ICH tripartite guideline for Good Clinical Practice (GCP) (1996), the U.S. Food and Drug Administration regulations (Title 21 CFR Parts 50, 54, 56, 312), the Declaration of Helsinki (2013), the EU Clinical Trial Directive (2001/20/EC, May 2001), and the EU GCP Directive (2005/28/EC). Clinical Trial Application approval was obtained from the Medicines and Healthcare Products Regulatory Agency in the United Kingdom (January 2, 2014), the Federal Agency for Medicines and Health Products, Belgium (January 27, 2014), and Health Canada (February 11, 2014). Protocols and informed consent forms were approved by independent ethics committees/institutional review boards at participating sites (►**Supplementary Material S1**). The trial was registered as EudraCT 2013-003401-26 and NCT 02227706.

Study Subjects and Procedures

Patients younger than 18 years, requiring nonemergent open/laparoscopic, and abdominal, retroperitoneal, pelvic, or thoracic (noncardiac) surgery, were considered. The patient's parent or legal guardian provided informed consent, as required by local regulations. Assent was obtained from patients possessing the intellectual and emotional ability to comprehend the study concepts. Patients in whom an appropriate TBS was identified intraoperatively were enrolled if none of the exclusion criteria were met, which included known intolerance to blood products or study product component(s), unwillingness to receive blood products, surgery indicated for trauma, TBS in an actively infected field[33]), or in an

anastomotic bleeding site (full list of exclusion criteria is given in ►Supplementary Material S2).

The study sponsor provided computer-generated randomization envelopes. For each subject, at least 1 Evicel and 1 Surgicel kit were prepared in the operation field room before randomization. Upon encounter of the first TBS, the subject was randomized. Neither investigators nor study subjects were blinded to treatment. Evicel was applied according to manufacturers' instructions[34] using the Evicel application device, tips and/or airless spray accessory,[14] the amount of study product being dependent on the area to be treated. The TBS was assessed at 4, 7, and 10 minutes after randomization. If, during the 10-minute assessment, hemostasis was not achieved or if breakthrough bleeding occurred, a second application of the assigned study product was allowed (with a 1–2-minute cure time between applications); if indicated, the surgeon could revert to standard of care. If, beyond the 10-minute observation period, bleeding persisted or rebleeding occurred, the use of any hemostatic method was allowed, per the surgeon's standard of care. Postoperatively, study subjects were followed until hospital discharge and reevaluated at postoperative day 30 (+14) via an in-office visit or a phone call.

Safety Endpoints

All adverse events (AE) and serious adverse events (SAE) occurring within the 30-day postoperative follow-up were captured and adjudicated for relationship with study product and procedure. The sponsor was required to submit any reportable events to Health Regulatory Authorities per local regulations. For reportable events, investigator causality assessment was not to be changed by the Sponsor, and if there was a difference in opinion, both assessments were to be presented. AEs were summarized using the Medical Dictionary for Regulatory Activities terms. Specific safety endpoints were the proportions of subjects with thrombotic and TBS rebleeding events, the estimated volume of blood loss, and the quantity of transfused blood and blood products.

Efficacy Endpoints

The primary efficacy endpoint was the time to hemostasis (TTH), defined as the time between randomization and cessation of bleeding at the TBS. The secondary effectiveness endpoints were the proportions of subjects achieving hemostasis ("treatment success") at the TBS at 4, 7, and 10 minutes, and the proportion of subjects who failed to achieve hemostasis within 10 minutes, or who required hemostatic treatment at the TBS other than reapplication of the assigned study product ("treatment failure").[10]

Statistical Analysis

Safety and efficacy endpoints were summarized descriptively, in the Safety and Intention-to-treat (ITT) set, respectively. Efficacy endpoints included the median TTH with 2-sided distribution-free 95% confidence interval (CI) (missing data not imputed; analysis in the per-protocol [PP] set was considered supportive), proportions of subjects with 4-, 7-, and 10-minute treatment success and treatment failure, with 2-sided Clopper–Pearson 95% CI (missing data considered as failures). The TTH was also analyzed by age group (neonates [birth–30 days], infants/toddlers [31 days–24 months], children [2–11 years], and adolescents [12–<18 years]). The SAS studio version 9.1 (EG) or higher was used.

