CASE REPORT

Intraoperative Anaphylactic Reaction: Is it the Floseal?

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When hemodynamic or respiratory instability occurs intraoperatively, the inciting event must be determined so that a therapeutic plan can be provided to ensure patient safety. Although generally uncommon, one cause of cardiorespiratory instability is anaphylactic reactions. During anesthetic care, these most commonly involve neuromuscular blocking agents, antibiotics, or latex. Floseal is a topical hemostatic agent that is frequently used during orthopedic surgical procedures to augment local coagulation function and limit intraoperative blood loss. As these products are derived from human thrombin, animal collagen, and animal gelatin, allergic phenomenon may occur following their administration. We present 2 pediatric patients undergoing posterior spinal fusion who developed intraoperative hemodynamic and respiratory instability following use of the topical hemostatic agent, Floseal. Previous reports of such reactions are reviewed, and the perioperative care of patients with intraoperative anaphylaxis is discussed.

INDEX TERMS: adverse drug reaction, anaphylaxis, coagulation, Floseal, hemostatic agent, topical

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INTRODUCTION

In an effort to limit the need for allogeneic blood products, there is an expanding armamentarium of topical anticoagulants and hemostatic agents to promote coagulation function and minimize intraoperative blood loss. While generally safe and effective, these products are derived from human thrombin, animal collagen, and animal gelatin.^{1–4} Although systemic responses to these products are uncommon and have not been widely reported, given their antigenicity, this possibility should be considered when intraoperative instability occurs. We present 2 pediatric patients undergoing posterior spinal fusion (PSF) who developed intraoperative hemodynamic and respiratory instability following use of the topical hemostatic agent, Floseal (Baxter Healthcare, Hayward, CA). Anaphylaxis can generally be divided into immune (anaphylaxis) versus non-immune (anaphylactoid). The differences between these will be defined. The potential perioperative implications of such problems are

discussed, previous reports reviewed, and treatment as well as preventative strategies suggested.

CASE REPORT

Institutional review board approval at Nationwide Children's Hospital (Columbus, OH) is not required for case reports involving no more than 2 patients.

Case 1

The patient was a 13-year-old adolescent with past medical history of idiopathic scoliosis, asthma, and a motor vehicle accident over 1 year prior with resultant moderate-severe traumatic brain injury and concurrent frontal skull, sinus, and tibial fractures status post repair. The patient was scheduled for PSF from the second vertebra in the thoracic spine to the third vertebra in the lumbar spine (T2–L3) for progressive idiopathic scoliosis. The patient was held nothing by mouth for 8 hours and brought to the operating room where standard American Society of Anesthesi-

ologists monitors were placed. Anesthesia was induced with sevoflurane in oxygen followed by the placement of 2 peripheral 16-gauge intravenous cannulae and a 20-gauge radial arterial cannula. The patient was placed into the prone position and surgery was started. Maintenance anesthesia included desflurane titrated to maintain the bispectral index at 50-60 and a remifentanyl infusion titrated up to 0.3 mcg/kg/min to maintain the mean arterial pressure (MAP) at 50 to 65 mmHg. Surgical dissection down to the lamina was uncomplicated. After placement of bilateral pedicle screws from the 12 vertebra in the thoracic spine to the third vertebra in the lumbar spine (T12-L3), minimal expected bleeding was noted. There was a mild decrease in blood pressure (BP) and a 5% albumin infusion was initiated for volume resuscitation. Floseal (Baxter Healthcare) was placed at the site of the pedicle screws to achieve hemostasis.

