

Original Article

Anaphylaxis to intravenous gelatin-based solutions: a case series examining clinical features and severity

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Summary

The proportion of patients receiving intravenous gelatin-based colloids has increased in the last decade due to safety concerns about starch-based products. Recent research suggests hypersensitivity reactions to intravenous gelatin-based solutions occur at similar rates per administration as non-depolarising neuromuscular blocking agents such as rocuronium (6.2/100,000 administrations). There are scant published data on clinical features, diagnosis and time course of these reactions. We undertook a review of cases reported and tested at one of the UK's largest drug allergy clinics. All patients seen in the drug allergy clinic at Imperial College Healthcare NHS Trust (London, UK) with a confirmed diagnosis of anaphylaxis to gelatin-based solutions between May 2013 and May 2018 were included. We retrospectively reviewed clinical histories, skin test results and severity of reactions in this cohort of patients. Twelve patients with anaphylaxis to gelatin-based solutions were identified (eight women, mean (SD) age 58 (17) years). Eleven reactions were severe or life-threatening with three progressing to cardiac arrest. Presentation was commonly delayed; only three patients suffered reactions within 5 min of the solution being administered with a further six presenting 10–70 min later. Where measured, tryptase was elevated in all patients (median (IQR [range]) 14.7 (8.2–23.8 [6.5–83.4]) ng.ml⁻¹). Reactions to gelatin-based solutions are usually severe and can present with latency uncommon with other intravenous anaesthetic triggers. The use of gelatin-based solutions in the peri-operative setting should be reassessed given the risk of severe allergy.

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Introduction

Despite the potential benefits of synthetic colloids as intravascular volume expanders, their safety has been called into question [1]. In particular, concerns about the risk of starch-based colloids causing renal failure [2–4] have led to the intravenous synthetic colloids of choice for fluid resuscitation shifting towards albumin and succinylated gelatin-based solutions such as Isoplex (Beacon Pharmaceutical Limited, Measham, UK), Volplex (Beacon Pharmaceutical Limited) and Gelofusine® (B. Braun

Melsungen AG, Melsungen, Germany). The choice of colloid varies between countries: in the UK, gelatin-based solutions have traditionally predominated, while Switzerland and the USA almost exclusively use starch-based colloids and albumin, respectively [5]. In a recent large, multinational trial, gelatin-based solutions were the second most commonly administered colloid after albumin [6]. In contrast, the 6th National Audit Project of the Royal College of Anaesthetists (NAP6) found gelatin-based products were the most frequently used colloid (1.7% of all

fluid administrations) with starch or starch-based products (0.2%) and albumin (0.1%) now rarely used [7]. This may be due to cost and ease of production as gelatin-based fluids are cheaper and more easily accessible than albumin, which is derived from human volunteers [8].

There appears to be few contraindications to the use of succinylated gelatin-based solutions. However, NAP6 suggested that the rate of anaphylaxis per instance of administration was not insignificant, equalling the most commonly implicated non-depolarising neuromuscular blocking agent, rocuronium, at 6.2 per 100,000 administrations [7]. Three reactions to gelatins were reported in the year-long NAP6 study, one of which was fatal. With only three reported cases it remains unclear whether the severity of these reactions followed the classic pattern seen in anaphylaxis to neuromuscular blocking agents and antibiotics: namely an immediate response (within 5 min) with hypotension dominating. An association between patients taking beta blockers and angiotensin-converting enzyme inhibitors (ACEi) and a poor outcome was also reported in NAP6. In addition, reactions were also more severe in patients who were older, obese and ASA physical status 3 or 4 [7].

We undertook a review of all patients with a confirmed allergy to intravenous gelatin-based solutions attending the drug allergy clinic in a UK teaching hospital. The aim of this review was to determine the typical clinical course of anaphylaxis to intravenous gelatin-based solutions in terms of timing and clinical presentation. Our secondary aim was to see if there was an association between severity of anaphylaxis to intravenous gelatin-based solutions and patient age, ASA physical status and/or the concurrent use of beta blockers or ACEi.