Results

Study Subjects

Between November 2014 and May 2019, a total of 130 subjects were screened at 14 centers, and 40 were enrolled at 8 centers in the United Kingdom and Canada (1–10 subjects per center; ►Fig. 1). The ITT set included 20 subjects in each group, and all subjects completed the study. The PP set comprised 18 Evicel and 20 Surgicel subjects. Three major protocol deviations occurred in 2 Evicel subjects, due to alterations in study procedure and randomization. For the first subject, the primary endpoint data were unavailable, but secondary endpoint analysis showed treatment success at 4, 7, and 10 minutes. For the second subject, data were available for all endpoints. The Safety set included 20 subjects in each group. Patient characteristics are shown in ►Table 1. The study populations had similar age ranges with subjects in every age group except neonates. Gender distribution was slightly skewed toward females for Evicel and toward males for Surgicel. Overall, the indications for surgery were neoplasms/cysts ($n = 19$, 47.5%), abnormalities in the gastrointestinal ($n = 12$, 30.0%) or urinary tract ($n = 2$, 5.0%), splenomegaly due to congenital spherocytosis ($n = 3$, 7.5%), and other indications ($n = 4$, 10.0%).

Surgical Procedures and Target Bleeding Sites

Both study arms showed a predominance of open (vs. laparoscopic) approaches and of abdominal procedures (►Table 2). The primary method to obtain hemostasis at the TBS was mostly electrocautery, or no other conventional method was used because they were considered impractical. In both groups, TBSs were mostly located in the abdomen, followed by the pelvic and retroperitoneal region in the Evicel group, and the thoracic and retroperitoneal region in the Surgicel group (►Table 2). The most frequent TBS tissue types in the Evicel arm were loose areolar connective tissue and liver, followed by fat tissue, and in the Surgicel arm loose areolar connective tissue followed by other tissues, fat, and muscle. In both arms, TBS bleeding intensity was 40% moderate and 60% mild, with a mostly diffuse bleeding pattern. The predominant source of bleeding was venous in both groups, followed by mixed arterial and venous. The THA were applied per manufacturer's instructions. Surgeons' preference for Evicel application method and device tips, as well as the quantities of product used are described in ►Supplementary Material S3. The median (range) surgery and operating room times were 143.0 (64.0, 506.0) and 212.5 (106.0, 553.0) minutes in the Evicel group, versus 167.0 (47.0, 415.0) and 224.5 (125.0, 496.0) minutes in the Surgicel group. Six Surgicel subjects (30.0%) and 2 Evicel subjects (10.0%) were admitted to intensive care unit (ICU). In all 8

