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Original article

Similar patient outcomes yet different hospital costs between flowable hemostatic agents

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Abstract

Introduction:
SURGIFLO™ and FLOSEAL® are absorbable gelatin-based products that form hemostatic matrices. These products are indicated as adjuncts to hemostasis when control of bleeding by conventional surgical techniques (such as suture, ligature or cautery) is ineffective or impractical. This study analyzed the effect of surgery time and the choice of product on cost to the hospital and patient outcomes.

Methods:
The data source was the Premier Hospital database from January 1, 2010–June 30, 2012. Eligible patients were ≥18 years of age with a spinal fusion or refusion surgery with either SURGIFLO™ (Ethicon Inc.) or FLOSEAL® (Baxter International Inc.). The hospital Charge Master was used to identify the amount of flowable product, whether it included Thrombin, and the cost. Multivariable models were performed on overall cost and likelihood of surgical complications. All models were adjusted for patient demographics and severity as well as hospital, and surgical characteristics.

Results:
A total of 24,882 patient records from 121 hospitals were analysed, which included 15,088 FLOSEAL® records and 9794 SURGIFLO™ records, with 1498 SURGIFLO™ with Thrombin patients. Little or no differences in surgical complications were found between surgeries with SURGIFLO™ vs surgery with FLOSEAL®. Regression models showed a reduction in cost of $65 associated with use of SURGIFLO™ with Thrombin and an additional $21 reduction in hospital cost for each additional hour of surgery. Modeling which accounts for hospital fixed effects suggest that, in addition to a gap of ~$300 favoring SURGIFLO™ with Thrombin, every additional hour of surgery was associated with an additional reduction in hospital costs of ~$26.

Conclusions:
While the choice of flowable product had no effect on clinical outcomes, use of SURGIFLO™ was associated with hospital cost savings for flowable product. These savings increased with the length of surgery, even when controlling for the amount of flowable product (mL) used.

Introduction

A whole host of topical hemostatic agents are available to control intraoperative bleeding in spine fusion surgery, with each playing a role based on the type and location of the bleeding. Flowables are among these topical hemostatic agents, which are found to be useful when traditional approaches are impractical, or when more than one hemostatic method is indicated, sometimes due to failure of conventional approaches such as sutures, cautery, or ligatures[1,2].

With their gel matrix, flowables remain in place more effectively than liquid Thrombin alone, a longstanding tool for topical hemostasis[3]. They can conform to the shape of the tissue[4], fill deep lesions, remove excess material with gentle

irrigation[2], and can be prepared in minutes[5]. As a result, flowable agents have gained traction[6,7] and are used in an array of surgeries besides spine[5,8], such as cardiac[9,10], vascular[3,11], renal[12–14], cranial[15,16], sinus[17], liver[6,18], and total knee arthroplasty[19,20].

Currently, SURGIFLO™ (Ethicon Inc., Somerville, NJ) and FLOSEAL® (Baxter International Inc., Deerfield, IL) are the two marketed flowable hemostatic agents in the US, both of which are useful in spinal surgery for their quick hemostatic effect[5,21]. SURGIFLO™, available in 8 mL tubes, is composed of absorbable porcine gelatin particles, and is packaged with and without Thrombin. FLOSEAL®, packaged in 5 mL and 10 mL tubes, is a mix of absorbable bovine gelatin particles and pooled human Thrombin[22]. A head-to-head comparison by Gazzeri *et al.*[5] indicated that the two have similar efficacy, as measured by time to bleeding control (less than 5 minutes), and safety in neurosurgery (no complications related to the hemostatic agents).

Given their comparable abilities to control bleeding, a question arises in today's utilization-conscious healthcare environment as to the economic benefits of using one vs the other. The cost impact of flowable hemostatic agents is substantial, as multiple units of the product are often required in spinal fusion surgery, a procedure in which intra-operative blood loss is common[23] and often excessive[8]. This cost is amplified as there are an estimated 400,000 spinal fusion and refusion surgery discharges annually in the US in recent years[24,25], with a mean cost of nearly $28,000 each[25].

Our study uses a large US hospital database to analyze and compare the economic impact of selecting SURGIFLO™ or FLOSEAL® in spinal fusion and spinal refusion surgeries. Our main objective was to compare economic and clinical outcomes of the two flowable hemostat agents: SURGIFLO™ with Thrombin and FLOSEAL® during spinal fusion and refusion surgeries. Main outcomes of interest included flowable products cost to the hospital overall for primary surgical procedure and the likelihood of clinical events related to bleeding during the hospitalization: blood transfusions, haemorrhage, and wound complications.

Materials and methods

Data source

The Premier hospital database was used as the data source for this study. This database contains complete patient billing, hospital cost, and coding histories from more than 600 healthcare facilities throughout the US. The data from which this study was derived were extracted from more than 25 million inpatient discharges and 175 million hospital outpatient visits from acute care facilities, ambulatory surgery centers, and clinics across the nation.

A protocol describing the analysis objectives, criteria for patient selection, data elements of interest, and statistical methods was submitted to the New England Institutional Review Board (NEIRB) and exemption was obtained (NEIRB# 13-230).

Inclusion criteria

Eligible patients were ≥18 years of age and had undergone a spinal fusion or refusion surgery during the time period of January 1, 2010 through June 30, 2012. Patients were categorized according to the type of fusion (primary or refusion), the location of the spine being fused (cervical, thoracic, lumbar, not specified), and the combination of fusions occurring (a patient can have more than one region of the spine being fused during the same surgery) and surgical approach (anterior, posterior, single incision, not specified). International Classification of Diseases, Ninth Edition (ICD-9) procedure codes were used to classify the type of surgery and approach (see Appendix A for a complete listing of the coded categories).

Spinal fusion and refusion procedures utilizing SURGIFLO™ or FLOSEAL® were identified if 'text' fields were found when mining the hospital Charge Master file for each patient indicating use of the specific gelatin hemostatic agent. Similarly, text mining was used to identify the total quantity in milliliters of the two flowable products, and, in the case of FLOSEAL®, how many 5 mL and 10 mL tubes were used.

