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ORIGINAL ARTICLE

# A Prospective, Randomized, Phase III Study to Evaluate the Efficacy and Safety of Fibrin Sealant Grifols as an Adjunct to Hemostasis as Compared to Cellulose Sheets in Hepatic Surgery Resections

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## Abstract

**Background** Local hemostatic agents have a role in limiting bleeding complications associated with liver resection.

**Methods** In this randomized, phase III study, we compared the efficacy and safety of Fibrin Sealant Grifols (FS Grifols) with oxidized cellulose sheets (Surgicel®) as adjuncts to hemostasis during hepatic resections. The primary efficacy endpoint was the proportion of patients achieving hemostasis at target bleeding sites (TBS) within 4 min ($T_4$) of treatment application. Secondary efficacy variables were time to hemostasis (TTH) at a later time point if re-bleeding occurs and cumulative proportion of patients achieving hemostasis by time points $T_2$, $T_3$, $T_5$, $T_7$, and $T_{10}$.

**Results** The rate of hemostasis by $T_4$ was 92.8% in the FS Grifols group ($n = 163$) and 80.5% in the Surgicel® group ($n = 162$) ($p = 0.01$). The mean TTH was significantly shorter ($p < 0.001$) in the FS Grifols group ($2.8 \pm 0.14$ vs. $3.8 \pm 0.24$ min). The rate of hemostasis by $T_2$, $T_5$, and $T_7$ was higher and statistically superior in the FS Grifols group compared to Surgicel®. No substantial differences in adverse events (AE) were noted between treatment groups. The most common AEs were procedural pain (36.2 vs. 37.7%), nausea (20.9 vs. 23.5%), and hypotension (14.1 vs 6.2%).

**Conclusions** FS Grifols was safe and well tolerated as a local hemostatic agent during liver resection surgeries. Overall, data demonstrate that the hemostatic efficacy of FS Grifols is superior to Surgicel® and support the use of FS Grifols as an effective local hemostatic agent in these surgical procedures.

**Keywords** Local hemostasis · Fibrin sealant · Oxidized cellulose · Liver resection · Parenchymous surgery

## Introduction

Advances in surgical technique, anesthesia, and postoperative management have resulted in liver resection becoming a routine procedure. However, the parenchymous structure as well as the highly vascular nature of the organ makes it important to utilize techniques to minimize blood loss during surgery. Intraoperative blood loss and transfusions impact

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the outcome of liver resection including morbidity, mortality, and recovery of liver function after major resections.[1] Mechanisms of hemostasis are less effective on open raw soft tissue surfaces in parenchymous organs or diffuse injuries due to tissue laceration such as those produced during liver resection procedures.

Patients undergoing elective liver resection often receive perioperative blood transfusion products to prevent excessive bleeding,[2] a practice that has been associated with negative postoperative outcomes.[3] Local hemostatic therapies (topical hemostats) are being investigated for the control of bleeding during liver resection when standard surgical techniques are insufficient.[4] Strategies based on oxidized cellulose matrices have demonstrated effectiveness in the prevention of bleeding in various surgical procedures. Surgicel® (Ethicon, Inc. Neuchâtel, Switzerland), the original representative of this class of topical hemostats, has been used as a comparator in clinical trials evaluating topical hemostatic agents for soft tissue bleeding during surgery.[5] Oxidized regenerated cellulose has proven to be safe and effective when used as a prophylactic agent covering the raw cut surface during hepatectomies reducing the volume and duration of drainage.[6]

Fibrin sealants, alone or in combination with supportive matrices, represent another approach to local hemostasis with agents that reproduce the final steps of the coagulation mechanisms. The use of fibrin sealant in combination with heterologous collagen in the management of liver injuries was reported more than three decades ago.[7] Fibrin sealants have been shown to be safe and efficacious in comparison to conventional procedures at achieving hemostasis in liver resection interventions.[8–10] Fibrin sealant patches have demonstrated superior efficacy to argon beam coagulator treatment[11] or to Surgicel® for achieving hemostasis in patients undergoing hepatic resection.[12]

Fibrin Sealant Grifols (FS Grifols; Instituto Grifols S.A., Barcelona, Spain) is composed of highly purified human fibrinogen and human thrombin and supplied as a ready-to-use kit that can be applied directly on vascular injuries[13] or conveniently sprayed on open raw surfaces. The present study has evaluated the effectiveness and safety of FS Grifols applied as a spray in comparison with standard Surgicel® sheets in the control of bleeding following open hepatic resections.

## Methods

### Study Design and Objectives

The study was designed as a phase III, randomized, controlled, multicenter international clinical trial carried out in 33 study centers located in the US, Europe and Russia (NCT01754480). The main objective was to assess the safety and efficacy of FS Grifols in achieving hemostasis during hepatic resection. To accomplish this objective, we compared the efficacy and safety of FS Grifols with standard oxidized cellulose sheets (Surgicel®) as adjuncts to hemostasis during hepatic resection open surgeries. The clinical trial was conducted in two parts, both having a 1:1 randomization into FS Grifols or Surgicel® treatment: (1) the preliminary part was designed to familiarize investigators with the use of study treatments and (2) the primary part where both efficacy and safety data were collected. The first four patients at each clinical site were to be enrolled in the preliminary part, before starting enrollment of further patients in the primary part. The trial was approved by the Institutional Review Boards of the participating sites and was conducted in accordance with local regulations and with the ethical principles of the current Declaration of Helsinki. A written informed consent was obtained from adult patients and from the parents or legal guardian on behalf of pediatric ones. Patients were followed up postoperatively for 3 months. The overall study design is presented in Fig. 1.