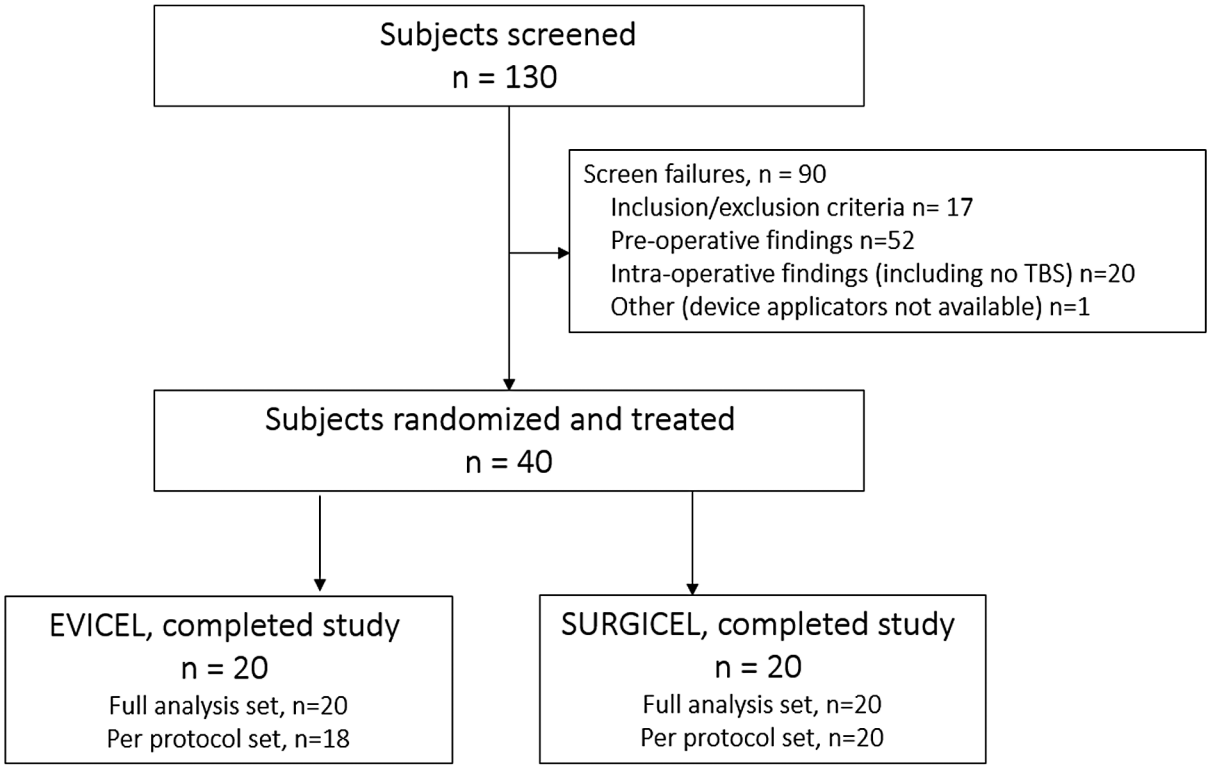

Fig. 1 Disposition of study subjects. TBS, target bleeding site.

Table 1 Subject demographics

	Evicel ($n = 20$)	Surgicel ($n = 20$)
Age at consent, y		
Median (range)	13.0 (0.9,17.0)	10.0 (1.0,17.0)
Mean (SD)	9.4 (6.5)	9.0 (5.9)
Age group, *n* (%)		
Neonates (birth–30 d)	0 (0.0%)	0 (0.0%)
Infants and toddlers (31 d– < 24 mo)	5 (25.0%)	2 (10.0%)
Children (2–11 y)	4 (20.0%)	9 (45.0%)
Adolescent (12–18 y)	11 (55.0%)	9 (45.0%)
Gender, *n* (%)		
Male	9 (45.0%)	13 (65.0%)
Female	11 (55.0%)	7 (35.0%)
Race, *n* (%)		
White/Caucasian	16 (80.0%)	16 (80.0%)
Asian	2 (10.0%)	2 (10.0%)
Other	2 (10.0%)	2 (10.0%)
Ethnicity, *n* (%)		
Hispanic	1 (5.0%)	0 (0.0%)
Not Hispanic	19 (95.0%)	20 (100.0%)
Height (cm)[a]		
Median (range)	144 (72,177)	135 (77,181)
Mean (SD)	128 (40)	130 (38)

Table 1 (*Continued*)

	Evicel ($n = 20$)	Surgicel ($n = 20$)
Weight		
Median (range)	33.0 (9.0,118.0)	31.5 (10.0,80.0)
Mean (SD)	42.6 (31.5)	34.4 (23.0)
Body mass index (kg/m^2)[a]		
Median (range)	17.2 (14.2,37.7)	17.6 (13.9,29.7)
Mean (SD)	20.3 (6.7)	18.0 (4.3)
Surgical indication, *n* (%)		
Neoplasms or cysts	11 (55.0%)	8 (40.0%)
Abnormality in gastrointestinal tract	6 (30.0%)	6 (30.0%)
Abnormalities in the urinary tract	0	2 (10.0%)
Splenectomy due to congenital spherocytosis	1 (5.0%)	2 (10.0%
Other	2 (10.0%)	2 (10.0%)

Abbreviation: SD, standard deviation.
[a]$n = 14$ for Evicel and $n = 12$ for Surgicel.

