

Exploring Adverse Events and Utilization of Topical Hemostatic Agents in Surgery

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ABSTRACT

Background and Objectives: This retrospective study provides preliminary qualitative assessment of the adverse events (AEs), focusing on pelvic and abdominal AEs and patient outcomes reported for three hemostatic agents used in gynecologic surgery.

Methods: Utilization rates for oxidized regenerated cellulose powder (ORC), polysaccharide powder (PSP), and fibrin sealant solution (FSS) were obtained from hospitals via the Premier Healthcare databases for all surgical procedures from January 1, 2018 to September 30, 2020. All reported cases were extracted from the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database for ORC and PSP and from the FDA Adverse Event Reporting System (FAERS) database for FSS. Distributions of AEs by anatomical site (MAUDE/FAERS) and surgical procedures by specialty (Premier) were evaluated for each product. Number of cases and number and types of AEs were compared to the total utilization for each product.

Results: PSP was the most used product during the period analyzed (n = 126,509 uses), followed by FSS (n = 80,628 uses), and ORC (n = 41,583 uses). Distribution of surgical procedures by anatomical site varied

significantly between hemostatic agents ($p < 0.001$). ORC was associated with more patient cases with AEs and numbers of reported AEs compared with PSP and FSS ($p < 0.001$). ORC was associated with higher number of infections than PSP ($p < 0.001$) and FSS ($p < 0.001$).

Conclusion: These findings suggest that ORC use in abdominal and pelvic surgery may result in more postoperative complications compared with non-ORC hemostatic agents. Further prospective randomized studies are needed to compare efficacy and safety of these products.

Key Words: Fibrin sealant system, Oxidized cellulose powder, Starch powder, Surgical hemostasis.

INTRODUCTION

Gynecologic surgical procedures have been associated with numerous complications due to the proximity of the female reproductive tract to the urinary tract, intestinal tract, pelvic nerves, and pelvic vasculature.¹ Although many abdominal and pelvic procedures are now performed with minimally invasive techniques, complications remain a concern.¹⁻⁴ Increased blood loss and blood transfusion, along with urologic and intestinal injuries, and prolonged surgical duration are intraoperative risk factors for postoperative infection, the most common complication of abdominal and pelvic procedures.⁵⁻⁷

Effective management of bleeding has been shown to lower the risk of complications and subsequent mortality.⁸ The use of topical hemostatic agents can reduce blood loss and the need for blood transfusion, both of which are associated with adverse events (AEs) and substantial cost.^{9,10} While topical hemostatic agents can be vital adjuncts, their use based on specific indications in pelvic and abdominal surgery is poorly documented in the literature. Some studies suggest that these agents have been used based on physician preference rather than clinical need.¹¹

Oxidized regenerated cellulose powder (ORC), polysaccharide powder (PSP), and fibrin sealant solution (FSS) are commonly used hemostatic agents with different biologic, chemical, and physical mechanisms of action. They

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are indicated as adjuncts when control of venous, capillary, and arteriolar bleeding by pressure, ligature, or other conventional procedures is ineffective or impractical.¹²⁻¹⁴ Due to their ease of application, these agents have been adopted for widespread use in both open and minimally invasive abdominal surgeries.^{15,16} While PSP was approved by the FDA for use in the US in 2006 and FSS in 1998, ORC was developed more recently and approved for use in 2017.^{12,13,17} As a relatively new product, there is limited information on AEs reported with use of ORC in the literature. Therefore, this analysis aimed to compare the normalized rates of patients with pelvic and abdominal AEs, as well as the normalized rates of AEs reported with the use of these hemostatic agents to determine the suitability and safety of their use in pelvic and abdominal surgery.