### Patient Population: Identification of a Target Bleeding Site

The clinical study included both adult and pediatric patients who required an elective, open, anatomic or non-anatomic resection of at least one anatomical hepatic segment, or equivalent tissue volume, for which a target bleeding site (TBS) had been identified. A bleeding area/site was defined as the TBS when it was determined by the surgeon that control of bleeding by conventional surgical techniques was ineffective or impractical and required an adjunct treatment. Patients were eligible to enter the study once they met all inclusion criteria, but none of the exclusion. Hemoglobin levels $\geq 8.0$ g/dL at baseline, open elective resection of at least one anatomical hepatic segment, or equivalent tissue with an identifiable TBS were part of the inclusion criteria. Exclusion criteria were having a traumatic injury or infective process in the anatomic surgical area, receiving an organ transplant during the same surgical procedure, history of severe reactions to any blood-derived product, FS Grifols- or Surgicel®-reported sensitivity, and pregnancy.

Surgical interventions were performed according to the respective institution's standards. Once a TBS was identified, the surgeon used two different three-point qualitative scales to rate the intensity of the bleeding [mild (oozing and capillary), moderate (gradual and steady), and severe (brisk and forceful)] and the TBS size [small ($\leq 10$ cm$^2$), medium ($10$ cm$^2 <$ TBS $\leq 100$ cm$^2$), and large ($> 100$ cm$^2$)]. If the nature of the bleeding became moderate once primary hemostatic measures were taken, the patient was considered eligible for enrollment and randomized to treatment with either FS Grifols or Surgicel®. Treatments were randomly assigned using statistics software function. Due to the differences between the two

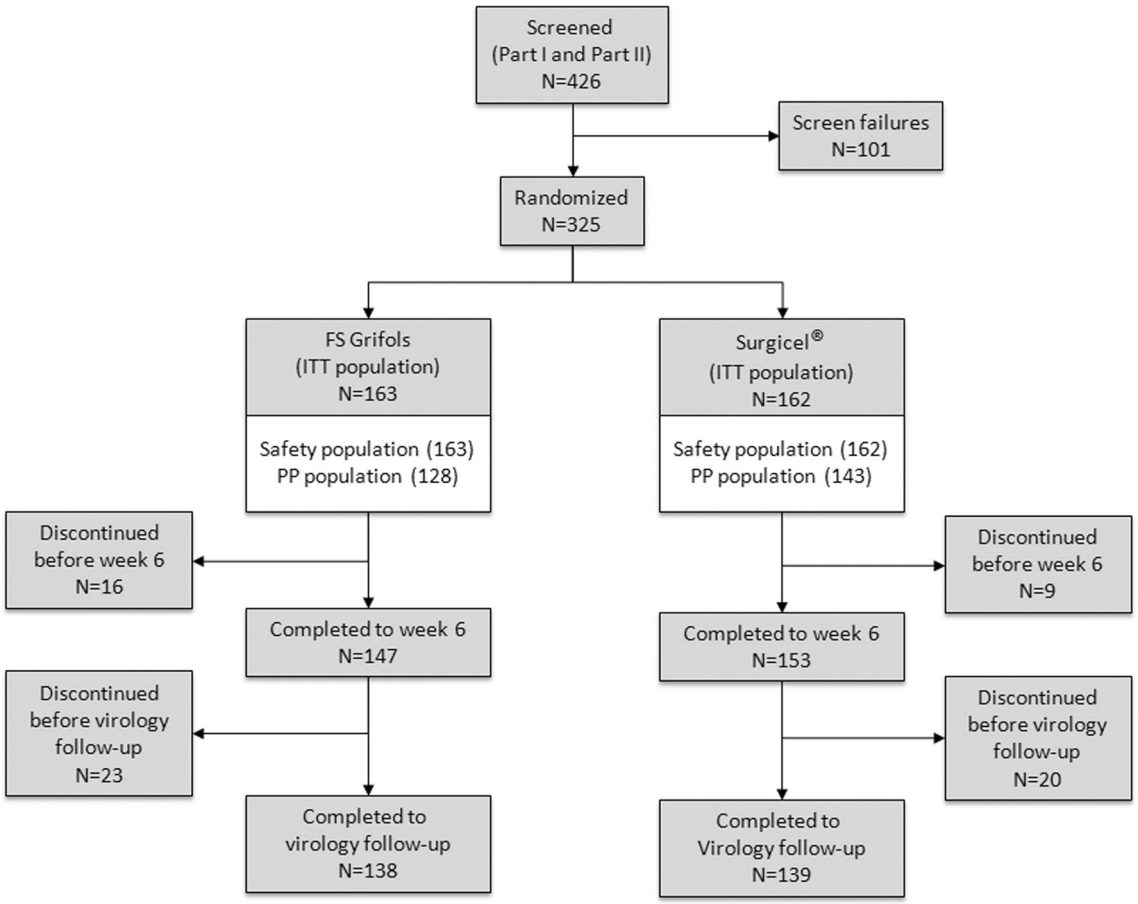


**Fig. 1** Flow diagram showing the study groups. ITT, intention to treat population; PP, per-protocol population

treatments, blinding of investigators was not possible following randomization. The use of intra- or postoperative blood products were recorded for both treatment groups.

## Investigational Treatments

FS Grifols is a product composed of frozen solutions of highly purified human fibrinogen (80 mg/mL) and human thrombin (500 IU/mL) with calcium chloride (5.9 mg/mL) supplied as a ready-to-use kit, in pre-loaded glass syringes assembled on a syringe holder.[13] For the specific use on the surface of hepatic resections, FS Grifols was delivered using spray applicator tips [Gas Assisted Applicator Kit, 5 $cm^3$. Micromedics, Inc. Eagan, MN, USA]. FS Grifols was applied onto the TBS surface by spraying (10 cm distance with a 1–1.75 bar pressure) in short bursts (0.1–0.2 ml). The maximum total volume of FS Grifols allowed was 12 mL (2 FS Grifols kits). For patients randomized to the Surgicel® group, four 4″ × 8″ Surgicel® original absorbable hemostat sheets (Ethicon, Inc. Neuchâtel, Switzerland) were allotted for each surgical procedure. These maximum amounts were estimated to be sufficient for the coverage of the TBS, without being a limiting factor for hemostatic efficacy.