Table 2 Surgical procedure and target bleeding site characteristics

Surgical procedure characteristics	Evicel ($n = 20$)	Surgicel ($n = 20$)
Surgical approach, *n* (%)[a]		
Open	14 (73.3%)	11 (55.0%)
Laparoscopic	5 (26.3%)	9 (45.0%)
Primary operative procedure, *n* (%)		
Thoracic	0 (0.0%)	4 (20.0%)
Abdominal	15 (75.0%)	14 (70.0%)
Genitourinary	1 (5.0)	0 (0.0%)
Other	4 (20.0%)	2 (10.0%)
Primary method for hemostasis, *n* (%)		
Cautery	8 (40.0%)	14 (70.0%)
Suture	3 (15.0%)	0 (0.0%)
Other	2 (10.0%)	1 (5.0%)
None (other methods impractical)	7 (35.0%)	5 (25.0%)
Target bleeding site characteristics		
Tissue type, *n* (%)		
Loose areolar connective tissue	5 (25.0%)	5 (25.0%)
Fat	3 (15.0%)	3 (15.0%)
Lymphatic tissue/lymph node beds	2 (10.0%)	1 (5.0%)
Muscle	2(10.0%)	3 (15.0%)
Liver	5 (25.0%)	2 (10.0%)
Pancreas	0 (0.0%)	1 (5.0%)
Spleen	1 (5.0%)	1 (5.0%)
Other	2 (10.0%)	4 (20.0%)
Intensity of bleeding, *n* (%)		
Mild	12 (60.0%)	12 (60.0%)
Moderate	8 (40.0%)	8 (40.0%)

(*Continued*)

Table 2 (*Continued*)

Surgical procedure characteristics	Evicel ($n = 20$)	Surgicel ($n = 20$)
Predominant source of bleeding, *n* (%)[b]		
Arterial	1 (5.0%)	1 (5.3%)
Venous	13 (65.0%)	15 (78.9%)
Mixed	6 (30.0%)	3 (15.8%)
Target bleeding site area (size), cm^{2}[a]		
Median (range)	4.0 (0.3,90.0)	1.0 (0.0,18.0)
Mean (SD)	11.9 (22.4)	4.2(5.9)
Target bleeding site area, pattern, *n* (%)[c]		
Discrete ($<1\ cm^{2}$)	5 (26.3%)	8 (44.4%)
Diffuse ($>1\ cm^{2}$)	14 (73.7%)	10 (55.6%)

Abbreviation: SD, standard deviation.
[a]$n = 19$ for Evicel, $n = 20$ for Surgicel.
[b]$n = 20$ for Evicel, $n = 19$ for Surgicel.
[c]$n = 19$ for Evicel, $n = 18$ for Surgicel.

subjects, the reasons for admission to the ICU were AEs that were classified by both investigator and sponsor as Not Related to study product. Of the AEs that occurred after their admission to the ICU, only one was classified as possibly related to Evicel: this subject had been admitted to ICU because of a SAE of possible hypoxic brain injury, which—as mentioned—was considered unrelated to study product. Two days after ICU submission, clotting tests in this subject showed values higher than normal: this was considered a mild, non-SAE, and possibly related to Evicel. In both groups, the median postoperative hospital stay was 5 nights, with a range of (1, 40 nights) for the Evicel and (1, 13 nights) for the Surgicel group.