Methods

All drug allergy skin tests and challenges performed at Imperial College Healthcare NHS Trust are prospectively recorded in a database. We used this database to identify all patients with confirmed peri-operative hypersensitivity to intravenous succinylated gelatin-based solutions attending the clinic between 2012 and 2017. We performed a retrospective review of the clinical notes. Information extracted included: clinical history of reaction; skin test results and subsequent management. The study was judged not to require institutional ethics committee approval and publication of the de-identified patient information was approved by the data protection officer. As a retrospective clinical notes review, it was not registered on a trial register. All patients were investigated in accordance with national and international guidelines [9, 10]. In addition

to a detailed history, each patient attending the clinic, as standard practice, had their charts reviewed by both an anaesthetist and an allergist and then proceeded to skin testing with the suspected colloid, latex, chlorhexidine and other agent(s) as indicated by the clinical details.

Skin prick testing was performed for succinylated gelatin-based solutions in clinically-used concentrations ('neat') and 1:10 diluted solutions. A wheal diameter of ≥ 3 mm at 15 min in comparison with a negative control was considered positive and significant in conjunction with the clinical history. When the skin prick test was negative or indeterminate, intradermal tests were performed. These were carried out on the forearm. A decreasing dilution scale was used for intradermal testing depending on the patient history (starting dose = 1:10,000, maximal concentration = undiluted). Intradermal tests with undiluted intravenous gelatin-based solutions were demonstrated as non-irritant in 10 control patients (not included in the current study). Specific immunoglobulin E (IgE) to gelatin was not routinely checked, as patients had had no further allergic reactions and were consuming gelatin-containing foods subsequent to their anaphylaxis without allergic reaction. For intradermal tests, a bleb of 4–6 mm was raised by injecting 0.03–0.05 ml and a wheal diameter of < 3 mm larger than the negative control at 20 min was considered positive. In cases where anaphylaxis to gelatin-based solutions was strongly suspected, but the patient had negative skin tests, the diagnosis was further investigated by intravenous challenge under controlled conditions.

Anaphylaxis was defined according to the recent NAP6 grading consistent with World Allergy Organization definitions [11] (Table 1). The latency period from the time of administration to the time of the reaction were stratified into four time periods: within 5 min; 5–10 min; 10–30 min and > 30 min.

Results

Twelve patients were identified that met the inclusion criteria (eight women, mean (SD) age 58 (17) years). Four of these 12 patients were conscious in the recovery room when the reaction occurred, with two of these four patients having previously had neuraxial anaesthesia (Table 2). One patient received intravenous succinylated gelatin-based solution to treat pre-existing hypotension but otherwise no indication for the choice of fluid was evident. Time between exposure to the gelatin-based solution and onset of symptoms was variable and sometimes delayed (Table 2). Six patients reacted within 10 min and two > 60 min later, with a median ((IQR) [range]) latency time of 15 (6.75–27.5 [2–70]) min.

Table 1 World Allergy Organization definitions of severity of allergic reactions [11].

Grade 1	Rash, erythema, angioedema
Grade 2	Unexpected hypotension and/or bronchospasm – not severe, for example, not requiring treatment $\pm$ grade-1 features
Grade 3	Hypotension (systolic arterial blood pressure nadir ≥ 50 mmHg) or bronchospasm together with any other features suggestive of anaphylaxis (e.g. rash, angioedema)
Grade 4	As per grade 3 but requiring cardiopulmonary resuscitation or where the lowest systolic arterial blood pressure < 50 mmHg
Grade 5	Fatal reaction

Reactions were severe and included three cardiac arrests but no deaths (Table 2). Half of all patients were subsequently admitted to intensive care or high dependency units. There were no associations between sex, age, ACEi/beta-blocker use and development of cardiac arrest. One patient had pre-eclampsia and remained hypertensive throughout the episode although her systolic fell by < 70 mmHg. There was no correlation between ASA physical status and likelihood of cardiac arrest.

The most common first presenting clinical feature was hypotension (eight patients), followed by bronchospasm, cough or desaturation (two patients), or flushing or angioedema (two patients). Other clinical signs and symptoms are shown in Table 3. The treatments administered to patients are shown in Table 4. Of note, three patients did not receive either intravenous or intramuscular adrenaline.