## Hemostatic Evaluations

Evolution of bleeding at the TBS was monitored during a 10-min period after the application of each treatment. Time to hemostasis (TTH) was measured in minutes from the treatment application start ($T_{start}$) to the achievement or failure of hemostasis at the end of the observational period. The TTH was then classified into one of the six defined hemostatic time categories (HTCs): $T_2$ ($\leq 2$ min), $T_3$ ($> 2$ to $\leq 3$ min), $T_4$ ($> 3$ to $\leq 4$ min), $T_5$ ($> 4$ to $\leq 5$ min), $T_6$ ($> 5$ to $\leq 7$ min), $T_7$ ($> 7$ to $\leq 10$ min), or into the non-HTC which was defined as persistent bleeding at the TBS beyond the 10-min observational period ($> 10$ min).

## Efficacy Endpoints

The primary efficacy endpoint of the study was the proportion of patients in both treatment groups who achieved hemostasis at the TBS by 4 min ($T_4$) following the $T_{Start}$ without occurrence of re-bleeding until the completion of the surgical closure. The 4-min time point was chosen based on efficacy results observed in previous studies with other FS products and previous data,[8,13–22] as well as on the US FDA feedback

provided to the sponsor in discussing the protocol design and its adequacy for the aim of supporting a marketing application in the claimed indication. Hemostasis was defined as a cessation of bleeding at the TBS. Re-bleeding was defined as bleeding from the TBS requiring a further hemostatic intervention after hemostasis was previously achieved at the TBS. Treatment failures were considered when (a) bleeding persisted at the TBS beyond $T_4$, (b) re-bleeding occurred before completion of the surgical closure, (c) breakthrough (brisk and forceful) bleeding appeared at the TBS that jeopardized patient safety, or (d) alternative hemostatic treatments or maneuvers where required at the TBS during the 10-min observational period and until the completion of the surgical closure.

The secondary efficacy variables were the TTH, measured in minutes from $T_{Start}$ to the achievement or failure of hemostasis at the end of the 10-min observational period; the cumulative proportion of patients achieving hemostasis at the TBS by each HTCs ($T_2$, $T_3$, $T_4$, $T_5$, $T_7$, $T_{10}$); and the prevalence of treatment failures. The precise TTH was not expressly determined, but if hemostasis was not achieved at an assessment time point, but was reached at the next one, then it was inferred that the true TTH lied between those two assessment time points.

### Safety Endpoints

The safety variables in the trial were vital signs, physical assessments, evaluation of adverse events (AEs), AEs potentially related to the study product (adverse drug reactions [ADRs]), and serious adverse events (SAEs), routine clinical laboratory tests, viral markers (serology testing and nucleic acid testing [NAT] monitoring markers for hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV] 1 and 2, and parvovirus B19), and immunogenicity (antibodies against human coagulation factor V, thrombin, and fibrinogen). For safety endpoints patients were postoperatively monitored up to week 6, with the exception of viral markers which were followed up until the third month of postoperative visit.

### Statistical Analysis

The sample size for the primary part of the study was estimated to provide at least 80% power to show non-inferiority of FS Grifols relative to Surgicel® in the proportion of patients achieving hemostasis by $T_4$. Assuming that 60–65% of the treated groups would exhibit hemostasis at the 4-min time point ($T_4$), a total of 212 patients in a 1:1 ratio (106 in FS Grifols and 106 in Surgicel®) would provide 80% power at the 5% significance level. Three analysis populations were defined for each part of the study: (a) the intent-to-treat (ITT) population including all patients randomized to FS Grifols or Surgicel®, (b) the per-protocol (PP) population, including all patients in the ITT population excluding any patient for whom there was at least one major protocol deviation that might have an impact on the primary efficacy assessment, and (c) the safety population consisting of all patients who received any amount of FS Grifols or Surgicel®.

Summary statistics for continuous variables included the number of patients, mean, standard error, median, minimum, and maximum values. For categorical variables, summary measures included the number and percent of patients in each category. All statistical testing were two-sided at the alpha = 0.05 level without adjustments for multiple testing. The SAS® software (SAS Institute Inc., Cary, NC, USA) version 9.2 was used for calculations.

The efficacy analysis was performed on the ITT population and data from the primary part of the study. The primary efficacy endpoint was analyzed in the PP population. FS Grifols was considered non-inferior to Surgicel® if the lower limit of the two-sided 95% CI exceeded 0.8. The Cochran-Mantel-Haenszel test was used for subgroup analyses of the primary efficacy endpoint.

The superiority for the secondary endpoints was tested once the non-inferiority for the primary efficacy endpoint was demonstrated. TTH was quantified in minutes according to its nominal time point and was tested by using both, the log rank test and a Kaplan-Maier plot. Analyses relating to secondary efficacy variables and the prevalence of treatment failures and each of its four sub-categories were also analyzed. Differences between treatments were tested using Fisher's exact test.