Safety Endpoints

Nearly all Evicel and Surgicel subjects experienced at least one AE, but SAE were few in both groups (►Table 3). There were no deaths or thrombotic events in either group and the frequency of rebleeding was low (►Table 3). Investigators adjudicated 50 AEs in the Evicel and 60 AEs in the Surgicel

Table 3 Adverse events

	Evicel $n = 20$	Surgicel $n = 20$
Total number of adverse events	87	101
Total number of serious adverse events	5	3
Number (%) of subjects with at least 1 event in the category		
AE[a]	19 (95.0%)	20 (100.0%)
Serious AE	4 (20.0%)[b]	3 (15.0%)[c]
Severe AE	2 (10.0%)	1 (5.0%)
AE related or possibly related to study product (investigator)	2 (10.0%)	2 (10.0%)
AE related or possibly related to study product (sponsor)	0 (0.0%)	0 (0.0%)
SAE related or possibly related to study product (investigator)	0 (0.0%)	0 (0.0%)
SAE related or possibly related to study product (sponsor)	0 (0.0%)	0 (0.0%)
SAE related or possibly related to Study Procedure	16 (80.0%)	18 (90.0%)
Subject deaths/ongoing (S)AE at death	0 (0.0%)	0 (0.0%)
Thrombotic events	0 (0.0%)	0 (0.0%)
AE related to rebleeding at TBS[d]	1 (5.0%)	2 (10.0%)

Abbreviations: AE, adverse event; SAE, serious adverse event; TBS, target bleeding site.
[a]AE that occurred in ≥5 subjects of either group were tachycardia, pyrexia, abdominal pain, vomiting, and procedural pain.
[b]Five SAEs in four subjects: possible hypoxic brain injury, chickenpox, *Clostridium difficile* infection, ureteric stent removal, and urinary bladder leak.
[c]Three SAEs in three subjects: Castleman's disease, febrile neutropenia, and central line leakage.
[d]All three events were intraoperative rebleeding and were captured as AE per protocol requirement.

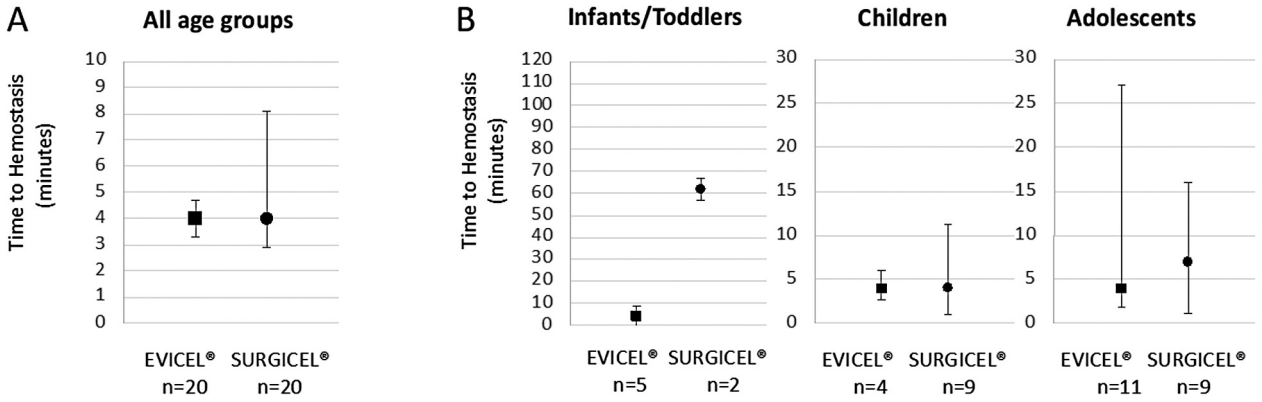

Fig. 2 Time to hemostasis (ITT Set). Shown is the TTH for (**A**) the total group (values indicate the median TTH [min] with distribution-free 95% CI) ($n = 1$ missing data in Evicel) and (**B**) the subgroups according to age (values indicate the median TTH [min] and range; $n = 1$ missing data in the Evicel Adolescents). CI, confidence interval; ITT, intention-to-treat; TTH, time to hemostasis.

