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Case Report

Severe allergic reaction caused by succinylated gelatin during gastric cancer surgery and review of 31 cases

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Abstract: Succinylated gelatin is a colloidal plasma substitute. Although we are aware that it rarely induces allergies, we evaluated cases to provide clues to establish diagnostic and treatment guidelines. Among 31 cases of succinylated gelatin allergy, 18 patients (58.06%) had no history of drug or food allergy, 6 (19.35%) had animal protein allergies, and 7 (22.58%) had other drug allergies. Intraoperative allergic reactions to succinylated gelatin usually occurred at infusion concentrations of 171.2 ± 102.8 mL delivered within 11.62 ± 10.89 min. Reactions included changes in respiratory function followed by cardiovascular alterations. Patients were treated successfully with 16.13% (5/31) requiring repeat surgery and 29.03% (9/31) requiring intensive care unit (ICU) stays. One of eight patients who received local anesthesia required tracheotomy. One patient died and rest of patients survived without complications. Postoperative succinylated gelatin prick tests were positive in 100%. Patient allergy histories are important. Those with a history of animal protein allergy should undergo a preoperative succinylated gelatin prick test.

Keywords: Allergic reaction, succinylated gelatin, gelofusine

Introduction

Succinylated gelatin injection is a plasma substitute containing 4% succinylated gelatin (modified fluid gelatin). Its expansion capability is better than that of crystalline products, so it is widely used for intraoperative fluid therapy. Our hospital has been using succinylated gelatin injection since 2002. Approximately 15000 mL has been administered to patients in operating rooms elsewhere with no occurrence of serious allergic reactions. Minimal allergic reactions have been reported in the literature. In our department, however, we witnessed severe anaphylactic shock in a gastric cancer patient following succinylated gelatin injection administered intravenously during surgery on March 24 2014. On account of this patient, we reviewed the literature to identify other patients who might have reacted to succinylated gelatin injection.

Case report

A 53-year-old man had intermittent upper abdominal pain for 2 years. Gastroscopic biopsy in our department revealed the presence of a poorly differentiated adenocarcinoma in the body of the stomach. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Peking Union Medical College Hospital. Written informed consent was obtained from participants. The patient's general condition was good at the time of admission. He reported that he was allergic to mutton (abdominal pain, diarrhea, allergies). He had no history of cardiovascular or cerebrovascular disease, and no history of drug or other food allergies. We performed a laparoscopic total (D2) radical gastrectomy for gastric cancer on March 24, 2014. During the surgery, he experienced severe anaphylactic shock following intravenous injection of succinylated gelatin. Anesthesia, operation, and rescue procedures is outlined in **Table 1**.

The total duration of the anesthesia, surgery, and rescue was 7.5 h. Cardiopulmonary resuscitation (CPR) continued for 46 min, and he was defibrillated three times. The total blood loss was 1000 mL, and his urinary output was 3600 mL. He was given 8400 mL of a crystalline solution, 600 mL of colloid solution, and eight units

Table 1. The detail procedures of allergic reaction

Time	Infusion liquid and rescue measures	Symptoms/signs	SpO_2 (100%)	$EtCO_2$ (100%)	RR (BPM)	TV/ PEAK	BP (mmHg)	HR (BPM)	Blood gas analysis
15:00-17:35	Sodium lactate Ringer's solution	-	98	32	12	27	120/70	75	-
17:35-17:36	Infusion of succinylated gelatine about 10 mL	The upper chest and bilateral arm sporadic shows patchy erythema	83	16	22	30	110/70	80	-
17:36-17:49	6 mg ephedrine * 1time 1 mg epinephrine * 2 times Shutdown Gelofusine (about 50 ml) For sodium lactate Ringer's solution	Erythema gradually integrated into the film	70	23	22	43	80/50	60	-
17:50	Sodium lactate Ringer's solution	Ventricular fibrillation	70 (min)	33	13	19	40/20 (min)	-	-
17:51-18:25	The ongoing CPR Ice cap; Ventricular fibrillation * 3 times Defibrillation * 3 times Hydrocortisone 150 mg * 1 time Diphenhydramine 40 mg * 1 time Lidocaine 100 mg * 2 times Adrenaline 1 mg * 2 times Calcium gluconate 1 g * 2 times $NaHCO_3$ continuous infusion Sodium lactate Ringer's fluid infusion	Ventricular fibrillation * 3 times, large areas of skin erythema was still on the upper chest and bilateral upper limb	80	16	22	44	55/20	160	PH=7.206, PCO_2=67, PO_2=40.4, K=3.2, Ca=1.28, Glu=11.3, HCO_3=26, BE=2.6, Hb=9.7, Lac=8.6
18:26-18:36	Sodium lactate Ringer's solution	Cardiac resuscitation, generalised urticaria resolved above 60%	100	44	13	28	170/110	103	-
18:37-22:30	The end of CPR, sodium lactate Ringer's solution	-	100	28	15	23	130/90	101	-

