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RESEARCH ARTICLE

Risk factors and prevention for perioperative anaphylaxis: a nested case-control study

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Abstract

Background Perioperative anaphylaxis is rare but often severe. Little is known about the risk factors regarding perioperative anaphylaxis and the effect of anti-allergy premedication on prevention of perioperative anaphylaxis. *Objective* To identify the risk factors of perioperative anaphylaxis and to evaluate the prophylactic effects of anti-allergy premedication on perioperative anaphylaxis and investigate the factors associated with anti-allergy premedication options in patients who previously experienced anaphylaxis with unidentified culprits. *Setting* Surgical operation unit of the University Hospital in Chongqing, China. *Method* We identified patients who underwent surgery between Oct. 2012 and Dec. 2017. The study included two parts: in part one, a retrospective nested case-control study was used to identify the risk factors of perioperative anaphylaxis by logistic regression with 1 in 4 matching between patients with and without perioperative anaphylaxis; in part two, patients with high-risk anaphylaxis were included, in which patients who previously experienced anaphylaxis with unidentified culprits had been given anti-allergy premedication prior to the operation according to the degree of risk and severity of anaphylaxis. The prophylactic effects of anti-allergy premedication were evaluated and the factors associated with anti-allergy premedication options were explored. *Main outcome measure* Perioperative anaphylaxis occurrence. *Results* In part one, in the multivariate logistic analysis, history of drug allergy (OR 6.78; 95% CI, 2.35–19.54; $P<0.01$) and history of allergies to food or other substances (OR 40.56; 95% CI, 8.12–202.52; $P<0.01$) were associated with a higher risk of perioperative anaphylaxis. In part two, none of these patients either who had avoided culprits or who had been given anti-allergy premedication developed anaphylaxis during the surgical procedure. In the multivariate logistic model, history of grade II or grade III perioperative anaphylaxis (OR 9.09; 95% CI, 1.34–61.55; $P=0.02$) was identified as factor associated with anti-allergy premedication options in high-risk perioperative anaphylaxis patients. *Conclusion* In this study, history of drug allergy and history of allergies to food or other substances were significantly associated with perioperative anaphylaxis. Avoiding culprit drugs or taking rational anti-allergy premedication was critical to prevent perioperative anaphylaxis for surgical patients with high-risk factors.

Keywords Allergy · Nested case-control study · Perioperative anaphylaxis · Premedication · Risk factors

Impacts on practice

- History of drug allergy and history of allergies to food or other substances are significant risk for occurrence of perioperative anaphylaxis.
- Anti-allergy premedication can effectively prevent perioperative anaphylaxis when it is difficult to identify and avoid culprit drugs for surgical patients with high-risk factors.

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Introduction

Perioperative anaphylaxis is becoming more common due to increased use of anesthetics and the complexity of drug combinations [1]. It can have fatal outcomes and potentially involves life-threatening respiratory or cardiovascular problems if not identified and treated quickly. The incidence of perioperative anaphylaxis has been reported as 1 in 13,000 in France [2, 3], and ranged from 1 in 10,000 to 1 in 20,000 in Australia [4], with an estimated mortality varied from 3 to 9% according to different studies [5].

The majority of perioperative anaphylaxis was caused by drugs or substances associated with anesthesia. Previous studies [6–11] found that antibiotics, neuromuscular blocking agents (NMBAs), latex, chlorhexidine and induction agents were the most common substances incriminated in perioperative anaphylaxis. However, identifying offending drugs has become a major clinical problem, as patients are concurrently exposed to a large number of drugs in a short period of time [2, 12]. Moreover, the early cutaneous symptoms induced by anaphylaxis are sometimes difficult to recognise as patients are covered by surgical drapes and sedated during surgical procedures. Most importantly, for the reason of patient safety, the provocation test which is considered to be the gold standard for identifying the trigger of allergy can be practically difficult to perform for the majority of perioperative anaphylaxis [13, 14].