Data elements

For all eligible patients, elements describing cost, surgery time, use of SURGIFLO™ or FLOSEAL®, type of fusion by location, and approach, as well as indication for procedure were obtained. The use of SURGIFLO™ or FLOSEAL® during surgery was captured through text mining the Premier hospital chargemaster. Product size (mL), quantity of tubes utilized, and whether or not Thrombin accompanied the product were all identified. FLOSEAL® had two different size packages (5 mL or 10 mL) and the package always was accompanied by Thrombin. SURGIFLO™, on the other hand, came in only 8 mL tubes and came with or without Thrombin.

Cost analysis reflected the cost of the product SURGIFLO™ with Thrombin, FLOSEAL®, and the procedure to the hospital. The pre-operative All Patient Refined Diagnosis Related Groups (APR-DRG) severity level was used as an index of comorbidity. The 3 M APR DRG Classification System is a widely adopted proprietary risk adjustment classification tool, which uses information from routine claims data to produce valid and reliable

severity measurement and risk adjustment scores[26]. It is used to account for differences related to an individual's severity-of-illness or risk-of-mortality in large data-sets. Admission type (emergency, urgent, elective, trauma) was also used to stratify patients' risk. Information on socio-demographic characteristics and health insurance status were also included. Cross-sectional specification also included descriptors of the care setting, namely census region, urban or rural setting, teaching hospital status, and facility bed count.

Surgical complications (identified by ICD-9 codes) included: blood transfusions, haemorrhage, and wound complications. Adverse events (identified by ICD-9 codes) that occurred intra-operatively were flagged and included in the analysis. These categories included: organ injury, cardiac, respiratory, stroke/transient ischemic attack (TIA), and neurological. A detailed list of each event and the corresponding ICD-9 code is found in Appendix B.

Statistical analyses

Outcomes of interest included flowable products cost for the primary surgical procedure and the likelihood of surgical complications (blood transfusion, haemorrhage, and wound complications). Two sets of multivariable model specifications were used to assess these outcomes of interest: the first was an ordinary least squares (OLS) cross-sectional specification and the second specification added hospital-level fixed effects. The fixed-effects model assists in controlling for unobserved heterogeneity when this heterogeneity is constant over time and correlated with the choice of flowable agent within hospitals. This constant is removed from the data through differencing. These variations in the model specifications were included to assess effect of flowable hemostatic agent use on costs and clinical outcomes across hospitals and within hospitals.

$$Y^{C}_{jikt} = \alpha_1 \cdot SURG_{jikt} + \alpha_2 \cdot L_{jikt} + \alpha_3 \cdot \left[SURG_{jikt} \times L_{jikt}\right] \beta \cdot X_{jikt} + \phi_t + \mu_i + \varepsilon_{jikt} \quad (1)$$

Where Y^{C}_{jikt} represents the dependent variable, which is either the cost of the flowable agent or clinical outcomes for patient j, in hospital i, receiving surgery k at time t. The main variables of interest are $SURG_{jikt}$, an indicator for the flowable agent (1 = SURGIFLO™ with Thrombin; 0 = FLOSEAL®), L_{jikt}, surgery length in hours, and the interaction between the flowable agent and the length of surgery. The coefficient estimate for the flowable agent's indicator would capture differences in cost to the hospital and complications between the agents. The coefficient estimate on surgery length captures the effect of prolonged surgeries on costs and outcomes. The interaction term would capture differences in cost and complications between the agents as surgeries become lengthier.

In addition, regression models included control for month and year indicators (ϕ_t), and a set of variables X_{jikt}, including milliliters per tube used, cost of Thrombin, patient characteristics (gender, age, age squared, race, and marital status), patient insurance type (Medicare and Medicaid fee for service, Medicare and Medicaid managed care with and without capitation, commercial managed care with and without capitation, commercial insurance, charity care, indigent care, self-pay, worker compensation, and direct pay by employer), mortality risk and patient severity measures (minor, moderate, major, and extreme), type of hospital admission (emergency, urgent, elective, or trauma), surgery characteristics (fusion vs refusion, number of vertebrae, technique, and location of surgery), and indicators for surgical complications.

Robustness checks were performed by varying surgery length 5–8 h vs surgeries lasting 9–12 h and by creating interaction terms for hemostatic matrices by surgery time categories in hours (1–4, 5–8, 9–12).

All analyses were conducted using *Stata Statistical Software: Release 12* (StataCorp LP, College Station, TX). *P*-values $\leq$ 0.05 were considered statistically significant.

Results

A total of 24,882 patient records from 121 hospitals were analyzed. There were 9794 patients identified with SURGIFLO™ use and 15,088 patients with FLOSEAL® use. Since FLOSEAL® always includes Thrombin, a serine protease that serves to catalyze coagulation-related reactions, our analysis focuses on a sub-set of 1498 SURGIFLO™ patients who were treated with Thrombin (SURGIFLO™ with Thrombin). The patient attrition process is shown in Figure 1. Of these procedures, 95.9% were fusions ($n = 23{,}873$), while 1009 (4.1%) were refusions.

Table 1 presents patient demographics by FLOSEAL® and SURGIFLO™ for the entire sample of 24,882 patients shown in three groups: 15,088 patients used FLOSEAL®, 9794 patients used SURGIFLO™ (all SURGIFLO™ group included 1498 patients with Thrombin and 8296 patients without Thrombin), 1498 SURGIFLO™ with Thrombin. Average patient age in our sample was 57.2 years for the all SURGIFLO™ group, 58.4 years for SURGIFLO™ with Thrombin, and 56.7 years for FLOSEAL®. The share of females was higher for all SURGIFLO™ and SURGIFLO™ with Thrombin (54.7% and 55.1%) than for FLOSEAL® (51.4%). Characteristics such as race, marital status, and insurance type were similar for all SURGIFLO™ and FLOSEAL® patients. All SURGIFLO™ patients were more likely to be characterized by low mortality risk compared to