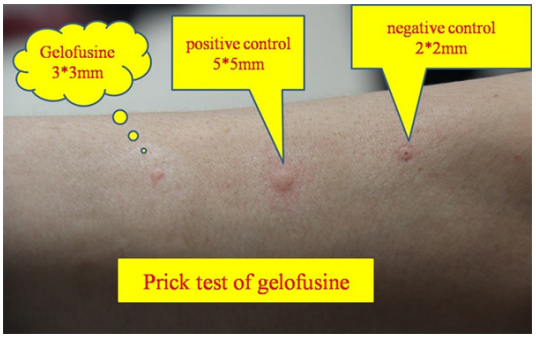

Figure 1. Skin prick test of gelofusine.

of red blood cells. By the end of the operation, his vital signs had stabilized: blood pressure 135/75 mmHg, heart rate 110 beats/min, and SpO_2 100%. The patient went to the intensive care unit (ICU) with a tracheal cannula and was extubated 2 days later. He was transferred to our department on postoperative day 3, and was discharged without incident 1 week after his surgery. There were no anesthesia or surgery-related complications.

One month after the operation his blood tryptase level was 2.44 g/L (normal 0-13.5 g/L), and the total immunoglobulin E level was 770 KU/L (normal 0-60 KU/L). The allergen test showed that the patient was severely allergic to beef, pork, chicken, turkey, milk, wheat gliadin, and rabbit. He was even more severely allergic to eggs. His in vivo succinylated gelatin liquid skin prick test was positive (**Figure 1**). The in vitro antigen stimulation test was also positive.

Review of the literature

The domestic and foreign literature on intraoperative succinylated gelatin-induced allergy shows that there were a total of 27 cases until 2014 (**Table 2**). While Chinese literature reported 22 cases, the foreign literature reported 5 cases, including one case of severe anaphylactic shock (3.7%, 1/27). In recent years, with more widespread use of succinylated gelatin, reports of cases of allergy have shown an increasing trend. Among the 27 patients, 11 were male (40.7%), and 16 were female (59.3%). Their ages ranged from 14 to 76 years (44.78 ± 16.32 years).

Sixteen patients (59.2%) had no history of drug or food allergies, four patients (14.8%) were allergic to penicillin; three patients (11.1%) were allergic to animal protein, including pork, beef, chicken, duck, and shrimp; one patient (3.7%) was allergic to fish; one (3.7%) was allergic to astemizole and medical adhesive tape; one (3.7%) was allergic to ibuprofen, and one (3.7%) was allergic to procaine.

Succinylated gelatin-induced allergic reactions occur intraoperatively usually with a169.7 ± 104.1 mL infusion given during a 11.78 ± 11.47 min time span. The initial clinical manifestations are usually an airway pressure surge with an increase in blood oxygen, blood pressure and heart rate; decreased central venous pressure; weakness of the eyes and ears; and severe edema of the conjunctiva, throat, and lips. Urticaria appeared on the upper limbs, chest, and body. In addition to these symptoms, one patient (3.7%) developed a red line along the vein that had received the infused succinylated gelatin. Intraoperative monitoring showed that all the patients' (100%) experienced decreased blood pressure and heart rate, S-T segment depression, and T-wave inversion of different levels. Of these, three patients (11.1%, 3/27) had unrecordable blood pressure. The skin of three patients (11.1%, 3/27) had shown an orange peel appearance, two patients (7.4%, 2/27) had ventricular fibrillation, and one patient (3.7%, 1/27) had cardiac arrest. Altogether, 22 patients (81.5%) completed their operation in one stage. The operation was terminated in five patients, who then had to undergo a second-stage operation (18.5%). Ten patients (37.0%) had an ICU stay after surgery, and 17 patients (62.9%) were returned to the common ward. The postoperative succinylated gelatin skin prick test was positive in 100% of the patients (All the patients in the Chinese studies did not undergo this test while all the foreign patients did, and had a 100% positive rate.