Although multiple risk factors for perioperative anaphylaxis, such as asthma, mastocytosis, spinal bifida, previous anaphylaxis during anesthesia, antibiotic allergy, seafood allergy, sensitization to exotic fruits or eggs/soybean oil etc, have been studied extensively in many descriptive studies [5, 15–17], little is known about risk factors regarding perioperative anaphylaxis in case control studies. Moreover, for patients with high-risk of perioperative anaphylaxis, prior studies [17, 18] suggested preoperative both anti-H1 and anti-H2 agents in conjunction with corticosteroids were the most commonly used medications to prevent anaphylaxis. In 2013, Manfredi et al. [18] proposed an anaphylactic risk score to mark some critical parameters associated with perioperative anaphylactic risk and to identify patients with high risk of developing perioperative anaphylaxis. According to calculated risk score, patients with perioperative anaphylactic risk were classed into three levels and the risk-oriented premedication protocols were recommended. However, this anaphylactic risk score has not yet been validated in large populations.

Aim of the study

This study aimed to (i) identify the risk factors of perioperative anaphylaxis by using a nested case-control design within the patients who underwent surgery and (ii) evaluate the prophylactic effects of anti-allergy premedication on perioperative anaphylaxis and investigate the factors associated with anti-allergy premedication options in high-risk perioperative anaphylaxis patients.

Ethics approval

This study was approved by the Institutional Review Board at the First Affiliated Hospital of Chongqing Medical University (2019-183). The requirement for informed consent was waived because of the anonymous nature and retrospective analysis of the data.

Method

Study population and patient selection

The study was conducted with surgical patients in the First Affiliated Hospital of Chongqing Medical University in China between Oct. 2012 and Dec. 2017. The study included two parts: for part one, we conducted a retrospective nested case-control study to identify risk factors of perioperative anaphylaxis. Cases covered patients who experienced perioperative anaphylaxis with a clinical diagnosis by anesthesiologists, controls covered patients who did not develop an allergic reaction on the day of surgery and did not use corticosteroids or antihistamines within a week before surgery. Four controls were individually matched to one case based on age range ± 5 years and the same date of operation. We excluded patients who experienced an allergic reaction one day before or after the surgery and whose data of anesthesia were missing. For part two, patients with high-risk anaphylaxis were included, in which patients who previously experienced anaphylaxis with unidentified culprits had been given anti-allergy premedication regimens prior to the operation according to the degree of risk and severity of anaphylaxis. The outcomes of anti-allergy premedication regimens were reviewed to evaluate the prophylactic effects on perioperative anaphylaxis. The factors associated with anti-allergy premedication regimen options were explored using logistic regression.

Diagnosis and severity review of perioperative anaphylaxis

The medical and anesthesia records of cases clinically diagnosed as perioperative anaphylaxis by anesthesiologists were reviewed again by two designated clinical

pharmacists according to the diagnostic criteria for perioperative anaphylaxis developed by Kroigaard and Garvey [19]. Anesthesia records with acute mucocutaneous signs (flushing, urticaria, erythema and angioedema), acute decrease in arterial blood pressure (hypotension was defined as systolic blood pressure <80 mmHg or a 40% decrease in systolic blood pressure within 5 min), and signs of dyspnea (wheezing consistent with increased ventilatory pressures, bronchospasm, or respiratory distress in a non-intubated patient) were examined. In addition, medical records were reviewed to identify other conditions that could lead to acute decompensation. The severity for perioperative anaphylaxis was assessed and classified into four grades according to Ring and Messmer system [12].

Patients considered as 'high risk' for perioperative anaphylaxis in this study were classified according to a history of perioperative allergic reaction, or a history of multiple drug allergies and/or multiple food or other substances allergies.

Access to risk factor data

Data were available on a range of established and hypothesized risk factors for perioperative anaphylaxis, including patient's gender, allergic diseases, history of drug allergy, history of allergies to food or other substances, anesthesia methods, surgery approaches, history of hypertension and using antihypertensive agents, such as ACE-inhibitors and Beta-blockers. The allergic diseases were involved with asthma, urticaria and allergic rhinitis. The surgery approaches were divided into abdominal, cardiothoracic, orthopedic, neurologic, otolaryngological, vascular and other surgery approaches. Risk factor data were obtained by abstracting data from medical and anesthesia records of the surgical patients.