METHODOLOGY

Data Sources for Utilization Rates

Utilization rates for ORC (Surgicel™ Powder Absorbable Hemostat, Ethicon, Raritan, NJ, USA), PSP (Arista™ Absorbable Hemostat, Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and FSS (Tisseel®, Baxter Healthcare Corporation, Deerfield, IL, USA) were extracted from the Premier Healthcare database recorded for all surgical procedures from January 1, 2018 to September 30, 2020. This time period was selected as it spans from the first full year that all three products were commercially available for use. The Premier Healthcare database is a comprehensive US-based electronic healthcare database. It contains administrative, healthcare utilization, and financial data from patient encounters that are submitted by more than 1,041 contributing hospitals and healthcare systems. This database also provides the breakdown of surgical procedures by specialty.¹⁸ Institutional Review Board approval was not required for this noninterventional, retrospective analysis.

Data Sources for Adverse Events and Patient Outcomes

Two distinct FDA databases were identified for tabulating adverse events and patient outcomes, with subsequent analysis using accepted statistical methods to address the database disparities to allow data comparison. Systematic searches of the FDA Manufacturer and User Facility Device Experience (MAUDE) database for ORC (Surgicel™ Powder Absorbable Hemostat) and PSP

(Arista™ Absorbable Hemostat) were performed because both of these hemostatic agents are classified as medical devices in the US. The MAUDE database was established by the FDA to house medical device reports (MDRs) submitted to the FDA by device manufacturers, including user facilities who are obligated to report events; and by clinicians, patients, and consumers, who may voluntarily report. MDRs are uploaded monthly and include a description of the occurred event.¹⁹

A systematic search of the FDA Adverse Event Reporting System (FAERS) database for FSS (Tisseel®) was performed to identify the available entries because this hemostatic agent is classified as a biologic agent in the US. The FDA FAERS database was established by the FDA to contain AE reports, medication error reports, and product quality complaints resulting in AEs that are submitted to the FDA. It is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA receives mandatory reports from manufacturers and voluntary reports directly from healthcare professionals (physicians, pharmacists, nurses, etc.) and consumers (patients, family members, lawyers, etc.).²⁰

Adverse Events, Number of Cases and Patient Outcomes

For each patient case reported to MAUDE or FAERS, one or more patient outcomes may be reported. Patient outcomes may include disability, hospitalization (defined as admission or prolongation of hospitalization), whether life threatening, requiring intervention, or resulting in death.

For both the MAUDE and FAERS databases, each patient case may be submitted with multiple corresponding AEs, but it is not a requirement to submit a patient outcome. Patient cases for which no outcome was reported are shown as "no outcome reported" in this analysis to reflect the number of patients for whom that information was not provided. Each patient case reported in the MAUDE or FAERS databases is associated with at least one AE. AEs are reported using Medical Dictionary for Regulatory Activities (MedDRA) codes in the FAERS database and MDR AE codes in the MAUDE database. To allow comparison between data for each hemostatic agent, MedDRA codes and MDR AE codes were aligned and combined under overarching AE categories (methodology is described in the **Appendix Table**).

The numbers of patient cases with AEs, as well as the numbers and types of AEs reported for each hemostatic

agent in the MAUDE and FAERS databases were evaluated and compared to the reported total utilization for each product, based on the Premier Healthcare database. AEs were aligned and combined by anatomic location with a pelvic and abdominal focus given their relevance to gynecologic surgery and outcomes.

Statistical Analyses

The utilization data was analyzed using a χ^2 test to compare the distribution of procedures across four surgery categories grouped by anatomic site (abdominal/pelvic surgery includes general, urologic, bariatric, obstetrics and gynecologic surgery; thoracic surgery includes cardiac, lung, and noncardiac thoracic surgery; ortho/neuro includes orthopedic, neurologic, and spine surgery; and other/unspecified includes ophthalmology, reconstructive, aesthetic, breast, ear, nose, throat, peripheral vascular surgery, and other/unspecified) between each product. The number of occurrences of different patient outcomes and AEs were assumed to follow a Poisson distribution (which is a discrete distribution that measures the probability of a given number of events happening in a specific time period). As a result, Poisson regression was used to compare the occurrences of patient outcomes and