Discussion

Succinylated gelatin injection, a colloidal plasma substitute, is the product of gelatin (macromolecular) modified first by succinic anhydride acylation, and then by enzymatic hydrolysis. The drug is widely used for blood volume replacement caused by hypovolemic shock, operative trauma, burns, and infection. It can increase the plasma volume by increasing the back-flow of venous and arterial blood pressure, and the peripheral perfusion volume.

Table 2. Cases from literature

Domestic cases (22)								
Year	Gender	Age	Department	Anaesthesia	Allergic constitution	History of allergy	Anamnesis	Reference
1998	Male	34	Urinary surgery	Epidural anesthesia	Yes	Amoxicillin and penicillin	Coronary heart disease, bronchitis	[1]
1998	Male	54	Urinary surgery	Epidural anesthesia	Yes	Cephalosporin and penicillin	—	[1]
1999	Male	62	Suprapubic prostatectomy	Epidural anesthesia	Yes	penicillin	—	[2]
2002	Female	34	Gynaecology	Inhibition anesthesia	No	—	—	[3]
2004	Female	55	Gynaecology	Inhibition anesthesia	No	—	—	[4]
2005	Female	48	General surgery	General anesthesia	Not mentioned	—	—	[5]
2006	Female	26	Obstetrics department	Inhibition anesthesia	Yes	Pork, beef, chicken, duck, shrimp meat	—	[6]
2006	Female	48	General surgery	General anesthesia	Not mentioned	—	—	[7]
2007	Male	37	Orthopedics	General anesthesia	No	Pork, beef,	—	[8]
2007	Male	39	Orthopedics	General anesthesia	No	—	—	[9]
2008	Male	25	Orthopaedics	Brachial plexus anesthesia	No	—	—	[10]
2008	Male	57	General surgery	General anesthesia	No	—	—	[11]
2008	Female	16	Orthopedics	General anesthesia	No	Medical adhesive tape and astemizole	—	[12]
2008	Female	46	Gynaecology	General anesthesia	No	—	—	[12]
2008	Male	67	Orthopaedics	Epidural anesthesia	No	—	—	[13]
2008	Male	14	Ear-nose-throat departmen	General anesthesia	Yes	Fish	—	[14]
2009	Male	57	General surgery	General anesthesia	No	—	—	[15]
2010	Female	50	Neurosurgery	General anesthesia	No	—	—	[16]
2010	Male	56	General surgery	General anesthesia	No	—	—	[16]
2010	Female	36	General surgery	General anesthesia	No	Beef	—	[17]
2010	Female	23	Obstetrics department	Inhibition anesthesia	No	—	—	[18]
2011	Male	56	General surgery	General anesthesia	No	—	Incomplete right bundle-branch block	[19]
2012	Female	38	General surgery	General anesthesia	No	Beef	—	[20]
2014	Female	27	Gynaecology	General anesthesia	No	—	—	[21]
2016	Female	53	Gynaecology	General anesthesia	No	—	—	[22]
2016	Male	63	Cardiac surgery	General anesthesia	No	—	—	[23]
Foreign cases (5)								
Year	Gender	Age	Department	Anaesthesia	Allergic constitution	History of allergy	Anamnesis	Reference
2002	Male	57	General surgery	General anesthesia	No	—	—	[24]
2007	Female	48	Neurosurgery	General anesthesia	No	Ibuprofen	—	[25]
2008	Female	55	Cardiology	—	No	—	—	[26]
2009	Male	72	Orthopaedics	General anesthesia	No	—	—	[27]
2011	Female	76	Cardiac surgery	General anesthesia	No	Penicillin	—	[28]

Occasionally, allergic reactions (e.g., rash) occur during the perioperative period (after anesthesia).

