

Review of topical gelatin-based haemostatic agents; an insidious culprit of intraoperative anaphylaxis?

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Abstract

Background: An under-recognized complication of gelatin-based haemostatic agents is their potential to cause anaphylactic reactions. This review aims to collate and analyse case in the literature of intraoperative anaphylaxis secondary to locally applied haemostatic agents.

Methods: An electronic search was performed on databases Medline, Embase, Pubmed and ProQuest. A total of 7671 articles were reviewed from title and abstract. After exclusion criteria and duplicates removed, 19 articles with 21 cases were included for analysis. Data extracted from each of the articles included patient demographics, haemostatic agent used, surgery type, known allergies and any objective evidence of hypersensitivity post anaphylactic episode, that is tryptase levels, IgE levels, skin prick testing.

Results: Fifty-seven percent of cases involved patients <18 years of age; 57% of cases involved spinal surgery; 100% of cases displayed objective evidence of hypersensitivity (tryptase levels, bovine or porcine IgE levels, or skin prick testing). Thirty-three percent of patients had exposure preoperatively to a known agent causing anaphylaxis or allergy which would preclude the use of a gelatin-based haemostat. These products included vaccines, spam meats, red meat, Jell-O and CollaPlug. Gelatin-based haemostat agents included Floseal, Gelfoam, Surgiflo, fibrin glue, Avitene, haemofibrine sponge, topical bovine thrombin and thrombin-soaked gelatin.

Conclusion: Increased awareness of allergy to gelatin-based haemostats for surgical and anaesthetic is imperative, with 33% of cases having a known contraindication to gelatin-based haemostat. This review highlights important aspects in the pre-operative patient history and post-event patient investigation that could assist anaesthetists and surgeons in the prevention of future events.

Introduction

Minimization of blood loss is an imperative surgical principle, with numerous tools at the disposal of the surgeon including ligation, pressure, diathermy, ultrasound, laser, topical haemostats and systemic haemostats. This is pivotal as intraoperative blood loss requiring transfusion has been shown to increase the post-operative risk of sepsis, pneumonia and 30-day mortality in general surgery patients.¹ Other immediate benefits of minimizing blood loss include clear surgical view and reduced operating times. Topical haemostatic agents composed of porcine gelatin and lyophilised

human thrombin are modern surgical adjuncts utilized to minimize intraoperative blood loss.² The first gelatin-based haemostat was used in 1940s,³ and has been a theatre staple with ease of use, accessibility and effectiveness. However, there have been rare reports of hypersensitivity reactions^{4–22} (Table 1).

This review aims to summarize the literature of an uncommon complication to an everyday surgical adjunct. Intraoperative hypersensitivity has been reported to occur in 1 in 677 cases,²³ with patients receiving a myriad of anaesthetic, fluids, antibiotics, blood products and exposure to latex rubber, it can be difficult to identify a culprit. Most of these products are given by the anaesthetic staff;

Table 1 Summary of literature for intraoperative anaphylaxis secondary to a gelatin-based topical haemostat