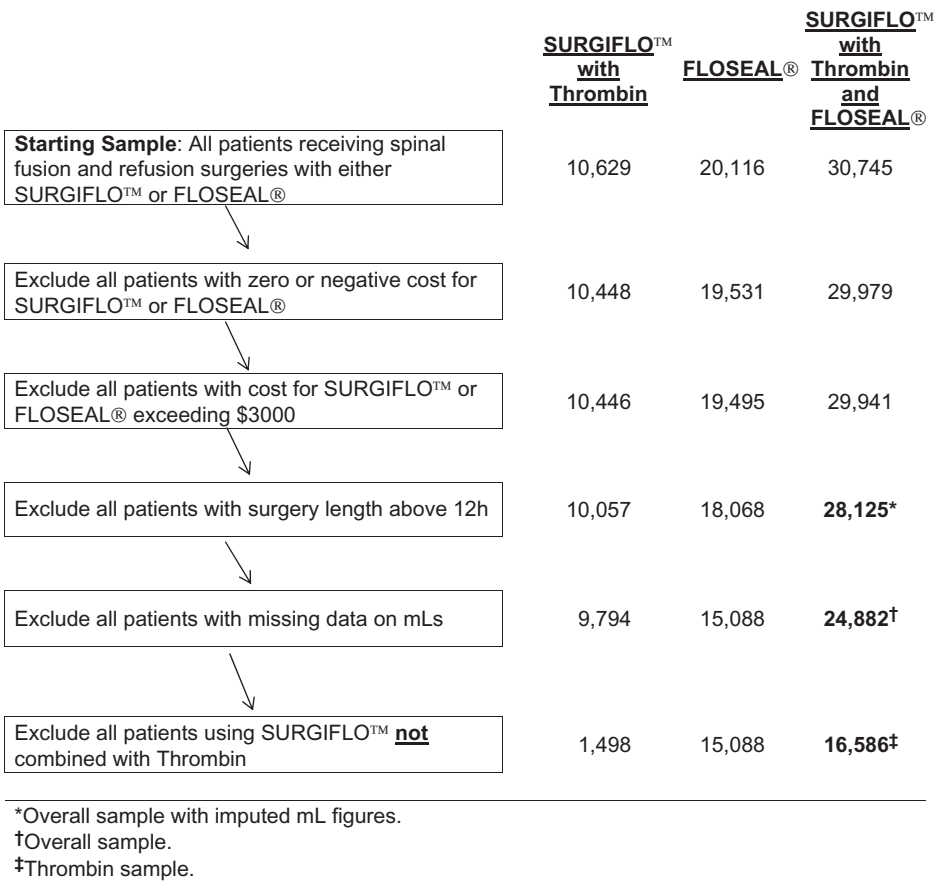

Figure 1. Attrition diagram.

SURGIFLO™ with Thrombin and FLOSEAL® patients. On the other hand, all SURGIFLO™ patients were more likely to have an emergency admission to the hospital (91.2% compared with 80.6% for FLOSEAL® and 88% for SURGIFLO™ with Thrombin), while FLOSEAL® patients were more likely to have an elective procedure (12% compared with 5.9% all SURGIFLO™ and 6.1% SURGIFLO™ with Thrombin).

Table 2 presents key surgical characteristics. Surgeries involving FLOSEAL® were longer than those involving all SURGIFLO™ or SURGIFLO™ with Thrombin (4 h 30 min vs 3 h 50 min and 3 h 55 min). Surgeries involving all SURGIFLO™ and FLOSEAL® were found to have similar surgery location, type, and technique. The size of units is given for each group, SURGIFLO™ is sold in 8 mL units, FLOSEAL® units were split between 5 mL and 10 mL units.

Table 3 presents the descriptive outcomes of interest. Most notably, hospitals spent, on average, $349.8 for FLOSEAL® vs $222.66 for SURGIFLO™ with Thrombin. The likelihood of surgical complications such as blood transfusion, haemorrhage, and wound complications were similar across the all SURGIFLO™ and FLOSEAL® products. The SURGIFLO™ with Thrombin group had a higher percentage of blood transfusions in these summary statistics, which is likely due to the older age, higher risk, and severity groups seen in demographic statistics of Table 1.

The regression results for hospital costs on flowable hemostatic agents are presented in Table 4. The analysis is performed on the restricted sample of 16,586 patients for whom either FLOSEAL® or SURGIFLO™ with Thrombin was used. The table presents results from the cross-sectional model and the fixed-effects model, each model includes seven columns representing differing degrees of variable saturation. The first column includes only our three variables of interest. In the second column, month and year indicators are added, in the third we control for product quantity in milliliters, in the fourth we add patient characteristics, in the fifth we add patient risk and severity scores as well as admission type, in the sixth we include surgery characteristics, and in the seventh—most saturated—model we include indicators for a set of surgery complications.

In all 14 specifications, the use of SURGIFLO™ with Thrombin is associated with statistically significant

Table 1. Patient demographics.

Variable	All SURGIFLO™			SURGIFLO™ with Thrombin			FLOSEAL®		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Age	9794	57.2	13.9	1498	58.4	14.4	15,088	56.7	14.8
Gender									
Female	5354	54.7%		825	55.1%		7753	51.4%	
Male	4440	45.3%		673	44.9%		7335	48.6%	
Marital Status									
Married	5343	54.6%		597	39.9%		8404	55.7%	
Single	4080	41.7%		856	57.2%		5936	39.3%	
Other	371	3.8%		43	2.9%		748	5.0%	
Race									
White	7685	78.5%		1293	86.3%		11,979	79.4%	
Black	707	7.2%		73	4.9%		1162	7.7%	
Hispanic	175	1.8%		33	2.2%		216	1.4%	
Other	1227	12.5%		99	6.6%		1731	11.5%	
Insurance Type									
Medicare	3674	37.5%		655	43.7%		5480	36.3%	
Medicaid	502	5.1%		69	5.9%		940	6.2%	
Managed Care	3131	32.0%		468	31.2%		5511	36.5%	
Commercial	798	8.2%		49	3.3%		1334	8.8%	
Charity/Self Pay	120	1.2%		24	1.6%		266	1.8%	
Other	1569	16.0%		173	11.6%		1557	10.3%	
Mortality Risk									
Minor	8012	81.8%		1148	76.6%		11,650	77.2%	
Moderate	1265	12.9%		224	15.0%		2204	14.6%	
Major	386	3.9%		87	5.8%		852	5.7%	
Extreme	131	1.3%		39	2.6%		382	2.5%	
Severity									
Minor	4695	47.9%		494	33.0%		6345	42.1%	
Moderate	3732	38.1%		690	46.1%		5767	38.2%	
Major	1162	11.9%		254	17.0%		2325	15.4%	
Extreme	205	2.1%		60	4.0%		651	4.3%	
Admission Type									
Emergency	8929	91.2%		1319	88.1%		12,155	80.6%	
Urgent	52	0.5%		0	0.0%		263	1.7%	
Elective	578	5.9%		92	6.1%		1808	12.0%	
Trauma	196	2.0%		55	3.7%		815	5.4%	