Anti-allergy premedication regimens in cases of high-risk perioperative anaphylaxis

The recognition and evaluation for the high-risk perioperative anaphylaxis cases were based on the previous medical and anesthetic history and completed by anesthesiologists and clinical pharmacists. The anti-allergy premedication regimens had been recommended to patients identified with high risk. Anti-allergy premedication regimens were abstracted from medical and anesthetic records. Premedication regimens were then categorized into two regimens according to the administration time and were presented in Table 1.

Table 1 Anti-allergy premedication regimens for patients with high-risk factors for perioperative anaphylaxis

Regimens	Anti-allergy premedication regimen
Regimen A	Dexamethasone 10 mg intravenous, diphenhydramin 20 mg intramuscular and ranitidine 100 mg intravenous at 30 min before surgery
Regimen B	Dexamethasone 10 mg intravenous at 12 h, 6 h before surgery in conjunction with dexamethasone 10 mg intravenous, diphenhydramin 20 mg intramuscular and ranitidine 100 mg intravenous at 30 min before surgery

Statistical analysis

For descriptive analysis, continuous variables were expressed as mean and standard deviation; categorical variables were presented by frequency and percentage. Comparisons were made using Chi square test or Fisher exact test for categorical variables and t-test for continuous variables. Conditional logistic regression was used to identify risk factors of perioperative anaphylaxis and factors associated with anti-allergy premedication options by estimating odds ratios (ORs) and 95% confidence intervals. Risk factors were included into the multivariable logistic model if they showed univariate association with perioperative anaphylaxis or anti-allergy premedication options (at the 10% significance level).

$P<0.05$ was considered statistically significant; and all P values were 2-tailed. All analyses were performed in SPSS Statistics 24.0 (IBM SPSS, Armonk, USA).

Results

In part one, a total of 60 patients with perioperative anaphylaxis in the original medical records were reviewed by clinical pharmacists. None of them were initially recommended for anti-allergy premedication. Fourteen patients were excluded, for seven patients with allergic reaction one day prior to surgery and five patients with anaphylaxis after surgery and two patients whose data of anesthesia were missed. Therefore, there were 46 cases and 184 controls included in this retrospective study. In part two, there were a total of 93 patients included with high-risk perioperative anaphylaxis, in which 58 patients had been given anti-allergy premedication prior to the operation.

Clinical characteristics and risk factors

Clinical characteristics and risk factors for perioperative anaphylaxis in case and matched control group were summarized in Table 2. The distributions of age were accordant for

Table 2 Characteristics and risk factors of surgical patients in case and matched control groups for perioperative anaphylaxis

Items	Cases ($n=46$)	Controls ($n=184$)	P value
Age, years (mean ± SD[a])	53.0 ± 15.7	53.2 ± 14.8	1.00
Sex, *n* (%)			0.07
Female, *n* (%)	28 (60.9)	84 (45.7)	
Allergic history, *n* (%)			
Allergic diseases	8 (17.4)	5 (2.7)	< 0.01
Drug allergy	15 (32.6)	12 (6.5)	< 0.01
Allergies to food or other substances	15 (32.6)	3 (1.6)	< 0.01
Anesthesia methods, *n* (%)			0.10
Local/regional	3 (6.5)	31 (16.8)	
General	43 (93.5)	153 (83.2)	
Surgery approaches, *n* (%)			0.01
Abdominal	18 (39.1)	87 (47.3)	
Cardiothoracic	4 (8.7)	26 (14.1)	
Orthopedic	13 (28.3)	21 (11.4)	
Neurologic	1 (2.2)	9 (4.9)	
Otolaryngological	3 (6.5)	12 (6.5)	
Vascular	4 (8.7)	3 (1.6)	
Other	3 (6.5)	26 (14.1)	
Concomitant diseases, *n* (%)			
Hypertension	8 (17.4)	41 (22.3)	0.55
Anti-hypertensive agents, *n* (%)			
ACE-inhibitors[b]	5 (10.9)	18 (9.8)	0.79
Beta-blockers	3 (6.5)	3 (1.6)	0.10