Safety analyses were based on the safety population. Depending on the comparison of AE onset date with the start of study treatment, they were classified as treatment-emergent AEs (TEAEs) or non-treatment-emergent AEs (non-TEAEs). A TEAE was defined as an AE which occurred on or after the start of study treatment up to including the date of the week 6 visit. The TEAEs incidences and severity, ADRs, and SAEs were summarized by treatment group. Vital sign data and their changes from baseline values were also summarized with the number of patients, mean, standard deviation, and additional statistical values. Modifications in clinical laboratory tests were similarly summarized. Viral safety data was described as number and percentage of patients with new positive results for HAV, HBV, HCV, HIV, and B19V. Elevated INR and aPTT ratios were used as conditions for performing immunogenicity. Physical assessment findings were also considered. The analysis of safety and patients characteristics was reported using descriptive statistics.

## Results

### Study Patients

A total of 101 patients were randomized during the preliminary part, 52 were treated with FS Grifols while 49 received

Surgicel®. Of the 52 evaluable patients in the FS group, 47 (90.4%) completed the study up to week 6 and 5 (9.6%) discontinued the study prematurely. Of the 49 randomized to Surgicel®, 45 (91.8%) completed the study and 4 (8.2%) discontinued prematurely. Disposition of patients participating in the study is summarized in Table 1.

For the primary part of the study, a total of 224 patients were randomized, 111 received FS Grifols while 113 were treated with Surgicel®. A total of 108 patients (95.6%) who received Surgicel® completed the study but 5 (4.4%) discontinued. In the FS group, 100 (90.1%) patients completed the study and 11 (9.9%) discontinued. PP population for Surgicel® group was 100 (88.5%) meanwhile in the FS Grifols group it was 87 (78.4%). Most of the exclusions were due to a major protocol deviation in study treatment application (30/35 in the FS Grifols group; 11/19 in the Surgicel® group). Of the 30 exclusions in the FS Grifols group, 12 were ascribed to a single center that applied the product using the improper process of assembling the spray tips.

Overall, a total of 325 patients were randomized into either FS Grifols or Surgicel® group (ITT population) and considered for the safety analysis population. Flow of patients through the study is shown in Fig. 1.

## Baseline Characteristics

As reported in Table 2, demographic and baseline characteristics of patients included in the study were generally similar between the two treatment groups across both parts of the study. Proportions of male and female patients were very similar for both treatment groups.

No pediatric patients (< 18 years old) were recruited in the primary part and only eight were randomized in the preliminary part. Overall, recruited patients were mostly adults (mean age 57.9 years; range 18–64 years). Most of the patients in the ITT population were Caucasian (295/325, 90.8%). The most frequent medical findings reported in the FS Grifols and the Surgicel® treatment groups were hypertension, gastroesophageal reflux disease, drug hypersensitivity, and metastases to liver (Table 2). Baseline liver function and coagulation parameters were similar in the two study groups (values for FS Grifols and Surgicel® were, respectively, ALT 32.1 ± 27.3 U/L and 38.3 ± 34.2 U/L; AST 34.9 ± 27.6 U/L and 38.4 ± 31.7 U/L; total bilirubin 11.2 ± 10.3 μmol/L and 11.0 ± 6.8 μmol/L; aPTT ratio 1.043 ± 0.170 and 1.059 ± 0.203; INR 1.126 ± 0.119 and 1.127 ± 0.142).

Numbers and distributions of TBS sizes in participating patients were homogenous and similarly distributed for the different treatments in both parts of the study (Table 2). The mean volume of FS Grifols used per patient was 8.3 mL and the mean number of Surgicel® treatment sheets used was 1.6 sheets. Reapplication before $T_4$ due to residual bleeding was needed in the two treatment groups (FS Grifols: $N = 28$, 17.2%; Surgicel®: $N = 34$, 21%).

## Efficacy Assessment

As summarized in Fig. 2a, the rate of hemostasis at the TBS by $T_4$ in the ITT population in both parts of the study was higher in the FS Grifols treatment group (preliminary part: $N = 42$, [80.8%]; primary part: $N = 103$, [92.8%]) than in the Surgicel® treatment group (preliminary part: $N = 27$,

**Table 1** Disposition of all patients screened

| Patient disposition | Preliminary part (I) | | Primary part (II) | | Part (I) + part (II) | |
|---|---|---|---|---|---|---|
| | FS Grifols *n* (%) | Surgicel® *n* (%) | FS Grifols *n* (%) | Surgicel® *n* (%) | FS Grifols *n* (%) | Surgicel® *n* (%) |
| Patients screened | 139 | | 287 | | – | |
| Patients randomized (ITT population) | 52 | 49 | 111 | 113 | 163 | 162 |
| Patients valid for PP population | 41 (78.8) | 43 (87.8) | 87 (78.4) | 100 (88.5) | 128 (78.5) | 143 (88.3) |
| Patients valid for safety population | 52 | 49 | 111 | 113 | 163 | 162 |
| Completed to week 6 | 47 (90.4) | 45 (91.8) | 100 (90.1) | 108 (95.6) | 147 (90.2) | 153 (94.4) |
| Discontinued before week 6 | 5 (9.6) | 4 (8.2) | 11 (9.9) | 5 (4.4) | 16 (9.8) | 9 (5.6) |
| Withdrawal of consent | 1 (1.9) | 2 (4.1) | 2 (1.8) | 4 (3.5) | 3 (1.8) | 6 (3.7) |
| Lost to follow-up | 1 (1.9) | 1 (2.0) | 4 (3.6) | 0 | 5 (3.1) | 1 (0.6) |
| Death | 3 (5.8) | 1 (2.0) | 4 (3.6) | 1 (0.9) | 7 (4.3) | 2 (1.2) |
| Other | 0 | 0 | 1 (0.9) | 0 | 1 (0.6) | 0 |
| Completed to virology follow-up | 42 (80.8) | 37 (75.5) | 96 (86.5) | 102 (90.3) | 138 (84.7) | 139 (85.8) |
| Discontinued before virology follow-up | 8 (15.4) | 9 (18.4) | 15 (13.5) | 11 (9.7) | 23 (14.1) | 20 (12.3) |
| Pediatric patients | 2 (3.8) | 3 (6.1) | 0 | 0 | 2 (1.2) | 3 (1.9) |