AEs between hemostatic agents. To allow for the multiple comparisons between each pair of hemostatic agents, the p-values from all analyses were given a Bonferroni adjustment (a correction to counteract the multiple comparisons problem). No formal analysis was performed when no occurrence of the patient outcome was observed with either hemostatic agent. Risk ratios (RR) were calculated for the total numbers of patient cases with AEs and total number of AEs between each pair of hemostatic agents. These were presented in corresponding 98.3% confidence intervals, an approach consistent with the adjustment of the p-values to allow for multiple testing; $p < .05$ was considered statistically significant throughout this analysis.

RESULTS

According to the data captured in the Premier Healthcare database (**Table 1**), PSP was the most widely used of the three hemostatic agents (n = 126,509 uses), followed by FSS (n = 80,628 uses) and ORC (n = 41,583 uses). The number of individual cases and the number of AEs were reported as a proportion of the total utilization (per 1,000 uses) since product utilization could be a factor leading to a differing number of reports.

Table 1.

Cases, Adverse Events, and Distribution of Oxidized Regenerated Cellulose Powder, Polysaccharide Powder, and Fibrin Sealant Solution Use by Surgical Specialty

	ORC (n = 41,583)	PSP (n = 126,509)	FSS (n = 80,628)	RR (98.3% CI); p-Values		
				ORC vs PSP ^f	ORC vs FSS ^f	FSS vs PSP ^f
Number of cases with AEs (per thousand uses) ^a	129 (3.1)	37 (0.3)	53 (0.7)	10.6 (6.8, 16.6); < 0.001	4.7 (3.2, 7.0); < 0.001	2.2 (1.3, 3.7); < 0.001
Number of AEs (per thousand uses) ^a	233 (5.6)	52 (0.4)	130 (1.6)	13.6 (9.5, 19.7); < 0.001	3.5 (2.7, 4.5); < 0.001	3.9 (2.7, 5.8); < 0.001
Anatomic site of surgical procedures (% of total procedures)						
Abdominal/pelvic surgery ^b	53.5	57.5	49.5	< 0.001	< 0.001	< 0.001
Thoracic surgery ^c	11.9	13.1	10.5			
Orthopedic or Neurologic ^d	17.7	7.6	24.0			
Other/unspecified ^e	16.9	21.8	16.1			

^aCases may include more than one adverse event; ^bGeneral, urologic, bariatric, obstetrics/gynecology surgery; ^ccardiac, lung, and noncardiac thoracic surgery; ^dorthopedic, neurologic, and spine surgery; ^eophthalmology, reconstructive, aesthetic, breast, ear, nose, throat, peripheral vascular surgery, and other/unspecified; ^fbaseline category in calculation of risk ratios. Abbreviations: AE, adverse event; FSS, fibrin sealant solution; ORC, oxidized regenerated cellulose powder; PSP, polysaccharide powder; RR, risk ratio; CI, confidence interval.

ORC use was associated with the highest case rate of AEs ($P < .001$), as well as the highest number of AEs per use ($P < .001$). The overall distribution of surgical procedures by anatomic site varied significantly between all three hemostatic agents ($P < .001$). This was largely due to the more frequent use of FSS in orthopedic, neurologic, and spine surgeries (24%) compared with the other two hemostatic agents (17.7% and 7.6% for ORC and PSP, respectively). The frequency of use of the three hemostatic agents were similar in general, urologic, bariatric, obstetrics or gynecologic surgeries, representing approximately half of all surgical procedures performed (53.5%, 57.5%, and 49.5% for ORC, PSP, and FSS, respectively). Specifically, all three products were used at comparable rates in gynecologic procedures.

While these data from the Premier Healthcare database provide some insight into the use of each hemostatic agent by type of surgery, the MAUDE and FAERS data do not provide the type of procedure associated with each reported patient case and therefore types of AEs could not be related to specific procedures.