Allergy was confirmed on skin testing (skin prick or intradermal tests) in 11 patients and on intravenous provocation in one patient with negative skin prick and intradermal tests (Table 5). Specific IgE to gelatin was also checked in this patient (the only specific IgE test performed in this cohort) as she reported an episode of angioedema several months postanaphylaxis; this was found to be negative.

Serum tryptase was measured in nine patients and in all nine a significant rise was observed (Table 5). A significant rise was defined by the international consensus equation where peak mast cell tryptase (usually measured up to 4 h after the reaction) is greater than $1.2 \times$ baseline tryptase + 2 ng.ml^{-1} [12]. Despite four of the nine patients' mast cell tryptase levels failing to reach the minimum level indicative of mast cell degranulation (11.5 ng.ml^{-1}), a significant rise as defined by the consensus equation was seen.

Discussion

This is the largest reported case series of peri-operative anaphylaxis to intravenous succinylated gelatin-based solutions. Previous reports have either evaluated the incidence of intravenous colloid allergy and presentation in the general hospital population or reported the incidence in the peri-operative period without the clinical features and any associations [12, 13].

Discussions about the benefits of intravenous colloid vs. crystalloid solutions and which synthetic colloid to use, continue internationally. There are wide geographical variations in types of intravenous fluids used and in which circumstance [5]. In the UK, NAP6 found that intravenous succinylated gelatin-based solutions were the colloid of choice and were estimated to be used in 1.7% of anaesthetics. NAP6 included three cases of anaphylaxis due to intravenous gelatin-based solutions from an estimated 52,160 administrations over the year-long audit period [7]. All three of these cases led to severe reactions including one cardiac arrest and subsequent death. That one of three cases led to death, out of a total of nine deaths from all 263 cases reported in NAP6 from other trigger agents, is a cause for concern notwithstanding the small numbers. In contrast to NAP6, our case series did not exclude minor (grade 1 and 2) reactions. Despite this, anaphylaxis to gelatin-based solutions appears from our data to be particularly severe in comparison with other triggers for peri-operative anaphylaxis with only one case of a grade-2 reaction from the 12 reported. Nevertheless, as with all cases of peri-operative anaphylaxis, this may reflect milder reactions (grade 1 and 2) being less likely to be noticed and referred for allergy testing when patients are anaesthetised.

Until recently, studies have suggested the rate of anaphylaxis to all gelatin-based solutions could be as high as 1 in 300 exposures in the general hospital population, and 38 cases per 100,000 exposures in peri-operative patients [12, 13]. However, data from the NAP6 study suggests the rate of anaphylaxis secondary to colloids to be lower at 6.2 per 100,000 exposures [7]. The discrepancy between incidence rates is likely to be due to the severity of reactions reported. The risk of life-threatening reactions is still approximately the same as the most commonly implicated non-depolarising neuromuscular blocking agent, rocuronium [7]. Studies have also shown that gelatin-based plasma expanders are three times more likely to cause anaphylaxis than crystalloids and albumin, and among all currently used colloids, are the most likely to cause anaphylaxis [12, 14]. Suspected fatal anaphylactic reactions due to intravenous gelatin-based solutions have also been

Table 2 Anaphylactic reactions to an intravenous succinylated gelatin-based solution given intra-operatively in the operating theatre and postoperatively in the recovery room. Three of the patients with a grade-4 reaction progressed to cardiac arrest (#).

Patient	Age; years	Sex	ASA	Anaesthetic technique	Reaction grade	Time to reaction; min	Blood pressure before colloid; mmHg	ACEi	Beta-blocker
1	43	Female	2	GA (intra-operative)	4	< 5	100/50	No	No
2	74	Male	3	GA (intra-operative)	4 [#]	11–30	110/80	No	No
3	82	Male	3	GA (postoperative)	4 [#]	< 5	100/60	Yes	Yes
4	46	Female	1	GA (postoperative)	3	> 30	120/70	No	No
5	53	Male	3	GA (intra-operative)	3	11–30	100/45	Yes	Yes
6	30	Female	3	Spinal (postoperative)	3	5–10	197/120	No	No
7	35	Female	1	Spinal (postoperative)	3	> 30	133/90	No	No
8	69	Female	2	GA (intra-operative)	3	11–30	80/40	No	No
9	62	Male	3	GA (intra-operative)	4	5–10	120/65	Yes	No
10	51	Female	3	GA (intra-operative)	2	> 30	130/60	No	No
11	78	Female	2	GA (intra-operative)	4 [#]	< 5	120/70	No	No
12	67	Female	3	GA (intra-operative)	3	5–10	105/65	Yes	No

GA, general anaesthesia; ASA, ASA physical status; ACEi, angiotensin-converting enzyme inhibitor.