All SURGIFLO™ includes both surgeries with and without Thrombin.

reductions in hospital costs for the flowable hemostatic agent. The magnitude of the reduction varies by specification. In the hospital fixed effects specification, the reduction in costs varies between $297.2–$388.7. Stated differently, when controlling for surgery length, month, year, quantity of product, patient demographics, admission type, mortality risk, severity, surgery characteristics, surgery complications, and controlling for the individual hospital, the use of SURGIFLO™ with Thrombin was associated with approximately a $300 reduction in hospital costs for flowable product. When performing the same analysis using all surgeries ($n = 24,882$), the results are qualitatively similar (see Appendix C).

Hospital costs on flowable hemostatic agents rise with the length of surgery. This relationship persisted even when controlling for the product quantity (in milliliters). Controlling for both surgery length and flowable agent, we sought to identify the effect on differential costs as surgeries became lengthier. To make this determination, we estimated an interaction term for the surgery length variable with the SURGIFLO™ with Thrombin indicator variable. The results suggest that, in addition to a gap of ~$300, a baseline favoring SURGIFLO™, every additional hour of surgery was associated with an additional reduction in hospital costs of ~$25.7. For example, an 8-h surgery with SURGIFLO™ with Thrombin would reduce hospital costs by ~$500 compared to an 8-h surgery with FLOSEAL® performed at the same hospital, and controlling for surgery, patients, and other characteristics.

In the most saturated hospital fixed-effect regression, *R*-squared equaled 0.903 (Table 4), indicating that our linear regression model explains more than 90% of the variability of the response data around its mean. These results were also confirmed by the cross-sectional model (Table 4), which showed that reduction in costs for utilizing SURGIFLO™ with Thrombin compared to FLOSEAL® was estimated at $65, with additional estimated reduction of $21 for each additional hour of surgery.

Given the differences in hospital costs on flowable hemostatic agents, it was important to analyze potential differences in outcomes between the two agents. To address this issue, we repeated our regression models

Table 2. Surgical characteristics.

Variable	All SURGIFLO™			SURGIFLO™ with Thrombin			FLOSEAL®		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Surgery length (h)	9794	3.85	2.00	1498	3.92	1.68	15,088	4.49	1.94
Surgery-location									
Cervical	3722	38.0%		554	36.0%		6119	40.6%	
Thoracic	616	6.3%		107	7.1%		1341	8.9%	
Lumbar	5539	56.6%		851	56.8%		7721	51.2%	
Surgery technique									
Anterior	4077	41.6%		742	49.5%		6998	46.4%	
Posterior	3712	37.9%		614	41.0%		5874	38.9%	
Lateral	2755	28.1%		434	29.0%		4071	27.0%	
Surgery type									
Fusion (2–3 V)	7543	77.0%		1072	71.6%		11,255	74.6%	
Fusion (4–8 V)	1466	15.0%		326	21.8%		2949	19.6%	
Fusion (9+V)	134	1.4%		20	1.3%		242	1.6%	
Refusion (2–3 V)	336	3.4%		45	3.0%		382	2.5%	
Refusion (4–8 V)	93	1.0%		23	1.5%		153	1.0%	
Refusion (9+V)	14	0.1%		1	0.1%		22	0.2%	
Size of units									
5 ml	0	0.0%		0	0.0%		8213	54.4%	
8 ml	9794	100.0%		1498	100.0%		0	0.0%	
10 ml	0	0.0%		0	0.0%		6875	45.6%	
Product quantity (ml)	9794	9.71	5.88	1498	9.27	5.20	15,088	8.76	6.67

All SURGIFLO™ includes both surgeries with and without Thrombin.

Table 3. Outcomes of interest.

Variable	All SURGIFLO™			SURGIFLO™ with Thrombin			FLOSEAL®		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Hospital flowable Cost ($)	9794	147.8	146.2	1498	222.66	146.25	15,088	349.8	319.7
Surgical complications									
Blood transfusion	889	9.1%		244	16.3%		1388	9.2%	
Haemorrhage	33	0.3%		8	0.5%		60	0.4%	
Wound complication	86	0.9%		22	1.5%		141	0.9%	

All SURGIFLO™ includes both surgeries with and without Thrombin.

looking at the following clinical end-points: evidence of blood transfusion, evidence of haemorrhage, and evidence of wound complications. The results are presented in Table 5. Overall, we found little or no differences in clinical outcomes measured by haemorrhage and wound complications between patients treated with SURGIFLO™ with Thrombin vs FLOSEAL®. Notably, in nine of the 12 model specifications, the use of SURGIFLO™ with Thrombin was associated with approximately an 11% reduction in the likelihood of blood transfusion. Although not conclusive at this time, this directional finding suggests the need for future prospective research.