ORC was associated with more patient cases with AEs, compared with PSP and FSS, respectively. ORC was also associated with an increase in total number of AEs compared with PSP and FSS respectively. FSS was associated with an increase in patient cases with AEs, and an increase in total number of AEs compared with PSP.

There were 122, 29, and 62 total patient outcomes reported with ORC, PSP, and FSS, respectively, in the MAUDE and FAERS databases (**Table 2**). When reporting the number of patient outcomes as a proportion of the reported utilization for each product, ORC was associated with the highest rate of adverse outcomes, of which most were classified as requiring intervention or other unspecified outcome. Of the adverse outcomes reported for PSP, most were classified as requiring intervention or other outcome with the rate lower than that for both ORC and FSS.

Of the adverse outcomes reported for FSS, more than half were classified as requiring intervention or other outcome and nearly one-third led to either prolonged hospitalization or readmission. Of note, the frequency of hospitalization reported with FSS was higher than for the other two products and the difference reached statistical significance when compared with PSP; however, it was not possible to determine from the available data if the hospitalization reported was a readmission event or prolonged hospitalization as a result of the initial surgical procedure. It is unclear if patient outcomes resulting from AEs in the MAUDE and FAERS databases were due to the surgical procedure itself or due to factors other than the hemostatic agent used because the FDA does not require a causal relationship between a product and event be proven or reported. Thus, differences in the types of surgeries performed, as shown in **Table 1**, may be an important

Table 2.

Patient Outcomes per 100,000 Uses Associated with Oxidized Regenerated Cellulose Powder, Polysaccharide Powder, and Fibrin Sealant Solution Reported as a Proportion of the Total Utilization

	Patient Outcomes per 100,000 uses			p-Values ^c		
	ORC (n = 122)	PSP (n = 29)	FSS (n = 62)	ORC vs PSP	ORC vs FSS	FSS vs PSP
Adverse outcomes ^a	291.0	22.1	74.4	< 0.001	< 0.001	< 0.001
Disability	0.0	0.8	2.5	1.00	1.00	1.00
Hospitalization	2.4	1.6	23.6	1.00	0.08	< 0.001
Life Threatening	0.0	1.6	5.0	1.00	0.91	0.56
Other/Required Intervention	288.6	18.2	43.4	< 0.001	< 0.001	< 0.001
No outcome reported	19.2	10.3	8.7	0.49	0.37	1.00
Death ^b	2.4	0.8	2.5	1.00	1.00	1.00

^aadverse outcome per 100,000 uses includes disability, hospitalization, life threatening, required intervention, other; ^bdeath is both a patient outcome and an adverse event in the MAUDE database but is only reported as an outcome in the FAERS database; ^cstatistical analysis performed using a Poisson regression to compare the outcome occurrences between groups.

Abbreviations: FSS, fibrin sealant solution; ORC, oxidized regenerated cellulose powder; PSP, polysaccharide powder.

factor contributing to the differences in outcomes reported.

One death was reported following a surgery in which ORC was used, one in which PSP was used, and two with FSS. There was no significant difference between the number of deaths reported in MAUDE and FAERS in surgeries that used the three hemostatic agents. ORC was used on the liver bed for a patient undergoing a laparoscopic cholecystectomy; three days after the initial procedure and following discharge, the patient returned to the emergency department and subsequently died of a pulmonary embolism. This patient had previously undergone

bypass surgery and presented with multiple comorbidities. The surgeon did not consider the pulmonary embolism to be related to ORC. PSP was used during the implantation of a pacemaker for an elderly patient who died shortly afterward, but the facility reported that the cause of death was not related to the use of PSP. FSS was used in two patients who subsequently died, one from a postprocedural stroke and the other from a cardiovascular event, with no further information available.

