

**Fatal anaphylactic shock induced by intravenous gelatin colloid: An allergological
postmortem 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 (NMBA) were the most frequent cause of perioperative HRs in countries such as France, Norway and Belgium as well as betalactam antibiotics (BA) in the United States [1, 2]. Recent studies, showed that also in Spain and United Kingdom, the main culprit of perioperative HRs were BA [3, 4]. Regarding colloid solutions, it has been reported that were 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 the most frequently involved NMBA, rocuronium, at 6.2 per 100,000 administrations in United Kingdom [5, 6].

Among colloids, gelatins are the most frequently involved triggers (95% of cases) followed by dextrans, 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 Caucasian man underwent a surgery for a type A aorta dissection on January 2018, presenting several post-operative complications requiring mechanical ventilation, tracheostomy and prolonged Intensive Care Unit stay (a total of 40 days). In this period he

received a colloid containing succinylated gelatin (40mg/ml) with good tolerance. Six days after hospital discharge, on March 2018, the patient was readmitted due to surgical wound infection and positive blood culture for *S. aureus*. Intravenous cloxacillin was initiated with good response. Eleven days later, the patient underwent a non-complex surgical procedure for skin debridement of median sternotomy and collection of samples for microbiological cultures. At the post cardiac surgery care unit (PCSCU) the patient presented tendency to hypotension with blood pressure of 90/70 mmHg and reported pain at the surgical wound. To relieve pain, morphine chloride (0.2 mg) was administered and in order to keep satisfactory levels of blood pressure and to prevent symptomatic hypotension succinylated gelatin (Gelaspan®, B. Braun Melsungen AG, Germany) were administered following PCSCU's protocols. Approximately 5 minutes after the initiation of gelatin infusion, the patient referred an intense lingual and oral pruritus and suffered abrupt loss of conscience and cardiac arrest. After the cardiopulmonary resuscitation and orotracheal intubation, the patient regained spontaneous circulation but was deeply hypotensive despite vasoactive drugs (adrenaline, norepinephrine, isoprenaline and even methylene blue) at very high doses, evolving to refractory hypotension and finally death. The infusion of plasma volume expander (Gelaspan®) was early interrupted at the suspicion of an anaphylactic shock, but a cumulative dose of 100 ml had already been administered.

Serum tryptase level measured in a blood sample obtained 40 minutes after the onset of the event (T-1 sample) was 378µg/L (normal 0-11.4µg/L) (ImmunoCAP®; Thermo-Fisher Scientific, Sweden). Then, PCSCU unit contacted with the allergy department and a post-mortem allergological work-up was performed. Baseline tryptase levels determined in a sample obtained prior to surgery (T-0 sample) and kept on the central laboratory of the hospital showed a normal value of 7.46µg/L. In this T-0 sample we also performed the following measurements: tIgE levels: 94.7 KU_A/L and gelatin sIgE levels: 5.84 KU_A/L, galactose-a-1,3-

galactose (α -Gal) and latex specific IgE (slgE) were both negative (normal < 0.35 KU_A/L) (ImmunoCAP®; Thermo-Fisher Scientific, Sweden). It is noteworthy that in T-1 serum sample, during the reaction, gelatin slgE levels decreased to 0.89 KU/L and tlgE was 40 KU/L, probably due to consumption during the acute reaction while slgE to α -Gal and latex were negative again.

To demonstrate that bovine gelatin was the culprit drug of the fatal reaction, an ImmunoCAP® inhibition assay was performed (Table 1). Two samples of the patient's T-0 serum sample were incubated, with Gelaspan® and with a purified human albumin of the same concentration of protein as negative control, retrospectively. The assay shows a 100% inhibition of gelatin slgE while human albumin shows no inhibition. It can be explained by gelatin slgE binding to Gelaspan® in a classic antigen-antibody reaction and the consequent depletion of slgE from the serum. This result confirmed our diagnostic suspicion of a fatal anaphylactic shock induced by gelatin based colloid.

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

The clinical course of the case, followed a pattern of an IgE-mediated anaphylaxis, characterized mainly by hypotension in less than 15 minutes as well as a rise in serum tryptase levels, similar to the case series published by Farooque et al [5] and Royal College of Anaesthetists' 6th National Audit Project (NAP6) [6] although in our patient, skin affection was not seen.

Gelatin induced HRs have also been described with the use of gelatin containing anti-infectious 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 gelatin intradermal reactivity in sensitized patients, suggesting that α -Gal could be a relevant antigen of gelatin. This possibility was ruled out in our reported case.

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

Additionally, the relationship between previous gelatin sensitization and increased risk after oral exposure is not well established. The presence of gelatin in food is ubiquitous, so it could be considered a potentially hidden allergen [10], but until date there is a lack of knowledge to inform guidance in such instances.

This case highlights the importance of withdrawing all intravenous drugs in the event of hypotension or loss of conscience, even in the paradoxical case when the treatment is indicated to prevent hemodynamic instability as well as having this fatal possibility in mind when administering this drug. In addition, this case show us the diagnostic value of performing a post-mortem study, emphasizing the use of serum tryptase measurements before and after the onset of the event, determinations of specific IgE to the most probable agents as well as the possible use of ImmunoCAP-inhibition assays underpin the cause of the reaction.

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