Within seconds, lung compliance was noted to be decreased as the peak airway pressures increased to 35 to 40 cmH₂O and the MAP decreased to 40 mmHg. Tachycardia and an increase in end-tidal CO₂ were noted with an obvious decrease in respiratory compliance and increase in resistance. Upon auscultation, the patient had limited air exchange. Bronchospasm was suspected as well as a possible anaphylactic reaction. Phenylephrine boluses for total dose of 250 mcg, epinephrine boluses for total dose of 30 mcg, albuterol metered dose inhaler (MDI), dexamethasone 12 mg, and hydrocortisone 50 mg were administered. There was prompt relief of bronchospasm and an increase in the BP after epinephrine. Within 2 to 3 minutes following the epinephrine bolus, the bronchospasm and hypotension recurred. Two to 3 additional bolus doses of epinephrine totaling 20 mcg were administered until the patient's clinical status stabilized. The chest radiograph was negative for pneumothorax or other acute changes. The decision was made to abort the surgical procedure. The pedicle screws were removed, and the surgical incision was closed. No hives, rash, or angioedema were noted in the operating room. As the patient's cardiorespiratory status had stabilized, his trachea was extubated. He was transferred to the pediatric intensive care unit for further monitoring.

In exploring the potential etiologic factors for the intraoperative event other than the acute administration of Floseal, it was noted that cefazolin

had been administered 3 hours prior to the event and rocuronium 1 hour prior to decompensation. Given the prolonged time between these administrations and patient decompensation, the antibiotic and neuromuscular blocking agent were deemed unlikely culprits. The family denied any prior history of anaphylaxis or food allergies. A tryptase level obtained within 1 hour of the event was elevated at 20.5 mcg /L (normal $\leq$ 10 mcg /L). Serum testing for latex as well as bovine and porcine gelatin immunoglobulin E (IgE) testing was negative. The patient returned to the operating room 7 days later, and the PSF was performed without incident. He was pre-treated with diphenhydramine, ranitidine, and hydrocortisone. Given the previous anaphylactic reaction, rocuronium, albumin, and Floseal were not administered. The case proceeded without incident, and the surgical procedure was completed. The patient's postoperative course was unremarkable.

Case 2

The patient was a 12-year-old, 42 kg female with congenital scoliosis and a complex past medical history significant for anal atresia, cardiac defects, tracheoesophageal fistula and/or esophageal atresia, and renal and radial anomalies and limb defects. She had an imperforate anus status postrepair, tethered cord status postrelease, eosinophilic esophagitis, sensorineural hearing loss with cochlear implants, stage 3 chronic kidney disease with ureterostomies, developmental delay, and gastric tube placement.

She presented for PSF due to progressive neuromuscular scoliosis. Allergies included milk, eggs, codeine, and "red man syndrome" with previous vancomycin infusions. Oral midazolam was administered preoperatively for anxiolysis. Once in the operating room, an inhalation induction was performed with sevoflurane, 2 large bore peripheral intravenous cannulas and a 20-gauge left radial arterial cannula were placed. Endotracheal intubation was facilitated with rocuronium (0.3 mg/kg).

Maintenance anesthesia included desflurane titrated to maintain the BIS at 50-60 and a remifentanyl infusion titrated up to 0.3 mcg/kg/min to maintain the MAP at 50 to 65 mmHg. The patient was then placed into the prone position. Single doses of gentamicin 88 mg and clindamycin 700 mg were administered for surgical site

prophylaxis. Incision of the posterior aspect of the spinous process was performed with subperiosteal elevation of the lateral aspect of the spinous process; however, there was difficulty exposing the lumbar portion during this process given the history of previous surgical correction of tethered cord release.