**Table 2** Detailed demographic and clinical characteristics of participants

| Characteristics | Preliminary part (I) | | Primary part (II) | | Part I + part II | |
|---|---|---|---|---|---|---|
| | FS Grifols ($N = 52$) | Surgicel® ($N = 49$) | FS Grifols ($N = 111$) | Surgicel® ($N = 113$) | FS Grifols ($N = 163$) | Surgicel® ($N = 162$) |
| Male | 26 (50.0) | 22 (44.9) | 59 (53.2) | 63 (55.8) | 85 (52.1) | 85 (52.5) |
| Caucasian | 44 (84.6) | 42 (85.7) | 106 (95.5) | 103 (91.2) | 150 (92.0) | 145 (89.5) |
| Age, mean (SD) | 56.6 (16.5) | 55.5 (18.4) | 59.9 (12.2) | 57.7 (13.6) | 58.8 (13.8) | 57.0 (15.2) |
| Weight (kg), mean (SD) | 77.3 (21.9) | 77.9 (19.1) | 77.4 (14.8) | 78.5 (17.1) | 77.3 (17.3) | 78.3 (17.7) |
| Medical history | | | | | | |
| Hypertension | 28 (53.8) | 29 (59.2) | 72 (64.9) | 61 (54.0) | 100 (61.3) | 90 (55.6) |
| Gastroesophageal reflux disease | 15 (28.8) | 6 (12.2) | 16 (14.4) | 12 (10.6) | 31 (19.0) | 18 (11.1) |
| Drug hypersensitivity | 12 (23.1) | 14 (28.6) | 19 (17.1) | 18 (15.9) | 31 (19.0) | 32 (19.8) |
| Metastases to liver | 6 (11.5) | 6 (12.2) | 22 (19.8) | 29 (25.7) | 28 (17.2) | 35 (21.6) |
| Hepatocellular carcinoma | 6 (11.5) | 9 (18.4) | 14 (12.6) | 13 (11.5) | 20 (12.3) | 22 (13.6) |
| Type 2 diabetes mellitus | 6 (11.5) | 4 (8.2) | 9 (8.1) | 14 (12.4) | 15 (9.2) | 18 (11.1) |
| Coronary artery disease | 5 (9.6) | 0 | 5 (4.5) | 5 (4.4) | 10 (6.1) | 5 (3.1) |
| Hyperlipidemia | 7 (13.5) | 9 (18.4) | 12 (10.8) | 8 (7.1) | 19 (11.7) | 17 (10.5) |
| Cirrhosis | 4 (7.7) | 3 (6.1) | 5 (4.5) | 2 (1.8) | 9 (5.5) | 5 (3.1) |
| TBS size, *n* (%) | | | | | | |
| Small ($\leq 10$ cm$^2$) | 17 (32.7) | 23 (46.9) | 10 (9.0) | 13 (11.5) | 27 (16.6) | 36 (22.2) |
| Medium ($> 10$ and $\leq 100$ cm$^2$) | 32 (61.5) | 24 (49.0) | 93 (83.8) | 94 (83.2) | 125 (76.7) | 118 (72.8) |
| Large ($> 100$ cm$^2$) | 3 (5.8) | 2 (4.1) | 8 (7.2) | 6 (5.3) | 11 (6.7) | 8 (4.9) |

[55.1%]; primary part: $N = 91$, [80.5%]). Rates of hemostasis by $T_4$ at TBS in the PP population was statistically and significantly higher in the FS Grifols treatment group compared to the Surgicel® treatment group (98.9 vs. 85%; $p$ value = 0.001). Inferential analyses of the ratio and 95% CI of proportion of patients meeting the primary efficacy endpoint in patients receiving FS Grifols relative to Surgicel® in the primary part of the study was 1.163 (1.068, 1.267), indicating that FS Grifols is non-inferior to Surgicel® and that the primary efficacy objective was achieved in the PP population. Additionally, the lower limit of the 95% CI above 1 indicates that FS Grifols is superior to Surgicel®.

The mean TTH was significantly shorter in the FS Grifols group ($2.8 \pm 0.14$ vs. $3.8 \pm 0.24$ min; (mean ± SEM; $p < 0.001$). In the secondary efficacy analysis, FS Grifols group had a higher rate of hemostasis by earlier time points [$T_2$: FS Grifols (55.9%) and Surgicel® (41.6%); $T_3$: FS Grifols (85.6%) and Surgicel® (62.8%)]. As summarized in Fig. 2b, statistical differences were observed for the FS Grifols treatment at $T_2$, $T_3$, $T_5$, $T_7$, but not at $T_{10}$ ($p$ values = 0.045, < 0.001, 0.002, 0.01, and 0.059, respectively). Prevalence of treatment failures was lower ($n = 8$, 7.2%) in the FS Grifols treatment group than in the Surgicel® treatment group ($n = 22$, 19.5%), with differences reaching statistical significance at $p$ value = 0.01. No differences in the use of intra-or postoperative blood products were observed between the FS Grifols and Surgicel® treatment groups. No reoperation was reported.

