Comparative Effectiveness of Fibrin Sealants in Cardiac Surgery

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BACKGROUND

- Achieving and maintaining hemostasis intraoperatively and post-operatively is a critical requirement of surgery. Failure to maintain intraoperative hemostasis can result in excessive bleeding, thereby complicating surgery and increasing the risk of morbidity and mortality.[1-3]
- In a retrospective analysis of more than 1.6 million surgeries performed in the US, Stokes et al. reported 45.8% of cardiac patients required blood transfusions, and across multiple surgery types, almost 30% of surgical patients experienced bleeding-related complications.[4]
- Topical hemostats, such as fibrin sealants, are often used during surgery as a sealant and/or to treat bleeding. However, head-to-head research comparing the effectiveness of these agents remains limited.

OBJECTIVE

- The objective of the study was to conduct a large retrospective observational database analysis to assess the effectiveness of fibrin sealants in an applied "real world" setting.
- We analyzed the clinical outcomes of two different fibrin sealants, TISSEEL and EVICEL, in a population of patients undergoing cardiac surgical procedures.

METHODS

Data Source

- Premier's Hospital Database
  - The Premier Hospital Database contains data from more than 6 million US hospital discharges annually.
  - Data from patients undergoing inpatient cardiac surgical procedures between 2008 and 2012 were extracted.

Patient Population

- Inclusion
  - Procedures including coronary artery bypass grafting (CABG), valve, or valvular with CABG
  - Surgeries using only the following:
    - FS-apr (fibrin sealant with aprotinin – TISSEEL: Baxter, Westlake Village, CA)
    - FS (fibrin sealant without aprotinin – EVICEL: Ethicon/J&J, Somerville, NJ)
- Exclusion
  - Surgeries using other sealants and/or hemostatic agents

Clinical Outcomes

- Nasso et al. published results of a prospective, randomized clinical trial of patients undergoing elective cardiac and/or thoracic aortic operations treated with a flowable hemostatic matrix, oxidized regenerated cellulose, or purified porcine gelatin sponge.[5] We used clinical outcomes similar to those in the Nasso et al. study.
- Primary clinical outcomes:
  - Major and minor complications, transfusions (up to 96 hours), surgical revisions for bleeding, patient mortality
- Secondary outcomes:
  - Operating room (OR) time in minutes, hospital length of stay (LOS), Intensive Care Unit (ICU) LOS

Covariates

- Covariates included:
  - Age, primary procedure, Charlson Co-morbidity Index (CCI) score, heparin use, protamine use, admission type, gender, race, teaching hospital, bed size, region

Analyses

- Descriptive statistics
- Logistic regression analyses were performed on categorical outcome variables.
- General Linear Models (GLM) regression analyses were performed on continuous outcome variables.

RESULTS

- This analysis of 207,923 patients undergoing cardiac surgery found that 3,579 patients received FS-apr only or FS only, with no other adjunctive products. (Figure 1)
  - 2,560 with FS-apr only
  - 1,019 with FS only
  - Most patients were male, had elective surgery, and underwent CABG. (Table 1)

Figure 1. Patient Selection

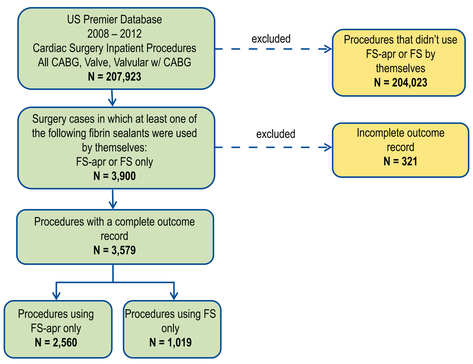

Table 1. Patient Characteristics

	FS-apr	FS
N (%)	2,560 (71.5)	1,019 (28.5)
Mean Age [sd] (range)	65.7 [11.7] (0–89)	65.9 [11.4] (23–89)
Gender – N (%)		
Female	761 (29.7)	308 (30.2)
Male	1,799 (70.3)	711 (69.8)
Mean CCI Score [sd] (range)	2.1 [1.8] (0–14)	2.3 [1.9] (0–12)
Cardiac Procedure – N (%)		
Valve Only	428 (16.7)	199 (19.5)
CABG Only	1,768 (69.1)	680 (66.7)
CABG & Valve	309 (12.1)	121 (11.9)
Aortic & Valve	40 (1.6)	16 (1.6)
Aortic & CABG	5 (0.2)	1 (0.1)
Aortic, Valve & CABG	10 (0.4)	2 (0.2)
Elective vs. Emergency/Urgent – N (%)		
Elective	1,337 (52.2)	567 (55.6)
Emergency/Urgent	1,223 (47.8)	452 (44.4)

CCI = Charlson Co-morbidity Index Score

RESULTS

- Cases were reported from 83 hospitals. (Table 2)
  - Most hospitals for both the FS-apr and FS cases were not teaching hospitals, were in the South, and had 300+ beds.