Authors	Age	Type of surgery	Haemostatic agent	Gelatin allergy preoperatively	Tryptase	IgE	Skin prick testing
Bordes <i>et al.</i> 2016	13	Posterior spinal fusion	FloSeal	—	Elevated	Negative porcine IgE	N/A
Bordes <i>et al.</i> 2016	12	Posterior spinal fusion	FloSeal	—	Normal	Elevated bovine gelatine and porcine IgE	N/A
Espinell <i>et al.</i> 2018	16	Posterior spinal fusion	Surgiflo	Gelatin-containing vaccines	Elevated	N/A	N/A
Lied <i>et al.</i> 2019	71	Atrial septal defect repair	Surgiflo	Red meat	Normal	Elevated alpha-1,3-galactose IgE	Positive gelatin
Luhman <i>et al.</i> 2013	11	Posterior spinal fusion	FloSeal	Jell-O + gelatin containing vaccines	N/A	Elevated bovine gelatin IgE	N/A
Luhman <i>et al.</i> 2013	9	Posterior spinal fusion	Surgiflo	—	N/A	Elevated porcine IgE	N/A
Khoriaty <i>et al.</i> 2012	2.5	Spinal cord repair	Gelfoam	Spam meat	NA	Elevated porcine IgE	Positive gelatin
Joonyoung <i>et al.</i> 2015	2	Dental rehabilitation	Gelfoam	—	NA	NA	Positive Gelfoam
Robbins <i>et al.</i> 2015	10	Liver biopsy	Gelfoam	—	Elevated	Elevated bovine gelatine and porcine IgE	NA
Agarwal <i>et al.</i> 2015	9	Segmental spinal instrumentation	FloSeal	Gelatin containing vaccines	Elevated	Elevated bovine gelatine and porcine IgE	NA
Spencer <i>et al.</i> 2012	14	Anterior spinal fusion	Gelfoam, FloSeal	—	Elevated	Elevated bovine gelatine and porcine IgE	NA
Woodruff <i>et al.</i> 2014	10	Alveolar cleft bone repair	Avitene	CollaPlug	N/A	N/A	N/A
McDonald 2019	N/A	Liver biopsy	Gelfoam	—	N/A	N/A	N/A
Raveendran 2017	12	Posterior spinal fusion	FloSeal	Large cutaneous reaction to gelatin containing vaccine	N/A	Elevated porcine and bovine IgE	N/A
Oswald <i>et al.</i> 2003	52	Lumbar disc herniation surgery	Fibrin glue	—	Elevated	Elevated antiaprotinin IgE	N/A
Milde 1989	57	Closure bronchopleural fistula	Fibrin glue	—	N/A	NA	NA
Wuthrich <i>et al.</i> 1996	54	Tooth extraction	Haemofibrine sponge	—	N/A	Elevated bovine IgE	NA
Kitamura 1995	55	Laparoscopic cholecystectomy	Avitene	—	N/A	N/A	Positive Avitene
Mitsuhashi <i>et al.</i> 1994	67	Lobectomy	Fibrin glue	—	Elevated	N/A	N/A
Rothenberg 1993	51	Decompressive lumbar laminectomy	Topical bovine thrombin	—	Elevated	N/A	Positive thrombostat
Park <i>et al.</i> 2018	38	Cervical discectomy	Thrombin soaked gelatin	—	N/A	Elevated porcine and bovine IgE	Positive bovine thrombin

N/A, not applicable.

however, topical haemostatic agents at the hands of the surgeon have been reported in the literature to cause hypersensitivity reactions. This article focuses on topical haemostatic agents use, mechanism, complications and role in hypersensitivity reactions. It is pertinent for surgical and anaesthetic staff to be aware of this common surgical tool, as it can lead to the early recognition and management of a patient displaying evidence of anaphylaxis.

Methods

Databases searched included PubMed, Ovid Medline, Embase and ProQuest. The titles and abstracts of articles were analysed to increase effectiveness of the literature search. The final search returned 7671 articles. Precise inclusion and exclusion criteria were

set as to answer the specific research subject of intraoperative anaphylaxis to topical gelatin-based haemostatic agents. The majority of articles were excluded by title or abstract as they related to atopic allergy toward gelatin-based fluids, vaccinations or meat.

Inclusion criteria

Articles describing intraoperative atopic allergy or anaphylaxis to locally applied gelatin-based haemostatic agents.

Exclusion criteria

Articles that were not published in English and were letters, conference papers or editorials. No date criteria were set, as intraoperative gelatin-based haemostatic agents were first introduced in 1940.

Articles relating to vaccines, colloid fluids and meat were excluded. Anaphylaxis that was not intraoperative was excluded.

Data extraction

Selected studies were read in full by the corresponding author, with patient demographics, surgery type, specific haemostatic agent applied, previous allergy to gelatin products and evidence of hypersensitivity; tryptase, IgE and skin prick testing.