Table 3 Clinical signs and symptoms associated with anaphylactic reaction to an intravenous succinylated gelatin-based solution.

Sign/symptom	Number (n=12)
Cutaneous signs	12
Hypotension	11
Tachycardia	4
Bronchospasm/raised airway pressures	4
Cardiac arrest	3
Reduction in end-tidal carbon dioxide level	3
Laryngeal oedema/stridor	2
Bradycardia	1
Pruritus	1
Nausea/vomiting/abdominal pain	1
Hypotension misdiagnosed as haemorrhage requiring surgical re-exploration	1

described in addition to the case reported in NAP6, with at least two further fatalities likely [15].

Little has been published about the clinical course of anaphylaxis to intravenous gelatin-based solutions. In an analysis of the immunological reactions of all intravenous colloids in the 1970s, Ring and Messmer described 15 cases of gelatin reactions out of a total of 69, ranking gelatin as the highest risk and most allergenic colloid [13]. The largest reported number of patients in a single study was an eight-year national audit of peri-operative anaphylaxis [16]. The authors reviewed the incidence of peri-operative anaphylaxis to different drugs over an eight-year period and identified 56

cases of intravenous gelatin hypersensitivity out of a total of 63 reactions to intravenous colloids. The severity and clinical features of anaphylaxis to individual drugs were not described. More recently Low et al. also reported three cases of intravenous gelatin hypersensitivity presenting to a joint anaesthetic allergy clinic over a seven-year period (2007–2014), representing 1.7% of the number of cases referred [17]. This figure is similar to the rate of cases referred in NAP6 cohort (3/266 (1.1%)). The remaining published literature largely consists of individual case reports.

We found that some aspects of anaphylaxis to intravenous gelatin-based solutions followed the typical clinical features of peri-operative anaphylaxis [18]. As in NAP6, the commonest presenting sign was hypotension and, consistent with peri-operative anaphylaxis, reactions were severe. Unusually, all patients developed cutaneous signs during the course of their anaphylaxis facilitating retrospective diagnostic certainty and, where measured, a tryptase rise was always seen. However, in our series, a median delay of 15 min to reaction time was observed with only three reactions occurring within 5 min. This is a new finding and suggests a more insidious onset of gelatin-related hypersensitivity reactions compared with other intravenous drugs. Notwithstanding the small numbers in this study, this time course significantly differs from anaphylaxis to other intravenous drugs; for example, neuromuscular blocking agents or antibiotics, where 83% and 72% of reactions in the NAP6 cohort occurred within 5 min of exposure, respectively [7]. In NAP6, anaphylaxis to colloids ran a substantially slower time course similar to that seen with anaphylaxis to chlorhexidine and patent blue dye [7]. Indeed,

excluding patent blue dye and chlorhexidine, only four cases in NAP6 (out of a total of 266) reacted after 30 min compared with three in this cohort of 12. Of the four cases in NAP6 where anaphylaxis was delayed beyond 30 min of agent exposure, one was an oral administration and a second was thought to be a data entry error, suggesting delayed reactions to intravenous medications are unusual. In the study by Low et al., all three reactions occurred postoperatively in the recovery room [17]. This may reflect the timing of the infusion, or that the reaction had a period of latency and only developed in the postoperative period. One potential risk of this latency is the potential for misdiagnosis of hypotension due to another cause such as ongoing postoperative haemorrhage. In our case series, the latency of the reaction in one case led to the unnecessary prolongation of surgery due to the need for re-exploration of the surgical site for suspected bleeding. The reason for this latency remains unknown but the authors hypothesise that this may reflect the large size of the succinylated