At approximately 3 hours into the case, it was noted that the patient's BP had been decreasing given the ongoing blood loss. Transfusion with a unit of directed-donor blood was started. Pedicle screws were then placed at the L4 pedicles bilaterally and a single screw at L3 when significant hemodynamic instability occurred. There was tachycardia with the MAP decreasing to 30 to 40 mmHg. There was also difficulty with ventilation with increased resistance and decreased compliance with peak inspiratory pressures increasing above 40 cmH₂O. The blood transfusion was stopped, the inhalation anesthetic agent (desflurane) reduced, the inspired oxygen concentration increased to 100%, and manual ventilation provided. Although the MAP increased momentarily following phenylephrine boluses (2-3 mcg/kg), the response quickly became less significant. The likelihood of pneumothorax was discussed and ultimately deemed unlikely given dissection at the lumbar level. However, the surgeons noted that they had placed Floseal at site of the pedicle screws. Transfusion reaction versus anaphylaxis given the recent administration of Floseal was entertained as likely etiologic events. With ongoing hypotension and ventilation difficulties, albuterol MDI and intravenous epinephrine boluses (10 mcg) were administered. Ventilation improved immediately with epinephrine boluses; however, there was only marginal improvement in BP. Calcium chloride was administered and an epinephrine infusion started at 0.04 mcg/kg/min.

The decision was made to abort case, the surgical instrumentation was removed, the incision was closed, and the patient turned to the supine position. Given the continued requirement of an epinephrine infusion, a central line was placed in the right internal jugular. Medications administered during the resuscitative efforts included phenylephrine total dose of 4300 mcg, epinephrine boluses total dose of 90 mcg, albuterol MDI, calcium chloride 100 mg, and an epinephrine infusion at 0.04 mcg/kg/hr. There was no change in the neurophysiological monitoring during the event. No overt rash was noted when the

surgical drapes were removed and the urine was normal in color. The patient was transferred to the pediatric intensive care unit with an ongoing epinephrine infusion. The epinephrine infusion was rapidly weaned and her trachea was extubated postoperatively within 2 to 3 hours.

Immunological studies revealed an elevated bovine gelatin IgE at 1.33 kU/L (normal < 0.35 kU/L) and an elevated porcine gelatin IgE at 5.95 kU/L (normal < 0.35 95 kU/L). The tryptase level, obtained 20 to 30 minutes after the onset of symptoms, was 3.1 mcg/L (normal ≤ 10 mcg/L). History elicited from parents was significant for several allergic reactions in the past that included milk and egg allergy as well as a large local reaction of arm swelling in response to vaccinations, which were gelatin containing. Laboratory evaluation was negative for a positive transfusion reaction and culture of the unit of blood was negative. The patient was eventually taken to the operating room 14 days later. Given the previous anaphylactic reaction, rocuronium and Floseal were avoided. Albumin was administered and no patient instability was noted. The case proceeded without incident, and the surgical procedure was completed. The patient's postoperative course was unremarkable.

DISCUSSION

In an effort to decrease intraoperative bleeding and the use of allogeneic blood products, there has been an expanding use of topical hemostatic agents such as sealants and adhesives. These products may be derived from human thrombin, animal collagen, and animal gelatin.¹⁻³ Floseal is a hemostatic agent composed of human plasma thrombin in combination with bovine gelatin.⁴ The 2 products are combined in a granular hemostatic agent that uses both active (coagulant) and mechanical components to achieve hemostasis. Floseal is approved for the treatment of bleeding in all types of surgical procedures except for ophthalmologic cases.⁴ Although rare, potential safety concerns include the transmission of blood borne viruses, swelling of the product that may lead to tissue compression if used within a confined space, as well as the potential for anaphylactic and anaphylactoid reactions in patients sensitive to bovine products. In addition to Floseal, other commonly used intraoperative agents that contain animal gelatin include

Gelfoam (Pfizer, New York, NY) and SurgiFlo (Ethicon, Somerville, NJ).