Comparisons between the rates of AEs for each hemostatic agent by anatomic site are summarized in **Table 3**. The rates of AEs for ORC were higher than those for both

Table 3.
Adverse Events Reported for Oxidized Regenerated Cellulose Powder, Polysaccharide Powder, and Fibrin Sealant Solution by Anatomical Category Reported as a Proportion of the Total Utilization

	Adverse Events ^a per 100,000 uses			p-Values ^b		
	ORC (n = 233)	PSP (n = 52)	FSS (n = 130)	ORC vs PSP	ORC vs FSS	FSS vs PSP
Abdominal and pelvic AEs						
Gastrointestinal	36.1	3.2	12.4	< 0.001	0.03	0.06
Urologic	0.0	0.0	2.5	-	1.00	0.55
Circulatory, lymphatic and respiratory AEs						
Blood/lymphatic	7.2	0.0	0.0	0.13	0.26	-
Cardiovascular	9.6	0.0	13.6	0.08	1.00	0.04
Hemorrhage	7.2	0.0	2.5	0.13	0.68	0.55
Respiratory/thoracic	14.4	0.8	7.4	0.02	0.75	0.14
Musculoskeletal and neurologic AEs						
Musculoskeletal and connective tissue	4.8	0.0	3.7	0.24	1.00	0.34
Neurologic	16.8	0.8	37.2	0.01	0.18	<0.001
Other complications						
Deep tissue/application site reaction	84.2	1.6	7.4	< 0.001	< 0.001	0.17
Dermatological/skin/wound problem	26.5	1.6	12.4	< 0.001	0.24	0.02
General/inflammatory/allergic conditions	72.1	18.2	39.7	< 0.001	0.06	0.01
Infection	156.3	4.0	8.7	< 0.001	< 0.001	0.54
Ocular	0.0	0.0	3.7	-	1.00	0.34
Death	2.4	0.8	0.0	1.00	1.00	1.00
Other						
Insufficient data	57.7	0.8	0.0	< 0.001	0.003	1.00
No code available	53.3	0.0	0.0	0.003	0.006	-
Product administration/quality	9.6	9.5	9.9	1.00	1.00	1.00

^aNumber of AEs reported in the MAUDE database (ORC and PS) and the FAERS database (FS) between 01/01/2018 and 09/30/2020;

^bstatistical analysis performed using a Poisson regression to compare occurrences between groups.

Abbreviations: AE, adverse event; FSS, fibrin sealant solution; ORC, oxidized regenerated cellulose powder; PSP, polysaccharide powder.

PSP and FSS for gastrointestinal, deep tissue/application site reaction and infection. Infection after use of ORC was the most frequent AE in any category and occurred significantly more often with ORC than with PSP or FSS ($P < .001$). Infection rates for PSP and FSS did not vary significantly. Rates of insufficient data or uncoded findings were also higher for ORC than for either PSP or FSS. The rates of AEs for ORC and FSS were both higher than those for PSP in neurologic, dermatologic, and general/inflammatory/allergic condition categories. Rates of AEs for PSP were lower than for ORC in the respiratory/thoracic categories and lower than for FSS in the cardiovascular category. The rates of neurologic AEs reported for PSP were lower than for both ORC and FSS. While this finding could potentially result from the more frequent use of FSS and ORC in neurologic surgery (**Table 1**), the available data precludes a determination of causality.

DISCUSSION

An analysis of the different mechanism of action of each hemostatic agent may provide preliminary insight into the observed rates of AEs. ORC is an absorbable glucose polymer-based sterile powder that acts as a matrix for clot formation and as a clot stabilizer by forming a gelatinous mass once saturated with blood.¹⁴ Use of ORC causes a local acidity which interferes with the action of thrombin, suggesting its mechanism of action may be chemical or physical.²¹ The instructions for use of ORC do not mention if the product can be safely or effectively used in heparinized patients or those receiving antiplatelet therapy.¹⁴