Table 2. Hospital Characteristics (N = 83)

Reporting Hospitals	FS-apr N (%)	FS N (%)
Number of cases	2,560 (71.5)	1,019 (28.5)
Teaching hospital		
No	1,454 (56.8)	649 (63.7)
Yes	1,106 (43.2)	370 (36.3)
Region		
East	590 (23.0)	129 (12.7)
South	1,003 (39.2)	551 (54.1)
West	967 (37.8)	339 (33.3)
Number of beds		
0–199	21 (0.8)	15 (1.5)
200–299	311 (12.1)	14 (1.4)
300–499	1,506 (58.8)	465 (45.6)
500 +	722 (28.2)	525 (51.5)

- Compared to FS only in cardiac surgical procedures (after adjusting for covariates), the FS-apr was associated with significantly lower: (Table 3)
  - Minor complications (21.1% vs. 27.1%, $p = 0.002$)
  - Day-1 transfusions (28.6% vs. 36.8%, $p = 0.015$)
  - ICU LOS (4.7 days vs. 7.1 days, $p < 0.0001$)
- No significant differences were found between FS-apr and FS for the other clinical outcomes.

Table 3. Regression Results: FS-apr vs. FS

					OR/LOS		
	FS-apr		FS		Ratio*	*p*-value	Model Fit
Primary Outcomes							
Major complications – N (%)	186 (7.3)	🟡	76 (7.5)	🟡	0.78	0.130	0.78
Minor complications – N (%)	541 (21.1)	🟢	276 (27.1)	🔴	1.37	0.002	0.73
Revisions for bleedings – N (%)	55 (2.1)	🟡	29 (2.8)	🟡	1.37	0.230	0.76
Transfusions – N (%)							
Day 1	733 (28.6)	🟢	375 (36.8)	🔴	1.27	0.015	0.81
Day 2–4	333 (13.0)	🟡	162 (15.9)	🟡	1.06	0.603	0.73
Blood transfusions	792 (30.9)	🟡	374 (36.7)	🟡	1.11	0.320	0.82
All transfusions	923 (36.1)	🟡	418 (41.0)	🟡	0.91	0.320	0.81
Patient mortality – N (%)	60 (2.3)	🟡	33 (3.2)	🟡	1.40	0.190	0.79
Secondary Outcomes							
Mean (sd) OR time (minutes)	346.5 (98.4)	🟡	345.3 (114.8)	🟡	1.01	0.230	1.01
Mean (sd) hospital LOS (days)	9.9 (6.9)	🟡	10.4 (7.5)	🟡	1.00	0.930	0.93
Mean (sd) ICU LOS (days)	4.7 (5.4)	🟢	7.1 (7.1)	🔴	1.41	<0.0001	0.95

*Reference group is FS-apr

🟢 Significantly superior results
🟡 Results at parity or not significant
🔴 Significantly inferior results

LIMITATIONS

- No adjustments were made for specific surgeon experience or their respective annual procedure volumes, as these variables were not available in the database.
- Clinical complications that could occur post-hospitalization were not assessed.
- Prescriptive transfusions are highly variable across the industry and are difficult to standardize in a retrospective observational study given institutional blood management practices and prescriptive clinical protocols/values. Transfusions assessed in this study were the values reported by hospitals; thus there should be consideration that disproportionate transfusion practices could highly impact transfusions results.
- Adjustments were made for patient severity and surgical complexity based on the available patient and hospital characteristics. However, other unobserved patient characteristics that were not controlled for may have influenced these results.

CONCLUSIONS

When analyzing the comparative effectiveness of fibrin sealants in cardiac surgical procedures, as compared to FS, the FS-apr patient group was associated with significantly lower rates of:

- Minor complications
- Day 1 transfusions
- ICU LOS

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