Discussion

The purpose of this study was to compare clinical and economic outcomes of two marketed flowable hemostatic agents, SURGIFLO™ with Thrombin and FLOSEAL®, during spinal fusion and refusion surgeries. The retrospective analyses showed no clinically significant difference between these two products in multiple outcomes, but there were substantial differences in cost between SURGIFLO™ and FLOSEAL®. On average, hospitals spent $349.8 for FLOSEAL® as compared to $222.66 for SURGIFLO™ with Thrombin, and cost differences rose with length of surgery. Specifically, every additional hour of surgery was associated with an additional reduction in hospital costs. This reduction in cost per hour was estimated at $21.3 from the cross-sectional models and $25.7 in favor of SURGIFLO™ with Thrombin estimated from the hospital fixed effects model. Also, in all 14 specifications, SURGIFLO™ with Thrombin use was tied to statistically significant reductions in hospital costs for this agent, with the magnitude of the reduction varying by specification. In the cross-sectional specification, there was an ~$65 difference in hospital costs and, in the hospital fixed effects specification, there was an ~$300 difference in hospital costs.

Table 4. Regression results for hospital costs on flowable hemostatic agents.

	Surgeries with Thrombin combinations only ($n = 16,586$) – Cross sectional							Surgeries with Thrombin combinations only ($n = 16,586$) – Hospital fixed effects						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
SURGIFLO™ Indicator	−238.1*	−236.3*	−53.97*	−63.94*	−65.07*	−64.02*	−64.48*	−388.7*	−386.3*	−300.8*	−299.6*	−297.5*	−297.2*	−299.0*
	[19.15]	[19.10]	[10.11]	[10.09]	[10.09]	[10.08]	[10.08]	[74.17]	[74.01]	[33.39]	[33.40]	[33.40]	[33.43]	[33.43]
Surgery hours	32.92*	33.75*	1.961*	1.457†	1.384†	1.595†	1.518†	47.68*	48.19*	2.958*	2.984*	3.233*	2.828*	2.823*
	[1.162]	[1.160]	[0.633]	[0.640]	[0.660]	[0.721]	[0.728]	[1.214]	[1.214]	[0.581]	[0.582]	[0.596]	[0.675]	[0.680]
SURGIFLO™ Indicator	−0.972	−1.84	−22.31*	−21.55*	−21.27*	−21.46*	−21.26*	−4.906	−4.979	−25.91*	−25.91*	−25.76*	−25.93*	−25.69*
x Surgery hours	[4.389]	[4.375]	[2.311]	[2.300]	[2.305]	[2.304]	[2.307]	[4.547]	[4.537]	[2.048]	[2.050]	[2.050]	[2.056]	[2.058]
Observations	16,586	16,586	16,586	16,586	16,586	16,586	16,586	16,586	16,586	16,586	16,586	16,586	16,586	16,586
R-squared	0.214	0.223	0.784	0.788	0.789	0.79	0.79	0.518	0.522	0.903	0.903	0.903	0.903	0.903
Month/Year dummies		☑	☑	☑	☑	☑	☑		☑	☑	☑	☑	☑	☑
Product mL			☑	☑	☑	☑	☑			☑	☑	☑	☑	☑
Patient characteristics				☑	☑	☑	☑				☑	☑	☑	☑
Risk/severity/admission					☑	☑	☑					☑	☑	☑
Surgery characteristics						☑	☑						☑	☑
Surgery complications							☑							☑

Standard errors in brackets; *$p < 0.01$, †$p < 0.05$; Month-Year Indicator variables are included but not reported.
☑ indicate controls used in each model as detailed here: Models [1–7] are cross-sectional, models [8–14] control for hospital fixed effects. Models [1] and [8]: No controls. Models [2] and [9]: add controls for month and year. Models [3] and [10]: add controls for product quantity in milliliters. Models [4] and [11]: add controls for patient characteristics. Models [5] and [12]: add controls for patient risk and severity score as well as admission type. Models [6] and [13]: add controls for surgery characteristics. Models [7] and [14]: add controls for surgery complications. The results for the additional controls are not reported due to space constraints and are available from the authors.

These findings are a meaningful addition to the literature, as few studies evaluate the clinical effectiveness of these two flowable hemostatic agents[5] or on hospital cost. Yao *et al.*[27] commented that, in neurosurgery, the evidence is limited to a randomized trial by Renkens *et al.*[28] published in 2001, which compared FLOSEAL® to a Gelfoam-Thrombin control; an animal study[29]; and a handful of small case studies. Gazzeri *et al.*[5] also noted the modest amount of literature describing use of flowable hemostatic agents in spinal surgery.

There is a published SURGIFLO™ vs FLOSEAL® comparison by Gazzeri *et al.*[5], which is a retrospective study of 318 patients who underwent cranial, cranialspinal, or spinal surgeries. Of this cohort, there were 227 cases of cranial neurosurgical procedures, four cases of craniocervical junction, and 89 spinal approach surgeries. Flowable hemostatic agents were used in 87 of the spinal surgeries. Overall, FLOSEAL® was used in 264 patients, for brain and spinal surgery, whereas SURGIFLO™ was used in 54 cases, all of which were brain surgery. The authors note the greater use of FLOSEAL® was due to its earlier entrance to the market. The study looked at several indications using bleeding control, efficacy, and safety in neurosurgery as end-points. Hemostasis was achieved in all but eight cases. No complications associated with the flowable agents occurred in any of the spinal patients. From the perspective of these end-points, the two agents were deemed 'equivalent', differing only by source of collagen, and proved to be valuable in cases with difficult hemostasis. No cost data were included.

There are few additional clinical comparative studies of SURGIFLO™ vs FLOSEAL®. Nogueira *et al.*[12] describe a comparison of the two agents in a consecutive sample of 35 patients (25 FLOSEAL®; 10 SURGIFLO™) who underwent partial laparoscopic nephrectomy between December 2006–August 2007. Patients were comparable in terms of age, tumor number and location, ischemia, and blood loss, and they were followed for 6 months. Median blood loss was 200 ml (range = 25–650 mL) in the FLOSEAL® group, and 150 mL (range = 50–1500 mL; $p = 0.5$) in the SURGIFLO™ group. Researchers found that intra-operative hemostasis was achieved in all cases, and there were no associated complications within 3 weeks of the procedure. They concluded that the two agents were comparable. Our study demonstrated a cost differential between the two, possibly linked, at least in some degree, to the finding that the average spinal fusion surgery or refusion surgery took 3 h 50 min when using SURGIFLO™, and 4 h 30 min for procedures using FLOSEAL®.