## Safety Assessments

In the FS Grifols group, 82.2% ($n = 134$) patients experienced a TEAE compared with 85.8% ($n = 139$) patients in the Surgicel® group (pooled safety population). SAEs were reported for 18.4% of FS Grifols patients and 14.2% of Surgicel® patients. These included 10 deaths (7 FS Grifols and 3 Surgicel® patients). All these fatal outcomes were deemed unrelated to study drug by the investigator, and only two patients had SAEs commence on the day of surgery; the SAEs reported for the remaining eight patients commenced 3–41 days after the surgery day. Of the two patients with SAEs commencing on the day of surgery, one was an FS Grifols-treated patient who developed hypotension on day 1, followed by respiratory and hepatic failure commencing day 4 with death on day 5. The second patient was Surgicel®-treated and developed hemorrhage, followed by venous injury, disseminated intravascular coagulation and cardiac arrest all on day 1. The deaths which occurred after surgery for the six FS Grifols-treated patients were due to cardiac arrest, septic syndrome/shock (occurred in two patients), brain injury, hepatic necrosis, and deep vein thrombosis, and hepatic failure and multi-organ failure for the two Surgicel®-treated patients.

No patients had an AE leading to withdrawal. A summary of safety assessments is provided in Tables 3, 4 and 5. Overall, the TEAEs and ADRs showed no consistent treatment-related pattern for any particular type of event. The most frequently

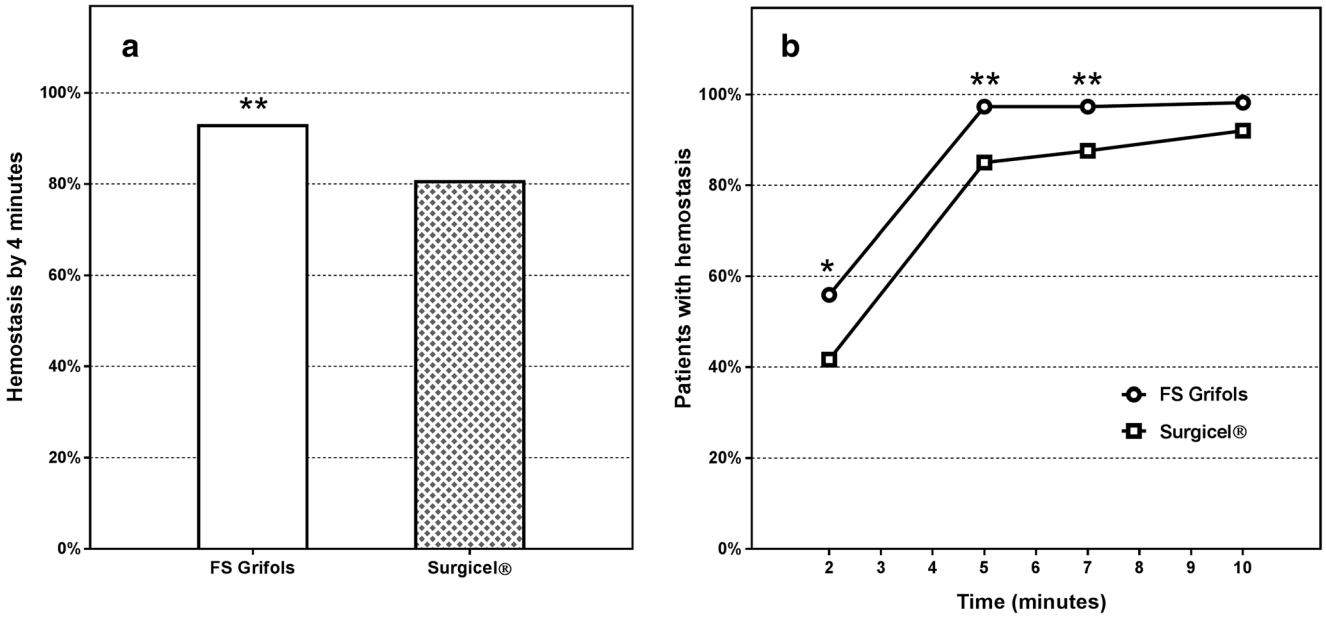


**Fig. 2** Summary of the main efficacy outcomes evaluated in the study. **a** Bar diagrams represent results of the primary efficacy endpoint: rates of hemostasis by 4 min ($T_4$) after treatment administration at defined target bleeding sites in the ITT population. Rates of hemostasis achieved in the FS Grifols treatment group were significantly higher than those observed in the Surgicel® treatment group (*** $p = 0.001$). **b** Graphs represent results of the secondary efficacy outcomes: the cumulative proportion of patients achieving hemostasis throughout the 10 min observational period. Statistical differences were observed for the FS Grifols treatment at observation times $T_2$, $T_5$, $T_7$, but not at $T_{10}$. *$p < 0.05$, **$p < 0.01$ vs. Surgicel®; Fisher exact test

reported TEAEs were in the injury and procedural complications class with 90/163 (55.2%) patients in the FS Grifols treatment group and 81/162 (50.0%) in the Surgicel® group. Gastrointestinal disorders were also commonly reported with 62/163 (38.0%) patients in the FS Grifols group and 71/162 (43.8%) patients in the Surgicel® group. The majority of TEAEs in both treatment groups (93%, FS Grifols; 97%, Surgicel® were either mild or moderate in severity. More precisely, 9.8% ($n = 16$) of the patients in the FS Grifols treatment group experienced a severe TEAE compared to the 3.7% ($n = 6$) of the Surgicel® group. One ADR (procedural pain in a FS Grifols patient) was considered definitely related to study treatment while six ADRs (three in each treatment group) were considered possibly related to study treatment (Table 5).

No relevant differences were noted in vital sign data (heart rate, respiration rate, systolic and diastolic blood pressure, and temperature) or clinical assessments. Mean changes for coagulation, hematology and serum clinical chemistry parameters from baseline to week 6 were small in both treatment groups at all time points (data not shown). Laboratory testing for viral markers by both serology and NAT methods showed no new acute infections for HAV, HBV, HCV, HIV, or B19V during the 3-months follow-up testing.