Although rare, significant physiologic disturbances may result from perioperative anaphylaxis and anaphylactoid reactions with cardiac arrest occurring in up to 10% of cases. Estimated incidences in the adult population range from 1:10,000 to 1:15,000 with a higher incidence reported in women.⁵ Anaphylaxis can generally be divided into immune (anaphylaxis) versus non-immune (anaphylactoid). Immune anaphylaxis is a type 1 allergic reaction that is mediated by IgE, IgG, and immune complex/complement.⁶ IgE-mediated anaphylaxis is a hypersensitivity systemic reaction with release of pro-inflammatory mediators from mast cells and basophiles.⁷ Mast cell degranulation can be triggered by several events including binding of the antigen to IgE molecules on the surface of cells. With mast cell degranulation, preformed substances are released including histamine, tryptases, cytokines, prostaglandin D₂, leukotrienes, thromboxane A₂, and platelet activating factor.⁷ These factors produce effects on target organs including the skin, mucosa, gastrointestinal, respiratory, and cardiovascular systems. IgE mediated type drug anaphylaxis does not require prior exposure to the triggering agent as sensitivity can occur with cross-reactivity alone.⁸

Non-immunologically mediated reactions that appear similar in symptomatology are classified as “non-immune” or “anaphylactoid” reactions.^{9,10} The difference between immune and non-immune anaphylaxis is significant since the latter cannot be detected with skin prick test or *in vitro* immunoglobulin testing. Furthermore, immune-mediated hypersensitivity precludes future administration without consideration for a desensitization procedure, whereas non-immune mediated mechanisms may not occur with subsequent exposure. IgE testing was noted to be negative in the first case while the tryptase levels were noted to be elevated. This was likely an anaphylactic type reaction. However, it should be noted that IgE testing is not 100% sensitive. The second case demonstrated positive IgE testing to bovine and porcine collagen in accordance with an anaphylactic type reaction. The tryptase level was not noted to be elevated; however, the blood sample was likely drawn too early prior to when the level peaked.

In the perioperative setting traditionally the

most common triggering agents for anaphylaxis are neuromuscular blocking agents (succinylcholine and rocuronium), followed by antibiotics and latex.^{5,8,9} However, when topical hemostatic agents have been used, the etiologic differential should be expanded to include animal collagen and gelatin. Though antibiotics and neuromuscular blocking agents were administered in both of our cases, the administration of these medications was performed long before patient decompensation was noted. Floseal was administered seconds before symptoms occurred in both of our cases. Although gelatin allergy has been widely reported in type 1 hypersensitivity reactions to vaccines that contain gelatin as a stabilizer, it has been less frequently reported in the context of surgical hemostatic agents.

Four previous reports of anaphylactic and anaphylactoid reactions to topical hemostatic agents (Floseal and SurgiFlo) are outlined in the Table.¹¹⁻¹⁴ An additional report outlines 3 patients who experienced a possible allergic response to Floseal with the formation of excessive granulation tissue and fibrosis that were associated with early postoperative pelvic pain, requiring additional surgical intervention.¹⁵ In comparison of the case reports outlined in the Table, it may be noted that all 5 of the patients described were undergoing major orthopedic spinal surgery. Four of the patients were pediatric scoliosis repairs and 1 was a 72-year-old undergoing spinal fusion. Of the 4 pediatric patients described, each anaphylactic event occurred after administration of Floseal or in 1 case SurgiFlo to bleeding screw holes in parallel to both our cases. The symptoms in all cases included drops in MAP, tachycardia, and difficulty in ventilation with abrupt increases in mean airway pressures. It may be noted that only 1 patient demonstrated rash. Though combinations of medications were utilized in the resuscitative efforts, all patients described ultimately improved with epinephrine administration. The case of the 72-year-old man undergoing spinal fusion was unique in that symptomatology was noted once the Floseal containing cell saver was administered back to the patient.¹⁴ As with 1 of our patients, 2 of the pediatric patients described had previous reactions to gelatin containing MMR vaccines and 1 patient developed an allergy to gelatin containing vaccines postsurgically. As with 1 of our patients, 3 of the 4 pediatric patients all had a history of

