Fatal Anaphylactic Shock Induced by Intravenous Gelatin Colloid: A Postmortem Allergological Work-up

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Hypersensitivity reactions (HRs) during perioperative procedures have an estimated prevalence of 1:10 000 to 1:20 000 cases [1]. In previous studies, neuromuscular blocking agents (NMBAs) were the most frequent cause of perioperative HRs in countries such as France, Norway, and Belgium, as were ß-lactam antibiotics in the United States [1,2]. Studies in Spain and the United Kingdom also showed that ß-lactam antibiotics were the main culprit of perioperative HRs [3,4]. Colloid solutions are a less frequent cause of severe perioperative HRs, involving up to 4% of cases [2]. However, recent data showed that the rate of anaphylaxis per administration was equal to that of the most frequently involved NMBA, rocuronium, at 6.2 per 100 000 administrations in the United Kingdom [5,6].

Among the colloids, gelatins are the most frequently involved triggers (95% of cases), followed by dextrins, albumin, and hydroxyethyl starch solutions [7]. Gelatins are heterogeneous mixtures of polypeptides produced by hydrolysis of bovine collagen.

We report the case of a fatal perioperative HR caused by an intravenous gelatin infusion. A 65-year-old white man underwent surgery for type A aortic dissection in January 2018. He experienced several postoperative complications requiring mechanical ventilation, tracheostomy, and prolonged intensive care unit stay (total, 40 days). During this period, he received a colloid containing succinylated gelatin (40 mg/mL), which he tolerated well. Six days after discharge from hospital, in March 2018, the patient was readmitted with surgical wound infection. Blood culture was positive for *Staphylococcus aureus*. Intravenous cloxacillin was initiated, and the patient

responded well. Eleven days later, he underwent a noncomplex surgical procedure for debridement of the median sternotomy wound and collection of samples for microbiological culture. In the post–cardiac surgery care unit (PCSCU), the patient experienced hypotension (90/70 mmHg) and reported pain at the surgical wound site. Morphine chloride (0.2 mg) was administered to relieve pain. In order to maintain satisfactory blood pressure levels and prevent symptomatic hypotension, succinylated gelatin (Gelaspan, B. Braun Melsungen AG) was administered following the PCSCU protocol. Approximately 5 minutes after initiation of the gelatin infusion, the patient complained of intense lingual and oral pruritus and experienced abrupt loss of consciousness and cardiac arrest. After cardiopulmonary resuscitation and orotracheal intubation, he regained spontaneous circulation but was deeply hypotensive despite high-dose vasoactive drugs (epinephrine, norepinephrine, isoprenaline, and even methylene blue). He developed refractory hypotension and eventually died. The infusion of a plasma volume expander (Gelaspan) was interrupted early because of the suspicion of anaphylactic shock, although a cumulative dose of 100 mL had already been administered.

Serum tryptase measured in a blood sample obtained 40 minutes after the onset of the event (T-1 sample) was 378 µg/L (normal range, 0-11.4 µg/L) (ImmunoCAP, Thermo Fisher Scientific). The PCSCU then contacted the allergy department, and a postmortem allergology work-up was performed. Baseline tryptase levels determined in a sample obtained prior to surgery (T-0 sample) and stored at the central laboratory of the hospital were normal (7.46 µg/L). In the T-0 sample, we also measured total IgE (tIgE) levels (94.7 kU/L) and gelatin specific IgE (sIgE) levels (5.84 kU_A/L). The results for galactose-a-1,3-galactose (α-Gal) and latex sIgE were both negative (normal, <0.35 KU_A/L) (ImmunoCAP, Thermo Fisher Scientific). It is noteworthy that in the T-1 serum sample, during the reaction, gelatin sIgE levels decreased to 0.89 kU/L and tIgE was 40 kU/L, probably owing to consumption during the acute reaction, whereas levels of sIgE to α-Gal and latex returned to negative values.

An ImmunoCAP inhibition assay was performed to demonstrate that bovine gelatin was the culprit drug in the fatal reaction (Table). Two samples of the patient's T-0 serum were incubated with Gelaspan and with purified human albumin containing the same concentration of protein as a negative control. The assay showed 100% inhibition of gelatin sIgE, while no inhibition was observed for human albumin, because gelatin sIgE bound to Gelaspan in a classic antigen-antibody reaction and sIgE was consequently depleted from serum. This result confirmed our diagnostic suspicion of fatal anaphylactic shock induced by a gelatin-based colloid.

Gelatin-based colloids are a known cause of drug allergy. In the present case, the most probable source of sensitization was previous administration of gelatin during the admission for the first surgical procedure in January 2018.

The clinical course in the present case, which followed a pattern of IgE-mediated anaphylaxis and was characterized mainly by hypotension in less than 15 minutes and increased serum tryptase levels, was similar to those reported by Farooque et al [5] and the Royal College of Anaesthetists' 6th National Audit Project (NAP6) [6]. However, skin involvement was not observed in the case we report.

Gelatin-induced HRs have also been reported with gelatin-containing anti-infection vaccines, recombinant human erythropoietin, and rectal suppositories [8-10].

Sensitization to α-Gal may also play a role in HRs to intravenous gelatin. Mullins et al [10] detected α-Gal in meat-derived gelatin and demonstrated a strong correlation between anti-α-Gal sIgE and positive intradermal reactivity to gelatin in sensitized patients, suggesting that α-Gal could be a relevant antigen of gelatin. This possibility was ruled out in the case we report.

Taken together, these data highlight the risk of HRs to gelatin-based colloids in patients undergoing repeated administrations and the need to consider alternative sensitization routes in the case of HRs upon first administration (eg, tick bites, vaccinations).

Additionally, the relationship between previous gelatin sensitization and increased risk after oral exposure is not well established. Given that gelatin is ubiquitous in food, it could be considered a potentially hidden allergen [10], although to date there are few data to guide clinicians in such instances.

The present case highlights the importance of withdrawing all intravenous drugs in the event of hypotension or loss of consciousness, even in the paradoxical case where treatment is indicated to prevent hemodynamic instability. The possibility of a fatal outcome should be borne in mind when administering Gelaspan. This case also highlights the diagnostic value of performing a postmortem study and, therefore, emphasizes the need for serum tryptase measurements before and after onset of the event, determination of specific IgE to the most probable agents, and the possible use of ImmunoCAP-inhibition assays to determine the cause of the reaction.

Table. ImmunoCAP Inhibition Assay With Gelatin Colloid and Human Albumin

Serum Samples	Total IgE, kU/L	sIgE Gelatin, kU_A/L	sIgE α-Gal, kU_A/L	Inhibition, %
Patient serum before surgery (undiluted)	94.7	5.84	0.00	–
Patient serum (diluted 1:3)	32.6	2.32	–	–
Patient serum (50 µL) preincubated with 100 µL of Gelaspan (40 mg/mL), (diluted 1:3)	34	0.00	–	100 %
Patient serum (50 µL) preincubated with 100 µL of human albumin as control (40 mg/mL) (diluted 1:3)	33.9	2.91	–	0 %

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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