These data fill a void by expanding the body of economic knowledge tied to use of flowable hemostatic agents for spinal fusion and spinal revision surgery in particular. For example, Schreiber and Neveleff[30] describe uncontrolled bleeding as linked to higher costs of care. Boucher and Hannon[31] refer to the increasingly high

Table 5. Regression results for outcomes.

	Surgeries with Thrombin – Cross-sectional						Surgeries with Thrombin – Hospital fixed-effects					
	1	2	3	4	5	6	7	8	9	10	11	12
Procedure for blood transfusion												
SURGIFLO™ indicator	−0.061,4* [0.019,9]	−0.060,0* [0.020,0]	−0.034,5 [0.019,9]	−0.038,8 [0.019,8]	−0.037,2 [0.019,2]	−0.042,3† [0.019,0]	−0.169* [0.027,1]	−0.168* [0.027,2]	−0.113* [0.027,4]	−0.123* [0.027,2]	−0.113* [0.026,3]	−0.107* [0.026,1]
R-squared	0.078	0.08	0.09	0.114	0.172	0.187	0.122	0.125	0.136	0.156	0.212	0.226
Diagnosis of haemorrhage												
SURGIFLO™ indicator	−0.006,91 [0.004,44]	−0.007,02 [0.004,45]	−0.004,2 [0.004,47]	−0.004,14 [0.004,49]	−0.004,49 [0.004,49]	−0.004,82 [0.004,49]	−0.003,98 [0.006,18]	−0.004,01 [0.006,20]	0.002,24 [0.006,27]	0.001,52 [0.006,29]	0.001,53 [0.006,29]	0.001,69 [0.006,30]
R-squared	0.004	0.006	0.008	0.01	0.014	0.017	0.012	0.013	0.016	0.017	0.021	0.024
Diagnosis of wound complications												
SURGIFLO™ indicator	−0.010,9 [0.006,85]	−0.011,1 [0.006,87]	−0.006,2 [0.006,89]	−0.005,59 [0.006,93]	−0.005,98 [0.006,90]	−0.006,8 [0.006,86]	−0.008,8 [0.009,52]	−0.007,46 [0.009,56]	0.001,23 [0.009,66]	−0.000,009,97 [0.009,69]	0.000,588 [0.009,65]	−0.00019 [0.009,61]
R-squared	0.005	0.006	0.009	0.01	0.024	0.037	0.015	0.016	0.019	0.021	0.034	0.046
Month/Year Dummies		§	§	§	§	§		§	§	§	§	§
Product mL & Thrombin			§	§	§	§			§	§	§	§
Patient characteristics				§	§	§				§	§	§
Risk/severity/admission					§	§					§	§
Surgery characteristics						§						§

Standard errors in brackets; *$p<0.01$, †$p<0.05$; Month-Year Indicator variables are included but not reported.
§ indicate controls used in each model as detailed here: Models [1–6] are cross-sectional, models [7–12] control for hospital fixed effects. Models [1] and [7]: No controls. Models [2] and [8]: add controls for month and year. Models [3] and [9]: add controls for product quantity in ml and thrombin. Models [4] and [10]: add controls for patient characteristics. Models [5] and [11]: add controls for patient risk and severity score as well as admission type. Models [6] and [12]: add controls for surgery characteristics. The results for the additional controls are not reported due to space constraints and are available from the authors.

cost of blood used in transfusions, and how its costs have doubled in recent years due to costs for high-skilled labor, procurement, storage, and processing. Those researchers cited the incremental hospital cost of red blood cell transfusion as $1840–$2760 per unit (2006 dollars), as compared to patients not receiving a transfusion or receiving autologous blood[30,31].

Limitations

Important strengths of this analysis include the prospectively developed protocol that directed the analysis, the broad geographic and demographic representation of US hospitals, and the fact that these data are relatively recent and represent a national setting. We considered tranexamic acid as part of the study design, since it is prevalently used in a procedure like orthopedic surgery. However, Blanchette *et al.*[32], using Premier data, reported that anti-fibrinolytics, including tranexamic acid, are used less than 1% in spinal surgery in the US, while the use of topical sealants is 67%. This study also had some noteworthy limitations. Because the data were mined from a hospital administrative database used for billing purposes, certain data points were unable to be captured or could not be clearly identified. Examples include patient body mass index, and patient behavior, such as smoking habits. During the 2-year period of the study, ICD-9 codes were used to identify surgery types and diagnosis codes of interest. Although they are specific, they are limited to hospital codes and do not include costs outside of the inpatient setting, costs tied to doctor visits, rehabilitation efforts, or medication costs. Furthermore, data on surgeon and institutional learning curves relative to the use of flowable agents were not available and could not be evaluated.

Conclusion

This study found that, while SURGIFLO™ with Thrombin has equivalent clinical outcomes to FLOSEAL® in spinal fusion or refusion procedures, SURGIFLO™ can significantly save hospital supply costs compared to FLOSEAL®, particularly as length of surgery increases. Moreover, supply cost savings rose as duration of surgery extended, even when the cost was adjusted for the amount of gelatin matrix (mL) used. Hospital decision-makers looking to improve cost-effectiveness while maintaining quality during spine surgery may benefit from this cost analysis.

Transparency

Declaration of funding

This study was funded by Ethicon, Inc. The publication of study results was not contingent on the sponsor's approval or censorship of the manuscript.