Table. Previous Reports of Hypersensitivity Reactions to Floseal

Reference	Patient Demographics	Intraoperative Problems and Management
Spencer et al ¹¹	14-year-old male with myelomeningocele, asthma, and scoliosis for anterior spinal fusion T12-L3	Gelfoam sponges were applied during preparation of the disc space. Approximately 1 hr later, Floseal matrix was applied to a briskly bleeding screw hole in the L3 vertebral body. The abrupt onset of hypotension and ventilation difficulty was noted. Epinephrine, dexamethasone, and blood products were administered for hemodynamic support while the surgical site was closed. Removal of the drapes revealed a widespread erythematous rash. Postoperative assays showed elevated levels of tryptase, total IgE, as well as porcine and bovine gelatin specific IgE.
Luhmann et al ¹²	11-year-old female with idiopathic scoliosis and asthma for posterior spinal fusion 9-year-old female with idiopathic scoliosis undergoing spinal surgery	During the placement of a pedicle screw, Floseal was applied. There was profound hypotension, tachycardia, and elevated airway pressures requiring intravenous epinephrine and phenylephrine for hemodynamic support. Postoperative workup was positive for antibodies toward bovine gelatin. Further history revealed allergy to blue suckers, blue Jell-O, or blue cake frosting. Postoperatively, patient developed allergy to Tdap booster though previously had no allergies to vaccines. SurgiFlo was placed into 2 pedicle tracts after which there was profound hypotension, tachycardia, and elevated airway pressures. Resuscitative efforts included intravenous atropine, epinephrine, and CPR. Surgery was aborted and repeated uneventfully 2 wk later without the use of SurgiFlo. Immunological testing was positive for porcine gelatin allergy.
Agarwal et al ¹³	9-year-old male with Marden Walker syndrome, asthma, tuna, and salmon allergy undergoing removal of spinal instrumentation for kyphosis	Sixty minutes into the procedure, Floseal was injected into the pedicle screw holes. Within minutes, the patient became tachycardic with an increase from baseline of 80 beats/min to 105 beats/min, and hypotensive with mean arterial pressure from 75 mm/Hg to 45 mm/Hg. Resuscitative efforts included epinephrine boluses, CPR for 1min, albuterol, and eventually infusions of epinephrine and vasopressin. No rash was noted. Immunologic workup yielded elevated tryptase 1 hr postevent and elevated IgE to bovine gelatin. Further history yielded anaphylaxis to MMR vaccine as well as a similar episode during a spinal operation 8 yr prior in which Floseal was utilized.
Kumar et al ¹⁴	72-year-old man undergoing placement of pedicle screws and lumbar spine fusion	Floseal used for hemostasis toward the end of surgery. Cell saver was also used intraoperatively. Although previous administration of salvaged blood resulted in no problems, the administration of cell saver blood after the use of Floseal resulted in hypotension. Erythematous rash and facial edema also noted. The authors postulate that the gelatin that was retrieved by the cell saver and reinfused was the cause of the intraoperative anaphylaxis.

CPR, cardiopulmonary resuscitation; IgE, immunoglobulin E; L, lumbar spine; Tdap, Tetanus, Diphtheria, Pertussis

asthma. All pediatric patients described had immunological workups that were positive for either porcine or bovine allergy or both.¹¹⁻¹³

The clinical presentation of anaphylaxis is variable between patients and even episodes within the same patient. Presentation under general anesthesia is often masked and may be confused with myocardial depression from an excessive depth of anesthesia, hypovolemia, or sympathectomy associated with neuraxial blockade. Anaphylaxis may occur at any time during anesthetic care and may progress slowly or rapidly.^{6,8} Ninety percent of reactions appear within minutes of administration of the triggering agent as was noted with both of our patients. The most common presenting signs relate to the cardiovascular system (hypotension) and the respiratory system (bronchospasm).^{16,17} Cutaneous reactions with rash and urticaria are less commonly reported during perioperative anaphylaxis. However, this may be related to the patient being covered under sterile drapes used for surgical procedures. Cutaneous symptoms may be more apparent in anaphylactoid reactions, whereas bronchospasm and cardiovascular collapse are more apparent in anaphylaxis.⁹