PSP is an absorbable hemostatic powder derived from purified plant starch whose hydrophilic particles act as sieves concentrating platelets, red blood cells and blood proteins to form a gelled matrix.¹² There is no specific guidance regarding the safety or effectiveness of PSP in heparinized patients or those receiving antiplatelet therapy. Both ORC and PSP are categorized as passive hemostatic agents because they do not directly interact within the coagulation cascade and are dependent on the patient's intact coagulation cascade to work.²²

FSS is an active absorbable hemostat that contains both thrombin and fibrinogen in separate chambers of a dual syringe. These two agents comprise the final stage of the coagulation cascade.¹³ Thrombin and fibrinogen combine at the site of application converting fibrinogen into fibrin polymer, forming a stable clot.¹³ FSS also contains aprotinin, which increases resistance of the clot to

fibrinolytic degradation.^{23,24} Importantly, as it acts independently of the patient's coagulation cascade, FSS can be used in patients receiving anticoagulants or antiplatelet therapies.²⁵

It was observed that ORC is associated with higher AE rates compared with PSP and FSS in multiple anatomical categories. Notably, the number of infections reported for ORC was disproportionately higher compared with PSP and FSS. While in vitro data suggest that ORC has bactericidal properties,¹⁴ several nonrandomized clinical studies of ORC use reported postoperative hepatic or pelvic abscesses or infections^{26,27} or bowel obstruction.²⁸ Although ORC is believed to be absorbed within one to two weeks, there are reports of persistent material with similar products up to 15 months postoperatively.²³ Products with delayed absorption can serve as a potential nidus for infection, when not completely reabsorbed. ORC can also trigger a foreign-body reaction, leading to the formation of granulomas or abscesses.^{23,29,30} The absorption time is 24–48 hours and 10–14 days for PSP and FSS, respectively.^{12,13} Further, ORC lowers local pH, which can increase the inflammatory response and may potentially increase the risk of AEs.²⁴ In contrast, there is no indication that PSP or FSS lower local pH. Combined, these factors may support the observed high rates of adverse outcomes for ORC, with the majority requiring intervention or other unspecified outcome. None of these three surgical hemostats are indicated for use on a dry surgical bed.

Limitations of this study include the absence of demographic data on the patient population and the use of two distinct FDA databases with different ways of coding for AEs, limiting the scope for comparison. As AEs for the two passive hemostatic powders are reported in the MAUDE database, and AEs from FSS are reported in the FAERS database, inconsistencies may result from differences in the reporting platforms, how case reports are submitted, as well as the type of AEs. However, this analysis did include comparison of AEs for ORC and PSP, which showed higher proportion of AEs reported with ORC and specifically for infection. In addition, these databases do not reflect all known safety information for a given product and may be subject to under and over-reporting of events. An indication of the incidence of AEs associated with each of the three hemostatic agents was calculated using US-based utilization rates from the Premier Healthcare database. However, AEs reported to the MAUDE and FAERS databases are not restricted to the US possibly inflating calculated rates in this report. Furthermore, there is no certainty that events reported

were product-related, as the FDA does not require that a causal relationship between a product and event be proven, and not every AE that occurs with a product is reported to the FDA. Therefore, this data cannot be used to calculate the specific or complete incidence of an AE. The retrospective, observational data presented here is only potentially indicative and should be interpreted with care.

CONCLUSIONS

In conclusion, this retrospective analysis suggests that ORC use in pelvic and abdominal surgery may lead to increased AEs compared with non-ORC hemostatic agents. No causal relationship between use of these products in gynecologic surgeries and the occurrence of pelvic AEs can be established with the available data. Further prospective randomized studies are needed to explore the safety and suitability between ORC and non-ORC products in gynecologic surgeries.

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Appendix Table.