Declaration of financial/other relationships

CG is an employee and GD is an academic affiliate of CTI Clinical Trial and Consulting Services, Inc., which is a paid consultant to Ethicon, Inc. SL, RK, and SR are employees of Ethicon, Inc., the study sponsor. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

1. Moss, R. Management of Surgical Hemostasis: An Independent Study Guide. AORN, Inc, Denver, CO; 2013
2. Lewis KM, Atlee HD, Mannone AJ, et al. Comparison of two gelatin and thrombin combination hemostats in a porcine liver abrasion model. J Invest Surg 2013;26:141-8
3. Sileshi B, Achneck HE, Lawson JH. Management of surgical hemostasis: topical agents. Vascular 2008;16(Suppl 1):S22-8
4. Emilia M, Luca S, Francesca B, et al. Topical hemostatic agents in surgical practice. Transfus Apher Sci 2011;45:305-11
5. Gazzeri R, Galarza M, Alfier A. Safety biocompatibility of gelatin hemostatic matrix (Floseal and Surgiflo) in neurosurgical procedures. Surg Technol Int 2012;22:49-54
6. Saif R, Jacob M, Robinson S, et al. Use of fibrin-based sealants and gelatin-matrix hemostats in laparoscopic liver surgery. Surg Laparosc Endosc Percutan Tech 2011;21:131-41
7. Spotnitz WD, Burks S. Hemostats, sealants, and adhesives: components of the surgical toolbox. Transfusion 2008;48:1502-16
8. Block JE. Severe blood loss during spinal reconstructive procedures: the potential usefulness of topical hemostatic agents. Med Hypotheses 2005; 65:617-21
9. Oz MC, Cosgrove III DM, Badduke BR, et al. Controlled clinical trial of a novel hemostatic agent in cardiac surgery. The Fusion Matrix Study Group. Ann Thorac Surg 2000;69:1376-82
10. Klemcke HG. Evaluation of FloSeal as a potential intracavitary hemostatic agent. J Trauma 2006;60:385-9
11. Reuthebuch O, Lachat ML, Vogt P, et al. FloSeal: a new hemostyptic agent in peripheral vascular surgery. Vasa 2000;29:204-6
12. Nogueira L, Katz D, Pinochet R, et al. Comparison of gelatine matrix-thrombin sealants used during laparoscopic partial nephrectomy. BJU Int 2008; 102:1670-4
13. Pace G, Saldutto P, Vicentini C, et al. Haemostatics in surgery and our experience in the enucleoresection of renal cell carcinoma. World J Surg Oncol 2010;8:37
14. Bak JB, Singh A, Shekarriz B. Use of gelatin matrix thrombin tissue sealant as an effective hemostatic agent during laparoscopic partial nephrectomy. J Urol 2004;171:780-2
15. Fiss I, Danne M, Stendel R. Use of gelatin-thrombin matrix hemostatic sealant in cranial neurosurgery. Neurol Med Chir (Tokyo) 2007;47:462-7
16. Gazzeri R, Galarza M, Neroni M, et al. Minimal craniotomy and matrix hemostatic sealant for the treatment of spontaneous supratentorial intracerebral hemorrhage. J Neurosurg 2009;110:939-42
17. Woodworth BA, Chandra RK, LeBenger JD, et al. A gelatin-thrombin matrix for hemostasis after endoscopic sinus surgery. Am J Otolaryngol 2009; 30:49-53
18. Izzo F, Di Giacomo R, Falco P, et al. Efficacy of a haemostatic matrix for the management of bleeding in patients undergoing liver resection: results from 237 cases. Curr Med Res Opin 2008;24:1011-15
19. Helito CP, Gobbi RG, Castrillon LM, et al. Comparison of Floseal(r) and electrocautery in hemostasis after total knee arthroplasty. Acta Ortop Bras 2013;21:320-2
20. Kim HJ, Fraser MR, Kahn B, et al. The efficacy of a thrombin-based hemostatic agent in unilateral total knee arthroplasty: a randomized controlled trial. J Bone Joint Surg Am 2012;94:1160-5

21. Gazzeri R, Galarza M, Neroni M, et al. Hemostatic matrix sealant in neurosurgery: a clinical and imaging study. Acta Neurochir (Wien) 2011;153:148-54; discussion 155
22. Floseal Hemostatic Matrix Instructions for Use. Hayward, CA: Baxter Healthcare Corporation
23. Elgafy H, Bransford RJ, McGuire RA, et al. Blood loss in major spine surgery: are there effective measures to decrease massive hemorrhage in major spine fusion surgery? Spine (Phila Pa 1976) 2010;35:S47-56
24. Rajaee SS, Bae HW, Kanim LE, et al. Spinal fusion in the United States: analysis of trends from 1998 to 2008. Spine (Phila Pa 1976) 2012;37:67-76
25. Steiner C, Andrews R, Barrett M, et al. HCUP Projections: Mobility/Orthopedic Procedures 2011 to 2012. HCUP Projections Report # 2012-03. Available from: http://www.hcup-us.ahrq.gov/reports/projections/2012-03.pdf [last accessed 13 Nov 2014].
26. 3M$_{tm}$ APR DRG Classification System, 3M Health Information Systems, Wallingford, CT. GRP-041 Version 26.1. 10/2008
27. Yao HH, Hong MK, Drummond KJ. Haemostasis in neurosurgery: what is the evidence for gelatin-thrombin matrix sealant? J Clin Neurosci 2013;20:349-56
28. Renkens Jr. KL,, Payner TD, Leipzig TJ, et al. A multicenter, prospective, randomized trial evaluating a new hemostatic agent for spinal surgery. Spine (Phila Pa 1976) 2001;26:1645-50
29. Ereth MH, Schaff M, Ericson EF, et al. Comparative safety and efficacy of topical hemostatic agents in a rat neurosurgical model. Neurosurgery 2008;63:369-72; discussion 372
30. Schreiber MA, Neveleff DJ. Achieving hemostasis with topical hemostats: making clinically and economically appropriate decisions in the surgical and trauma settings. AORN J 2011;94:S1-20
31. Boucher BA, Hannon TJ. Blood management: a primer for clinicians. Pharmacotherapy 2007;27:1394-411
32. Blanchette CM, Wang PF, Joshi AV, et al. Cost and utilization of blood transfusion associated with spinal surgeries in the United States. Eur Spine J 2007;16:353-63

Appendix A: List of ICD-9 procedure codes for surgery type, approach, and vertebrae