A total of seven patients from the FS Grifols and Surgicel® treatment groups required testing for antibodies against human coagulation factors. No antibody response was observed in patients treated with FS Grifols or Surgicel in the clinical study, demonstrating a comparable safety profile with respect to immunogenicity.

## Discussion

The present trial has compared the safety and efficacy of FS Grifols with Surgicel® in the setting of bleeding during surgical liver resections. FS Grifols showed to be safe and effective as an adjunct to local hemostasis in these procedures. Rates of hemostasis evaluated in primary and secondary efficacy analysis were significantly higher in the FS Grifols treatment group than those in the Surgicel® group used as comparator. Moreover, rates of treatment failure were significantly lower in the FS Grifols treatment group compared to the Surgicel® treatment group. Taken together, these results demonstrate that the hemostatic efficacy of FS Grifols is superior to Surgicel® and support the use of FS Grifols as an effective local hemostatic agent during hepatic resection open surgeries.

Surgicel® has become a standard topical hemostat, used as a comparator in different clinical trials on various surgical settings including hepatic surgeries.[6,12] Results of the present study demonstrate a significant reduction in times to hemostasis with FS Grifols suggesting that this sealant provides a more efficacious control of bleeding than Surgicel®.

**Table 3** Summary of treatment-emergent adverse events (pooled safety population)

| | FS Grifols $N = 163$ $n$ (%) | Surgicel® $N = 162$ $n$ (%) |
|---|---|---|
| Patients with any TEAE | 134 (82.2) | 139 (85.8) |
| Total number of TEAEs | 737 | 694 |
| Patients with any ADR | 11 (6.7) | 3 (1.9) |
| Total number of ADRs | 24 | 10 |
| Patients with any ADR attributable to application technique | 0 | 0 |
| Total number of ADRs attributable to application technique | 0 | 0 |
| Patients with any SAE | 30 (18.4) | 23 (14.2) |
| Total number of SAEs | 78 | 38 |
| Patients with any TEAE with outcome of death | 7 (4.3) | 3 (1.9) |
| Patients with any serious ADR | 4 (2.5) | 0 |
| Total number of serious ADRs | 9 | 0 |
| Patients with any AE leading to withdrawal | 0 | 0 |
| Total number of AEs leading to withdrawal | 0 | 0 |

*TEAE* treatment-emergent adverse events, *ADR* adverse drug reaction (AEs potentially related to the study product), *SAE* serious adverse event, *AE* adverse event

Different comparative approaches using multiple hemostatic strategies with other fibrin sealants alone or on active matrices have been evaluated in the setting of liver resection. A specific fibrin sealant patch (EVARREST®, Ethicon US) was shown to be safe and effective vs. standard of care in controlling parenchymal bleeding following hepatectomy.[23] In a clinical trial similar in design to our present study, fibrin sealant patch (FSP, TachoSil®; Takeda Pharma A/S) was compared with oxidized regenerated cellulose as a treatment of local bleeding after hepatic resection. The fibrin sealant patch was safe and superior to Surgicel® for achieving hemostasis in these patients.[12] Sangustop® (B. Braun Surgical S.A.) is a felt-like mechanical hemostatic agent composed of absorbable collagen. In a randomized controlled multicenter trial, this collagen hemostat showed as effective as the fibrin sealant patch Tachosil® in achieving secondary hemostasis during liver resection.[24] In the absence of head to head comparative trials, the efficacy of FS Grifols in the present clinical trial would be compatible with similar studies with local hemostatic agents. Saving the differences among other study designs, the reduction in times to hemostasis achieved with FS Grifols in the present study would be similar to those reported for Crosseal® a FS administered by spraying,[20] or Tachosil® patches[12] in similar surgical procedures.

Fibrin and platelets are the main components of hemostasis.[25] Topical hemostats such as Surgicel®, integrate absorbable foam that will conform a matrix acting as a barrier at the site of bleeding. These spongeous materials activate the intrinsic coagulation pathway that leads to the conversion of fibrinogen into fibrin, favoring the interaction of platelets with the foreign structures.[26] In contrast with the previously mentioned mechanical hemostats, FS Grifols contains fibrinogen and thrombin, which play a dual role on hemostasis. On the one hand, thrombin is a powerful activating agent for

**Table 4** Treatment-emergent adverse events reported in ≥ 5% of patients within a treatment group (pooled safety population)

| | FS Grifols $N = 163$ $n$ (%) | Surgicel® $N = 162$ $n$ (%) |
|---|---|---|
| Patients with any TEAE | 134 (82.2) | 139 (85.8) |
| Procedural pain | 59 (36.2) | 61 (37.7) |
| Nausea | 34 (20.9) | 38 (23.5) |
| Hypotension | 23 (14.1) | 10 (6.2) |
| Anemia | 22 (13.5) | 26 (16.0) |
| Constipation | 20 (12.3) | 23 (14.2) |
| Pyrexia | 17 (10.4) | 20 (12.3) |
| Tachycardia | 14 (8.6) | 24 (14.8) |
| Hypertension | 14 (8.6) | 12 (7.4) |
| Peripheral edema | 14 (8.6) | 11 (6.8) |
| Vomiting | 13 (8.0) | 17 (10.5) |
| Pruritus | 12 (7.4) | 12 (7.4) |
| Incision site pain | 12 (7.4) | 11 (6.8) |
| Pleural effusion | 12 (7.4) | 9 (5.6) |
| Atelectasis | 11 (6.7) | 10 (6.2) |
| Abdominal pain | 11 (6.7) | 3 (1.9) |
| Procedural hemorrhage | 9 (5.5) | 4 (2.5) |
| Hypophosphatemia | 8 (4.9) | 15 (9.3) |
| Hypokalemia | 6 (3.7) | 11 (6.8) |
| Hyperglycemia | 6 (3.7) | 11 (6.8) |
| Dyspnea | 3 (1.8) | 11 (6.8) |