Alignment of Adverse Event Reporting Codes from the Manufacturer and User Facility Device Experience and Food and Drug Administration Adverse Event Reporting System Databases

Adverse Event Category	FAERS (MedDRA Codes) Reaction preferred term	MAUDE (MDR AE Codes) Patient problem description
Abdominal and pelvic		
Gastrointestinal	Adhesions; fistula; gastrointestinal anastomotic leak; gastrointestinal inflammation; intestinal obstruction; nausea; postoperative adhesion, scan with contrast abnormal	Abdominal pain; adhesions; failure to anastomose; fistula; injury; nausea; obstruction/occlusion; vomiting
Urologic	Neurogenic bladder; ureteric stenosis	Renal failure
Circulatory, lymphatic, and respiratory		
Blood/lymphatic	Coagulopathy; neutropenia; oedema; white blood cell count decreased	Anemia
Cardiovascular	Anaphylactic shock; blood pressure decreased; cardiac arrest; cardiogenic shock; embolism; pulmonary embolism; shock; thrombosis; venous thrombosis	Air embolism; airway obstruction; high blood pressure/ hypertension; low blood pressure/ hypotension; pulmonary embolism
Hemorrhage	Hemorrhage; skin hemorrhage; vaginal hemorrhage	Blood loss; hemorrhage/bleeding
Respiratory/thoracic	Dyspnea; obstructive airways disorder; pleural effusion; pneumothorax; tachypnoea	Airway obstruction; pleural effusion; pneumonia; pneumothorax; pulmonary edema; respiratory failure
Musculoskeletal and neurologic		
Musculoskeletal and connective tissue	Back pain; extra-skeletal ossification; fistula; spinal disorder	Cramp(s)
Neurologic	Cauda equina syndrome; cerebrospinal fistula; cerebrospinal fluid leakage; cerebrovascular accident; gait inability; hydrocephalus; memory impairment; meningitis chemical; monoparesis; muscular weakness; nervous system disorder; neurogenic bladder; paresis; pneumocephalus; post procedural stroke; sensory disturbance; thinking abnormal	Nerve damage; paralysis; paresis
Other complications		
Deep tissue/application site reaction	Application site granuloma; application site hematoma; application site necrosis; excessive granulation tissue; necrosis; procedural site reaction	Granuloma; hematoma; seroma; tissue damage
Dermatological/skin/wound problem	Dermatitis; impaired healing; injection site erythema; papule; pruritus; skin burning sensation; skin exfoliation; subcutaneous emphysema; wound	Burn(s); erythema; impaired healing; skin discoloration; wound dehiscence
General/inflammatory/allergic conditions	Adverse drug reaction; adverse event; anastomotic leak; angioedema; application site reaction; asthenia; autoimmune disorder; condition aggravated; disease complication; drug hypersensitivity; drug ineffective; general physical health deterioration; hypersensitivity; pain; post procedural complication;	Bruise/contusion; Fever; hypersensitivity/allergic reaction; inflammation; irritation; local reaction; pain; rash; reaction; skin irritation; swelling; urticaria; swelling/edema

Appendix Table. Continued

Adverse Event Category	FAERS (MedDRA Codes) Reaction preferred term	MAUDE (MDR AE Codes) Patient problem description
Infection	pyrexia; rash; swelling; tissue injury; urticaria; vulvovaginal inflammation Abscess; abscess neck; application site infection; Escherichia infection; infection; post procedural infection; postoperative wound infection; subdural empyema	Abscess; bacterial infection; cellulitis; sepsis; unspecified infection
Ocular	Conjunctival hyperemia; lacrimation increased; periorbital oedema	
Death	Death	Death
Other		
Insufficient data	No corresponding MedDRA code	No information; not applicable
No code available	No corresponding MedDRA code	No code available
Product Administration/quality	Device malfunction; device use error; drug administration error; incorrect dose administered; off label use; poor quality drug administered; product quality issue; product use in unapproved indication; product use issue	Foreign body in patient; device embedded in tissue or plaque; no consequences or impact to patient

Abbreviations: FAERS, Food and Drug Administration Adverse Event Reporting System; MAUDE, Manufacturer and User Facility Device Experience; MDR, medical device reporting; MedDRA, Medical Dictionary Regulatory Activities.