group as (possibly) related to study procedure. Two AEs in two Evicel subjects (10.0%) (coagulopathy [abnormal values on laboratory clotting test] and pyrexia) and two AEs in two Surgicel subjects (10.0%) (tachycardia and hypotension) were considered possibly related to study product by the investigator; the study sponsor considered these events Not Related to study product due to the lack of a plausible causal mechanism (►**Table 3**). The median estimated blood loss (for the entire surgical procedure) was 50.0 mL in both groups, with a range of (0.0, 2,000.0 mL) for Evicel and (0.0, 400.0 mL) for Surgicel. Two Evicel subjects experienced excessive blood loss, but in neither subject was this related to the TBS. The first subject experienced a 2,000 mL procedural hemorrhage prior to being randomized. The second subject had a mild TBS bleeding but suffered a total operative blood loss of ± 1,500 mL. In both subjects, the TBS showed hemostasis at 4 minutes with no rebleeding. Between randomization and study completion, 7 Evicel subjects (35.0%) received a total of 13 units of blood products and 3 Surgicel subjects (15.0%) a total of 5 units.

Effectiveness Endpoints

The median (range) TTH was 4.0 minutes (1.8, 27.1) (95% CI: 3.3, 4.7) for the Evicel group and 4.0 minutes (1.1, 115.5) (95% CI: 2.9, 8.1) for the Surgicel group (►**Fig. 2**). One Surgicel subject experienced rebleeding at 114 minutes, as described below. By age group, the TTH in the Evicel and Surgicel groups were 4.0 (2.8, 6.3) versus 61.8 minutes (8.1, 115.5) for infants/toddlers, 4.0 (2.6, 6.0) versus 4.0 minutes (1.1, 11.2) for children, and 4.0 (1.8, 27.1) versus 7.0 minutes (1.2, 16.0) for adolescents, respectively (►**Fig. 2**). Effectiveness analyses in the PP set showed similar results (not shown).

The treatment success rates in the Evicel and Surgicel groups were 16/20 subjects (80.0%, 95% CI: 56.3, 94.3) versus 13/20 subjects (65.0%, 95% CI: 40.8, 84.6) at 4 minutes, 20/20 subjects (100.0%, 95% CI: 83.2, 100.0) versus 16/20 subjects (80.0%, 95% CI: 56.3, 94.3) at 7 minutes, and 19/20 subjects (95.0%, 95% CI: 75.1, 99.9) versus 18/20 subjects (90.0%, 95% CI: 68.3, 98.8) at 10 minutes, respectively (►**Fig. 3**). For 1 Surgicel subject, the 10-minute assessment was not completed, but

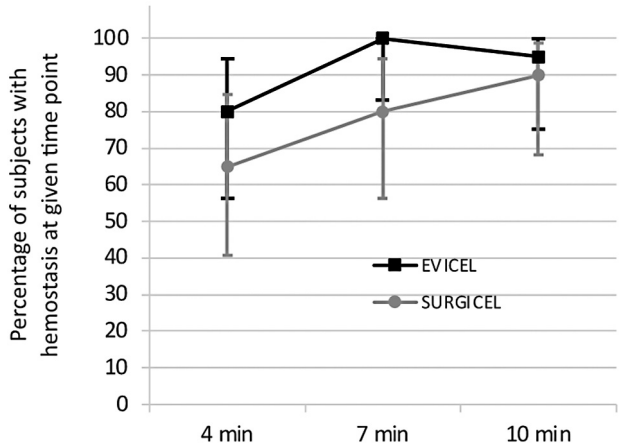

Fig. 3 Treatment success (ITT Set). Shown is the percentage of subjects who showed hemostasis at 4, 7, and 10 minutes after randomization, with two-sided Clopper–Pearson 95% CI. CI, confidence interval; ITT, intention-to-treat.