Results

Nineteen articles were identified for inclusion in the study consisting of 21 cases of intraoperative anaphylaxis. There were two cases series, one single centre prospective cohort study and 16 case reports.

Ages ranged from 2 to 71 with 57% of cases involving children (<18 years of age); 57% of cases involved spinal surgery. All operations included in the study can be seen in Table 1. Hundred percent of cases displayed objective evidence of anaphylaxis or hypersensitivity with either elevated tryptase levels, bovine or porcine IgE levels, or skin prick testing.

Thirty-three percent of cases had exposure preoperatively to a known agent causing anaphylaxis or allergy, which would preclude the use of a gelatin-based haemostat. Identified agents included vaccines, jell-O, red meat, spam and previous haemostat agent (CollaPlug (Zimmer Biomet, Warsaw, IN, USA)). Five cases involved Floseal (F, Baxter BioSurgery, Vienna, Austria), four cases of Gelfoam (Pfizer, New York, NY, USA), three cases involved Surgiflo (Johnson & Johnson Wound Management, Somerville, NJ, USA), three cases involved fibrin glue (unspecified pharmaceutical), two cases involved Avitene (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), one case involved a haemofibrine sponge (unspecified pharmaceutical), one case involved topical bovine thrombin (unspecified pharmaceutical) and one case involved thrombin soaked gelatin (unspecified pharmaceutical).

Discussion

To the best of authors knowledge, there are 21 documented cases of intraoperative hypersensitivity to gelatin containing topical haemostat agents (Table 1). This review aims to bring awareness to surgeons and anaesthetic staff, and illustrate the mechanism of haemostats, their role in anaphylaxis, anaphylactoid reactions, intraoperative haemodynamic compromise and the alternatives available.

The physiology of haemostasis is a well-studied and understood the concept, with Virchow's triad being an integral component of a surgeons training.²⁴ It is a complex interplay of numerous factors including platelets, clotting factors, the blood vessel wall and blood pressure control. The detailed mechanism of the clotting cascade is beyond the scope of this article; however, when a vessel is damaged during surgery, platelets provide a primary haemostasis, with secondary haemostasis coming from intrinsic and extrinsic clotting cascades. Secondary haemostasis results in an insoluble fibrin

meshwork via the conversion of prothrombin to thrombin.²⁵ Gelatin containing haemostatic agents are saturated with purified thrombin and come in different forms including sponge and liquid.³ When applied to a bleeding surgical site thrombin actively participates in the coagulation cascade to form a fibrin clot, whereas the gelatin portion acts as a mechanical haemostat as it swells, causing a tamponade, with the secondary benefits of platelet activation and aggregation.²⁶

While gelatin-based haemostats are beneficial at achieving haemostasis without need for suture, ligature or cautery, it is not without risk. Gelatin haemostats contain biological derivatives of human and animal products with the potential to cause immune-related complications. Gelatin is an animal product; a denatured protein synthesized from boiled bovine or porcine skin, horns and/or hoofs.²⁷ Gelatin allergy is a contraindication to gelatin-based haemostatic agents; however, there is concern regarding physician awareness of individual components of haemostatic agents with protein derivatives.²⁸ This is evidenced in this study with 33% of cases having a pre-identified reaction to gelatin containing products.

There is a paucity of published cases in the literature of anaphylaxis and hypersensitivity to gelatin containing products, however it is unclear if this is due to the rarity, or if this is an under recognized allergy, with events being labelled idiopathic. Other examples or gelatin-based compounds documented as causing allergic reactions include shampoos with hydrolysed proteins, collagen body implants, catgut sutures, collagen-based lenses, vaccines, jelly and gummy candy and medications.²⁹ Despite being a recognized allergen, its knowledge among surgery is minimal, with its activity dependent on type, processing, chemical characteristics and dosage.¹⁷