Milton showed that a conservative estimate of the incidence of operative succinylated gelatin allergy rate was 0.066-0.146%, with severe reactions occurring in only 0.007%. In recent years, more widespread application of succinylated gelatin has resulted in an increased number of allergic episodes being reported in our country and abroad.

Succinylated gelatin allergy is categorized as an immediate type (Type I) hypersensitivity, since urticaria is the first symptom of Type I hypersensitivity, which is associated with raised levels of IgE [19]. In the case reported herein, the surgical staff did not promptly find the urticaria, because the patient's skin was draped. Thus, awareness of this possibility will require anesthesiologists/anesthetists and nurses to observe vital signs and skin conditions more closely during operation. The heightened awareness can ensure that the appropriate treatment is given to avoid progression to anaphylactic shock.

It is difficult to diagnosis succinylated gelatin-induced allergy intraoperatively. First, the clinical manifestations of allergic reactions are not specific. Most anesthetics can dilate blood vessels, with a drop in blood pressure leading to cardiac dysfunction. It is thus difficult to distinguish an allergic reaction from anesthetic efficacy. Second, many drugs are used simultaneously during anesthesia application. Hence, it is difficult to identify the drug causing the allergic reaction. In our case, because of using antibiotics/narcotics throughout the operation, we could basically distinguish between antibiotic and anesthetic allergy. The allergic reaction became obvious within one minute of starting the succinylated gelatin infusion, and the amount of blood loss was about 50 mL. The airway pressure surged, while the oxygen saturation and the blood pressure suddenly dropped. Thus, succinylated gelatin allergy was the most likely possibility.

On questioning the patient post-operatively about his allergic history, we discovered that he was allergic not only to mutton, but also had some discomfort in the form of palpitation, shortness of breath, and urticaria, when consuming beef and pork. Reports in the literature indicate that patients who are allergic to seafood, chicken, and/or fish are also allergic to succinylated gelatin [5-8]. Among the 27 total patients with succinylated gelatin allergy, 16 (59.2%) had no history of animal protein allergy, suggesting that clinicians should understand the history of allergy in detail. We should be cautious even when using succinylated gelatin in patients with no history of an animal protein allergy.

A review of the literature suggested that succinylated gelatin allergy has no relation to either age or sex. Succinylated gelatin allergic reaction usually occurs intraoperatively with a 169.7 ± 104.1 mL infusion over an interval of 11.78 ± 11.47 min. The initial clinical manifestations are an airway pressure surge with decrease in blood oxygen, blood pressure, heart rate, and central venous pressure. These changes are followed by functional alterations in the cardiovascular system. At the onset, urticaria develops on the patient's face, chest, bilateral upper limbs, and other body parts individually or simultaneously, and throughout the pathogenetic process.

The literature review also showed that the one-stage operation completion rate was 81.5% for all of the patients with succinylated gelatin injection-related allergy intraoperatively. Although succinylated gelatin may result in severe anaphylactic shock, we should not give it up. So long as the rescue is timely, active, and effective, we can save a life or even complete an operation. The effect of treatment and the prognosis are good

Conclusion

Succinylated gelatin is widely used intraoperatively for fluid expansion and though it can induce a severe allergic reaction, the rate of its occurrence is only 0.007%. If present, however, it could endanger the patient's life if not identified and treated on time. Thus, we recommend that when using gelatin preparations we should question the patient in addition to their drug allergy history, about their history of food allergies in detail, especially beef, mutton, and other animal-derived food allergies, even if they initially declare that they have no special drug or food allergies. Clinicians and anesthetists should comprehensively understand the trig-

gering mechanism, clinical manifestations, screening methods, and treatment principles of succinylated gelatin allergy. Such knowledge will involve close observation, timely discovery, decisive treatment, and active rescue measures. We can save the lives of these patients

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Disclosure of conflict of interest

None.

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