with a 7-minute TTH and no rebleeding, the subject was considered a treatment success. The treatment failure rates were 1/20 (5.0%) Evicel and 5/20 (25.0%) Surgicel subjects. One Evicel subject exhibited TBS rebleeding at 10 minutes but did not require additional hemostatic treatment. In the Surgicel group, 6/20 subjects (30.0%) received additional hemostatic treatment. One of these subjects received additional Surgicel but was not considered a treatment failure. The 5 other subjects were treatment failures: 3 required electrocautery and manual compression; 1 required additional Surgicel, manual compression and electrocautery, 1 required additional Surgicel, manual compression and FS patch; the remaining 2 subjects, after achieving hemostasis at 10 minutes, showed rebleeding at 14 and 114 minutes that required additional Surgicel and diathermy, respectively.

Discussion

This phase III study was done as a regulatory requirement to support a clinical indication for Evicel Fibrin Sealant in the

treatment of mild-to-moderate soft tissue and parenchymatous surgical bleeding in children. The randomized study, albeit small scale, supports that Evicel is safe and performs comparably to the widely used oxidized regenerated cellulose THA Surgicel, in a wide range of surgical procedures.

Hemostatic efficacy was evident from a similar time-to-hemostasis in both Evicel and Surgicel groups, and a comparable increase in success rates, reaching 100% for Evicel and 90% for Surgicel at 10 minutes. The efficacy of Evicel across age groups, surgical indications, procedure types, and bleeding site characteristics support its value in the general pediatric surgery setting. The surgical indications varied and concerned mostly tumors or cysts and gastrointestinal or genitourinary abnormalities. The TBSs included similar proportions of mild and moderate bleeding intensities were mostly diffuse in nature and occurred mostly in loose areolar tissue or liver parenchyma, but a wide range of bleeding types and tissues were represented.

Small between-group differences were noted in patient demographics and procedure characteristics, but intraoperative randomization ensured that investigator bias was excluded. Despite a slight difference in median age, the age ranges were similar. Developmental hemostasis is recognized as the physiological maturation of the coagulation system,[35–37] but age-related changes of coagulation and fibrinolysis are most prominent before the age of 6 months.[35,38] No neonates were enrolled, but the Evicel arm counted 5 subjects aged 1 to 24 months. While very small, age groups did not show major differences in efficacy.

In a substantial proportion of subjects in both study arms, the adjunctive hemostat was used as a primary hemostatic method because any other method was considered impractical to use due to a (fragile) tissue condition, a large TBS area or an anatomical location impractical for conventional methods. This underscores the value of topical hemostats in the control of mild-to-moderate surgical bleeding.[14,15]

Similar to the adult Evicel phase III trial, new safety signals were not identified.[10] Most AE were considered (possibly) related to surgical procedure and could be anticipated in the populations treated. In the Evicel group, variability was noted in surgical parameters such as total procedural blood loss, but none of the outlier values were related to the TBS. Rather, the limited overall blood loss is consistent with the inclusion criteria of mild-to-moderate bleeding and supports the efficacy of the THA. Documentation of blood loss was not standardized. Total blood loss of 0 mL in 3 Evicel and 1 Surgicel subject probably related to nonbloody surgical procedures, meticulous dissection, and/or the use of energy-based sources.

Although this clinical trial is limited by its descriptive design and small sample size, the favorable outcomes were associated with critical surgical markers supporting the efficacy of Evicel, including a larger median TBS area, and lower rates of treatment failure and additional treatment relative to the Surgicel group, arguing in favor of Evicel's place among THAs used in the pediatric population. Due to the nature of the study products, the investigators could not be blinded. This limitation was addressed by the randomization process that occurred intraoperatively, after the TBS had been identified. While the limited sample size did not allow stratification for procedure type, the heterogeneity of surgical indications supports the THA's safety.

Conclusion

In accordance with clinical studies in adults, this phase III study supports the safety and efficacy of Evicel in achieving rapid and sustained hemostasis of mild-to-moderate surgical bleeding in a pediatric population undergoing a broad range of surgical procedures.

Conflict of Interest

None declared.

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