gelatin molecules (approximately 30 kDa) leading to slower IgE binding times [19, 20]. In comparison, rocuronium is approximately fifty times smaller, weighing only 610 Da [21]. Although we noted a delay in diagnosis due to confounding symptoms in only one case, namely the hypotension that the i.v. colloid was being used to treat, we observed that three of the 12 patients in this cohort were not treated with adrenaline compared with only 11% of patients in NAP6 [7]. This may reflect the delay in these reactions leading to diagnostic confusion, or the fact that some of these reactions occurred postoperatively and therefore anaesthetists were not the first-responders. A similar problem was identified in the NAP6 series with a correct but delayed diagnosis to recognition and treatment [7]. The potential that persistent hypotension could be caused by the agent being used to treat it should always be considered in cases where an intravenous gelatin-based solution is being used for volume resuscitation. Prompts for the management of unexplained hypotension or suspected anaphylaxis should be available to aid teams in excluding hypersensitivity to the resuscitation fluid as a cause [22].

Another surprising feature in this cohort was the ambiguity as to why the colloid was administered with only one patient being hypotensive before its commencement. Intravenous succinylated gelatin-based solutions have traditionally been used to treat intra-operative hypotension because it has been thought a lower volume of colloid is required to achieve the same haemodynamic outcomes [23, 24]. However, a meta-analysis examining the safety and efficacy of gelatin-based solutions concluded that, despite

Table 4 Frequency of treatment received by patients with an anaphylactic reaction to an intravenous succinylated gelatin-based solution.

Treatment	Number (n=12)
Chlorpheniramine (intravenous)	12
Intravenous fluid bolus	12
Hydrocortisone (intravenous)	11
Adrenaline (intravenous)	8
Adrenaline (intramuscular)	1

Table 5 Investigations in patients with confirmed anaphylactic reaction to an intravenous succinylated gelatin-based solution.

Patient	Skin testing		Tryptase; ng.ml ⁻¹		
	Skin prick (neat)	Intradermal	Baseline	Peak after reaction (2–4 h)	Significant rise ^a
1	Negative	Positive (1:100)	1.0	6.5	Yes
2	Negative	Positive (1:10)	Not done	Not done	N/A
3	Negative	Positive (1:10,000)	5.5	15.4	Yes
4	Negative	Positive (1:10)	2.1	7.9	Yes
5	Negative	Positive (1:100)	Not done	Not done	n/a
6	Positive (3 × 3 mm)	Positive (1:10)	Not done	Not done	n/a
7	Negative	Positive (neat)	3.0	11.3	Yes
8	Negative	Negative ^b	3.7	8.2	Yes
9	Positive (9 × 6 mm)	Not done	9.9	23.8	Yes
10	Negative	Positive (1:10)	6.7	14.7	Yes
11	Positive (3 × 3 mm)	Positive (1:100)	4.9	83.4	Yes
12	Negative	Positive (neat)	4.4	45.9	Yes

^aBased on the consensus equation [26].

^bPatient 8 was confirmed as reacting on intravenous provocation.

its use over several decades, there were few trials supporting its use [25].

Our cohort was too small to confirm any associations between severity of anaphylaxis and age, ASA physical class and concurrent use of beta blockers or ACEi. This may be due to the relatively small number of patients or because anaphylaxis to colloids affects a different cohort of patients, with obstetric patients being relatively over-represented [7]. It is also possible that minor reactions were not referred to the allergy clinic as they were not recognised. Minor, cutaneous reactions are rarely reported peri-operatively due to the absence of pruritus and other symptoms under anaesthesia. In addition, the predominant early feature of the reactions was hypotension before the cutaneous signs developed. This hypotension may also have been misdiagnosed by the treating anaesthetists and not referred, likely underestimating the true incidence of the rate of reactions.

In conclusion, the role of intravenous gelatin-based solutions in the peri-operative setting should be re-assessed given the risk of allergy and lack of evidence of clinical benefit. Furthermore, the latency and severity of reactions seen in this case series should give cause for reflection to the risk of missing severe, life-threatening reactions.

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