This review brings light to gelatin-based haemostats as an under recognized cause of intraoperative anaphylaxis. In the operating theatre the identification of a singular agent, or multiple, deemed as the cause of anaphylaxis can be difficult, or may not be found. This is due variety of different drugs given in succession over a varied timeline, with additional exposures of colloid fluids, blood products and exposures to surgical staff latex gloves. The diagnosis can additionally be confounded by the immunological and non-immunological reactions with unclear mechanistic pathology.³⁰ The issue without identifying a clear agent is the lack of diagnosis may lead to re-exposure in subsequent operations, the seriousness of an event established by mortality rates reaching as high as 4.3% anaphylactic deaths under general anaesthesia.³¹ In the perioperative setting, the traditional factors eliciting an anaphylaxis or immune-mediated event include neuromuscular blocking agents, antibiotics and latex.³² The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) provide a perioperative anaphylaxis investigation guideline which covers common precipitants and tests, however, does not have recommendations for testing for topical haemostat agents,³³ which likely represents the rarity in reactions. The guidelines suggest colloid fluids containing gelatin can be tested for, however if a patient did not receive this compound, but received a gelatin haemostat, a gelatin-based anaphylaxis may go undiagnosed. It would be worthwhile for patients who have undergone intraoperative haemodynamic compromise to be followed up

with standard skin prick testing for common compounds, but to also undergo either IgE or skin prick testing for bovine or porcine gelatin.

It is valuable discussion to differentiate anaphylaxis from other sequelae of topical haemostats, as not all intraoperative haemodynamic compromise is immune mediated. Anaphylaxis is an IgE-mediated type I hypersensitivity reaction with systemic release of pro-inflammatory mediators including histamine, tryptase, cytokines and prostaglandins. However, authors note that tryptase levels are not 100% sensitive,³⁴ with plasma levels peaking at 60–120 min post event,²² allowing for insignificant results if taken prematurely or late, and IgE sensitivity ranging from 60% to 95%.³⁵ It typically occurs on secondary exposure with a specific antigen, however, has been reported to occur on primary exposure due to cross reactivity among many products. Typical signs include flushing, pruritis, angioedema, bronchoconstriction, vomiting, diarrhoea, tachycardia, hypotension and shock. The difficulty of surgery being patients are draped, not allowing for early recognition of cutaneous changes, and due to general anaesthesia patients cannot report their discomfort.³⁶ This means patients may not have their anaphylaxis recognized till late in the course. The degree of severity of anaphylaxis presentations varies and does not allow for differentiation between anaphylactoid responses. These responses are characterized by medication intolerances, idiosyncratic reactions and pseudo allergy. Anaphylactoid reactions are clinically indistinguishable from anaphylaxis with similar symptomatology without the elevation in tryptase, IgE or skin prick testing.²²

Under a general anaesthesia in a surgical procedure, cardiovascular collapse may be the only sign anaphylaxis is occurring, and causes need be investigated. It is reported an intravenous infusion of gelatin in a colloid based fluid will take approximately 15–30 min to manifest a reaction, whereas the identified cases in this review, topical application of gelatin haemostats occurred within minutes.^{4–22} Causes of cardiovascular collapse are outside the scope of this article; however pertinent to this article is the adverse effect of haemostat emboli. The incidence of venous thromboembolism secondary to gelatin haemostats in tumour removal ranges from 4.7% to 8.4%, with patients receiving ≥ 10 mL of gelatin haemostat at a higher risk.³⁷ There are other reported cases of pulmonary embolus, right heart failure, disseminated intravascular coagulation and cerebral infarction with a high incidence of mortality.^{38–42}

Of note, the one adult case with an intolerance of red meat and history of tick bite was diagnosed with Alpha-gal syndrome.¹⁷ Alpha Gal syndrome is a tick-borne disease that produces an IgE mediated hypersensitivity against the oligosaccharide epitope, Gal- $\alpha 1$ -3Gal β 1-(3)4GlcNAc-R (α -Gal). In Australia, the *Ixodes holocyclus* is implicated in producing the disease. In patients with known Alpha-Gal syndrome, intolerance of red meats, or history of tick bites should consider alternative haemostatic agents if surgery is required.²⁸