*TEAE* treatment-emergent adverse events

**Table 5** Incidence of adverse events potentially related to the study product (adverse drug reactions) (pooled safety population)

| | FS Grifols ($N = 163$) | | Surgicel® ($N = 162$) | |
|---|---|---|---|---|
| | *n* (%) | Causal relationship | *n* (%) | Causal relationship |
| Patients with any ADR | 11 (6.7) | | 3 (1.9) | |
| Procedural pain | 2 (1.2) | 1 Possibly | 2 (1.2) | 1 Unlikely |
| | | 1 Definitely | | 1 Possibly |
| Postprocedural bile leak | 2 (1.2) | Unlikely | 0 | |
| Pulmonary embolism | 2 (1.2) | Unlikely | 0 | |
| Deep vein thrombosis | 2 (1.2) | Unlikely | 0 | |
| Atrial fibrillation | 1 (0.6) | Unlikely | 0 | |
| Hyperthermia | 1 (0.6) | Possibly | 0 | |
| Abdominal abscess | 1 (0.6) | Unlikely | 0 | |
| Liver abscess | 1 (0.6) | Unlikely | 0 | |
| Contusion | 1 (0.6) | Possibly | 0 | |
| Procedural hypotension | 1 (0.6) | Unlikely | 0 | |
| Blood glucose increased | 1 (0.6) | Unlikely | 0 | |
| Hyperkalemia | 1 (0.6) | Unlikely | 0 | |
| Plasma cell myeloma | 1 (0.6) | Unlikely | 0 | |
| Pleural effusion | 1 (0.6) | Unlikely | 0 | |
| Pleurisy | 1 (0.6) | Unlikely | 0 | |
| Pancreatitis | 0 | | 1 (0.6) | Possibly |
| Asthenia | 0 | | 1 (0.6) | Unlikely |
| Urinary tract infection | 0 | | 1 (0.6) | Unlikely |
| Hematocrit decreased | 0 | | 1 (0.6) | Unlikely |
| Hemoglobin decreased | 0 | | 1 (0.6) | Unlikely |
| Weight decreased | 0 | | 1 (0.6) | Unlikely |
| Cough | 0 | | 1 (0.6) | Unlikely |

*ADR* adverse drug reaction

platelets,[27] facilitating the recruitment of platelets on damaged vascular areas on the raw resection surface. Furthermore, thrombin once combined with fibrinogen will foster the conversion of fibrinogen into a solid fibrin network that will consolidate hemostasis. Clot formation can be reduced to several seconds when concentrations of thrombin used are around 500 NIH,[28] as it is the case of FS Grifols. The significant reduction in times to hemostasis with FS Grifols suggest that the components on this sealant provide a more rapid control of bleeding than that offered by Surgicel®.

No substantial differences in the incidence of adverse events were noted between treatment groups. The majority of TEAEs in both treatment groups were either mild or moderate in severity. The most common TEAEs (experienced by ≥ 5% of patients in either treatment group) and ADRs were compatible with those communicated in clinical trials using local hemostats on similar surgical procedures.[12,20,23] Ten deaths occurred during the study (seven FS Grifols patients and three Surgicel® patients). All of these fatal outcomes were considered not related to the study treatments. Guidelines for blood-derived products recommend a close-up follow-up of patients for viral contamination.[29] Components of FS Grifols are derived from plasma donors and undergo three dedicated viral safety steps with validated capacity for elimination and/or inactivation of potential pathogens using patented technologies.[30,31] Patients in the FS Grifols and Surgicel® treatment groups were monitored for potential viral transmission. No treatment-emergent viral infection was detected by viral NAT or viral serology testing. No immunogenic response was observed in patients exposed to FS Grifols.

Despite their prolonged approved therapeutic use, there are no guidelines about the use of fibrin sealants or their adequacy for patients or specific indications.[32] There is controversy on whether the use of fibrin sealants of other local hemostats contributes to clinically important outcomes and what would be their related cost-effectiveness.[14] Although it is accepted that fibrin sealants can be effective as adjunct therapies to achieve hemostasis during liver resections, there seems to be weak evidence on the efficacy of fibrin sealants in reducing the use of blood products, postoperative complications and mortality.[32,33] The cost-savings efficacy of local hemostatic agents has been also object of debate, with reports in favor[34,35] or against.[36]

## Conclusion

Results of the present study confirm that FS Grifols was safe and well tolerated during liver resection surgeries. Overall, data from the present study demonstrate that the hemostatic efficacy of FS Grifols delivered as a spray is superior to Surgicel® and support the use of FS Grifols as an effective local hemostatic agent in these surgical procedures.

## Fibrin Sealant GRIFOLS in Hepatic Resection Clinical Investigation Study Group

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**Author Contribution** MB was the lead investigator. MB, RDK, MS, AV, SN, EW, SE, and GX recruited the patients and collected the data. JNP contributed to the study design and analyzed the data. MB, RDK, and JNP interpreted the results. MS, AV, SN, EW, SE, and GX contributed with intellectual content. All authors read and approved the final manuscript.

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## Compliance with Ethical Standards

**Conflict of Interest Statement** Jaume Ayguasanosa, Jordi Navarro-Puerto, Kecia Courtney, and Gladis Barrera are employees of Grifols, the manufacturer of Fibrin Sealant Grifols and the funder of the study. The other authors state that they have no other conflict of interest.

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