81.00 Spinal fusion, not otherwise specified
81.01 Atlas-axis spinal fusion
81.02 Other cervical fusion, anterior technique
81.03 Other cervical fusion, posterior technique
81.04 Dorsal and dorsolumbar fusion, anterior technique
81.05 Dorsal and dorsolumbar fusion, posterior technique
81.06 Lumbar and lumbosacral fusion, anterior technique
81.07 Lumbar and lumbosacral fusion, lateral transverse process technique
81.08 Lumbar and lumbosacral fusion, posterior technique
81.30 Refusion of spine, not otherwise specified
81.31 Refusion of atlas-axis spine
81.32 Refusion of other cervical spine, anterior technique
81.33 Refusion of other cervical spine, posterior technique
81.34 Refusion of dorsal and dorsolumbar spine, anterior technique
81.35 Refusion of dorsal and dorsolumbar spine, posterior technique
81.36 Refusion of lumbar and lumbosacral spine, anterior technique
81.37 Refusion of lumbar and lumbosacral spine, lateral transverse process
81.38 Refusion of lumbar and lumbosacral spine, posterior technique
81.39 Refusion of spine, not elsewhere classified
81.61 360° spinal fusion, single incision approach
81.62 Fusion or refusion of 2–3 vertebrae
81.63 Fusion or refusion of 4–8 vertebrae
81.64 Fusion or refusion of 9 or more vertebrae
84.51 Insertion of interbody spinal fusion device

Appendix B: List of ICD-9 procedure and diagnosis codes for events of interest

- Blood Transfusion – 99.0, 99.02, 99.03, 99.04, 99.05, 99.07, 99.08, 99.09
- Haemorrhage – 998.11
- Wound complications (local superficial infections, hematoma, seroma, cellulitis, wound dehiscence) – 998.12, 998.13, 998.30, 998.31, 998.32, 998.3
- Organ injury – 998.2
- Cardiac (arrhythmia, MI, or heart failure (pulmonary edema)) – 997.1, 428.1, 428.21, 428.23, 428.31, 428.33, 428.43, 514, 518.4
- Respiratory (atelectasis, pneumothorax, prolonged air leak, pneumonia, chylothorax, bronchopleural fistula, empyema) – 997.39, 998.59, 518.81, 518.84, 518.5, 512.0, 518.0, 510.9, 510.0, 512.1, 512.2, 512.8, 457.8, 507.0, 487.0, 490, 491.21, 491.22, 511.0, 511.1, 511.89, 511.9, 519.01, 480.xx, 482.xx, 483.xx, 484.xx, 485.xx, 486.xx, 513.xx
- Venous thromboembolism (deep vein thrombosis (DVT), pulmonary embolism (PE)) – 415.1, 453.4, 453.8, 453.9
- Neurologic (stroke – hemorrhagic or ischemic, TIA) – 997.02, 997.09, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 437.1

Appendix C. Regression results for all surgeries (with and without Thrombin)

	All surgeries ($n=24,882$) – Cross-sectional							All surgeries ($n=24,882$) – Hospital fixed-effects						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
SURGIFLO™ Indicator	−271.6*	−266.8*	−150.6*	−147.2*	−148.9*	−150.4*	−151.1*	−211.2*	−199.7*	−113.7*	−115.2*	−115.4*	−115.9*	−116.3*
	[7.658]	[7.662]	[4.979]	[5.027]	[5.033]	[5.034]	[5.038]	[13.72]	[13.85]	[8.082]	[8.107]	[8.105]	[8.108]	[8.109]
Surgery hours	32.92*	33.47*	8.308*	7.958*	7.068*	5.946*	5.736*	49.09*	49.43*	13.03*	12.98*	12.96*	11.88*	11.77*
	[1.008]	[1.008]	[0.666]	[0.670]	[0.686]	[0.732]	[0.738]	[1.036]	[1.035]	[0.630]	[0.631]	[0.643]	[0.708]	[0.712]
SURGIFLO™ Indicator	−11.19*	−11.80*	−24.36*	−25.03*	−24.82*	−24.28*	−24.21*	−26.77*	−27.47*	−36.13*	−36.08*	−35.99*	−35.92*	−35.92*
x Surgery hours	[1.573]	[1.571]	[1.015]	[1.024]	[1.024]	[1.024]	[1.024]	[1.709]	[1.707]	[0.996]	[0.997]	[0.997]	[1.000]	[1.000]
Constant	335.6*	306.1*	50.01*	64.34*	74.14*	53.21†	41.33	238.0*	220.9*	20.91*	41.24*	52.39†	43.78*	33.87
	[5.583]	[10.47]	[6.888]	[14.77]	[22.96]	[25.04]	[25.39]	[7.514]	[10.66]	[6.284]	[13.18]	[20.87]	[22.57]	[22.82]
Observations	24,882	24,882	24,882	24,882	24,882	24,882	24,882	24,882	24,882	24,882	24,882	24,882	24,882	24,882
R-squared	0.289	0.294	0.706	0.71	0.711	0.714	0.714	0.57	0.573	0.855	0.855	0.855	0.856	0.856
Month/Year Dummies		§	§	§	§	§	§		§	§	§	§	§	§
Product mL & Thrombin			§	§	§	§	§			§	§	§	§	§
Patient characteristics				§	§	§	§				§	§	§	§
Risk/severity/admission					§	§	§					§	§	§
Surgery characteristics						§	§						§	§
Surgery complications							§							§

Standard errors in brackets; *$p<0.01$, †$p<0.05$; Month-Year Indicator variables are included but not reported.
§ indicate controls used in each model as detailed here: Models [1–7] are cross-sectional, models [8–14] control for hospital fixed effects. Models [1] and [8]: No controls. Models [2] and [9]: add controls for month and year. Models [3] and [10]: add controls for product quantity in milliliters and thrombin. Models [4] and [11]: add controls for patient characteristics. Models [5] and [12]: add controls for patient risk and severity score as well as admission type. Models [6] and [13]: add controls for surgery characteristics. Models [7] and [14]: add controls for surgery complications.