Alternative gelatin-free haemostat products

This article is not intended to educate surgeons on haemostasis, with a wide variety of techniques available, however what

alternatives topical haemostats exist for use if there is a contraindication to gelatin? Few surgeons would undertake an operation without haemostatic techniques available. Most readily available fibrin sealants contain purified bovine thrombin⁴³; however, fibrin sealants are available which do not contain synthetic or bovine aprotinin, which are proposed to reduce allergic reactions.^{3,44} Evicel (Ethicon/J&J, Somerville, NJ, USA), is a new formulation of previous fibrin sealants (Crosseal (OMRIX Biopharmaceuticals, Ltd., Machelen, Belgium) in the USA, or Quixil in the EU) which are composed of human fibrinogen and thrombin.⁴⁴ Other haemostatic agents available which are gelatin-free include oxidized regenerated cellulose and cyanoacrylate adhesives. Cyanoacrylate adhesives were proposed to be used in the First World War, however did not receive approval for use until 1998.³ Dermabond (Ethicon/J&J) is an available product composed of 2-octyl cyanoacrylate monomers which polymerize into long chains when in an exothermic reaction when exposed to hydroxyl ions.⁴⁵ Oxidized regenerated cellulose products are plant based, free of human or animal products. More commonly known as Surgicel (Ethicon/J&J), plant-derived cellulose is oxidized into a knitted fabric which acts as a scaffold for clot formation.³

Implications for clinical practice

Herein, we have presented a literature review of gelatin-based topical haemostat agents and discussed their role in intraoperative anaphylaxis, anaphylactoid reactions and thromboembolic events. It is imperative surgeons and anaesthetic staff are educated to an uncommon complication of an everyday adjunct, especially when its incidence may be underreported secondary to the multitude of compounds given in theatre. This review increases awareness of allergy and intraoperative anaphylaxis to topical gelatin-based haemostats for surgeons and anaesthetists. Awareness of allergy or intolerance to gelatin-based products include (but is not limited to) jelly, gummy candies, shampoos, vaccines, meat (alpha-gal), spam meats, collagen body implants, catgut sutures, collagen-based lenses, and capsule medications. This should alert the surgeon or anaesthetist to the contraindication of gelatin-based haemostats, with alternatives utilized. In this review, it was identified 33% of patients had a preoperative agent identified as a contraindication to gelatin-based haemostats. With anaphylactic deaths under general anaesthesia reaching 4.3%, it is imperative an appropriate history is taken relating to previous reactions, and anaphylaxis, not just for medications, but including vaccines and food products. There is no special history required for prevention, only the fundamental questions regarding previous allergies. We believe the deficit in identifying a gelatin allergy is secondary to not understanding everyday products which contain gelatin, and how this impacts operative planning. Hence, the fundamental prevention is by educating our doctors to;

- (1) Identify everyday products which contain gelatin.
- (2) The awareness that topical haemostats may contain bovine or porcine thrombin.
- (3) Allergy to gelatin products is a contraindication to topical gelatin-based haemostats.

Therefore, by having the appropriate knowledge of gelatin containing products, doctors can simply plan alternate haemostat agents if a patient has identified a pre-existing allergy.

For patients who undergo intraoperative haemodynamic compromise, the use of a gelatin-based topical haemostat should be considered outside of the normal culprits, with the caveat the response could be anaphylaxis, anaphylactoid or thromboembolic. For patients who do undergo anaphylaxis, bovine and porcine gelatin IgE and skin prick testing should occur, to avoid its use in the future.

Author Contributions

Roland White: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization; writing-original draft; writing-review and editing. **Lachlan Kerr:** Conceptualization; data curation; formal analysis; methodology; project administration; resources; visualization; writing-review and editing. **Tyler White:** Conceptualization; investigation; methodology; writing-original draft; writing-review and editing. **Matthew Sampson:** Conceptualization; project administration; supervision; validation; visualization; writing-review and editing.

Conflicts of interest

None declared.

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