Identification of the problem is mainly performed clinically in the intraoperative setting. Blood tests should be sent at the time of the event if anaphylaxis is suspected. Laboratory investigation should include a tryptase level, obtained within 1 to 4 hours of symptom onset. Plasma histamine levels may aid in the diagnosis, but peak early, approximately 15 minutes after the onset of reaction and return to normal within 60 minutes. If exposure to a gelatin-containing agent occurred, then bovine and porcine serum specific IgE levels should be obtained. However, as noted in our patients, none are completely sensitive or specific as the IgE to gelatin was positive in 1 of our patients while the serum tryptase was elevated in the other.^{10,16,18} Tryptase is a mast cell tetrameric neutral serine protease that exists in 2 forms. Plasma levels increase within 30 minutes of the event, but are highest 60 to 120 minutes after the onset of symptoms.^{17,18} In our second patient, given our experience with the first patient, the tryptase level was drawn within 20 minutes of the start of the event, which was likely too early. Serum tryptase has a half-life of approximately 120 minutes and the levels return to baseline in 24 hours.¹⁰ Other *in vivo* testing that can

be performed includes skin prick testing. These should be performed 4 to 6 weeks after the event because of mast cell and basophil mediator cell depletion. These are performed by introducing 0.2 to 0.3 mL of the presumed provocative agent intradermally with the elicitation of a response from the deeper mast cell population. A positive test has a high positive predictive value in the setting of a positive history.¹⁶ Other than penicillin, skin prick testing is not commercially available or validated for the majority of medications used in the perioperative setting. A method for estimating the probability of adverse drug reactions was developed by Naranjo et al²² in 1981. The algorithm divides reactions into definite, probable, possible, or doubtful. Both of our cases scored a 5 falling into the category of probable adverse drug reaction.

Treatment, though weight adjusted, remains the same for all ages and consist of identification with immediate elimination of the inciting agent and general resuscitation based on end-organ involvement.⁶ This includes the use of epinephrine and volume resuscitation to support hemodynamic function. Epinephrine is first-line medical therapy for all cases of anaphylaxis, regardless of the cause, as it can treat and reverse all signs and symptoms associated with anaphylaxis.¹⁹ Albuterol administered using a MDI and intravenous epinephrine are used to improve respiratory compliance and resistance. As was noted in our patients, hemodynamic instability may be resistant to phenylephrine while bronchospasm may be resistant to routine treatments such as albuterol. In refractory cases, an epinephrine infusion may be required to stabilize hemodynamic and respiratory function. Additional care may include the administration of corticosteroids as well as H₁ and H₂ antagonists (ranitidine and diphenhydramine) although their efficacy in acute anaphylactic reactions has not been systematically studied.^{18,19} Corticosteroids, in particular, offer no benefit in the acute management of anaphylaxis given their delayed onset and should not be administered as first-line therapy.

Our cases and those from the literature demonstrate that when anaphylaxis is encountered in the perioperative setting, animal gelatin-containing products such as the agent Floseal should be considered as an inciting trigger and eliminated. Preventive strategies include a thorough preoperative history of past aller-

gies to alert the anesthesia provider to potential sensitivity to bovine or porcine gelatin. These include allergies to gelatin containing vaccines (mumps-measles-rubella), and food allergies to gelatin containing food products such as Jell-O and gummy candies. A potential association has also been suggested in children with milk and meat allergies, although the clinical relevance has not been fully elucidated.²¹ Identification of the problem through *in vivo* testing of tryptase and IgE levels following the event as well as skin prick testing may help support the diagnosis. Furthermore, when intraoperative problems occur, communication between surgical and anesthetic teams is imperative to identify these products as the potential inciting factor.

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Abbreviations BP, blood pressure; IgE, immunoglobulin E; L, lumbar spine; MAP, mean arterial pressure; MDI, metered dose inhaler; PSF, posterior spinal fusion; T, thoracic spine

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