[a]SD: Standard deviation

[b]ACE-inhibitors: Angiotensin converting enzyme inhibitors

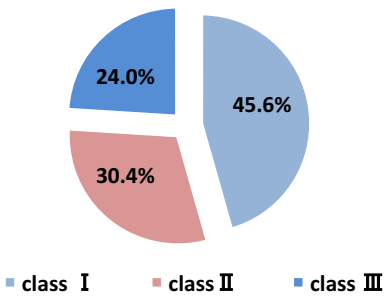

Fig. 1 The pie graph of severity for perioperative anaphylaxis in case group ($n=46$)

cases and controls. In case group of 46 patients, 28 (60.9%) were female, 8 (17.4%) had a history of allergic diseases, 15 (32.6%) had a history of drug allergy, 15 (32.6%) had a history of allergies to food or other substances, while three patients alone developed anaphylaxis during local anesthesia. There were significant differences with risk in history of allergic diseases, drug allergy, allergies to food or other substances and surgery approaches between the two groups ($P<0.05$). The severity for perioperative anaphylaxis of these 46 patients in case group was presented in Fig. 1.

Logistic regression analysis for risk factors in perioperative anaphylaxis

ORs and adjusted ORs with univariate and multivariate logistic regression analysis for perioperative anaphylaxis in case and matched control group were presented in Table 3. In univariate analysis, possible risk factors for anaphylaxis were identified: history of allergic diseases, history of drug allergy, history of allergies to food or other substances, surgery approaches ($P<0.05$). In multivariate model, after adjustment for the other variables, there was no significant difference in history of allergic diseases but the other risk factors identified in univariate analysis showed significant difference associated with perioperative anaphylaxis. Thus, compared with those who without a history of drug allergy, the patients with a history of drug allergy had a 6 times increased risk for perioperative anaphylaxis (OR 6.78; 95% CI, 2.35–19.54; $P<0.01$). Similarly, if the patient had a history of allergies to food or other substances, the risk for perioperative anaphylaxis was 40 times higher (OR 40.56; 95% CI, 8.12–202.52; $P<0.01$). Relative to abdominal surgery, orthopedic surgery (OR 3.03; 95% CI, 1.06–8.63; $P=0.04$) and vascular

Table 3 Logistic regression analysis for risk factors in perioperative anaphylaxis cases

Risk factors	Univariate analysis			Multivariate analysis		
	ORs[a]	95% CI	*P* value	ORs[a,b]	95% CI	*P* value
Sex						
Female	1.82	0.96–3.58	0.07	1.83	0.77–4.36	0.17
Allergic history						
Allergic diseases	7.54	2.34–24.31	0.01	3.88	0.67–22.47	0.13
Drug allergy	6.94	2.96–16.23	< 0.01	6.78	2.35–19.54	< 0.01
Allergies to food and other substances	29.19	7.98–106.78	< 0.01	40.56	8.12–202.52	< 0.01
Anesthesia methods						
General	2.90	0.85–9.96	0.09	3.64	0.72–18.39	0.12
Surgery approaches						
Abdominal		Reference			Reference	
Cardiothoracic	0.74	0.23–2.39	0.62	0.28	0.05–1.51	0.14
Orthopedic	2.99	1.27–7.06	0.01	3.03	1.06–8.63	0.04
Neurologic	0.54	0.06–4.51	0.57	0.42	0.04–4.01	0.45
Otolaryngological	1.21	0.81–4.72	0.79	0.57	0.08–4.10	0.58
Vascular	6.44	1.33–31.31	0.02	16.56	2.95–92.90	0.01
Other	0.56	0.15–2.04	0.38	0.18	0.02–2.04	0.17
Concomitant diseases						
Hypertension	0.73	0.32–1.70	0.47			
Anti-hypertensive agents						
ACE-inhibitors[c]	1.14	0.37–3.54	0.82			
Beta-blockers	4.21	0.82–21.58	0.09	0.16	0.00–16.56	0.44

[a]ORs: odds ratios

[b]Adjusted for the other variables in the table apart from hypertension and ACE-inhibitors

[c]ACE-inhibitors: Angiotensin converting enzyme inhibitors

surgery (OR 16.56; 95% CI, 2.95–92.90; $P < 0.01$) were at increased risk for perioperative allergic reaction.

Clinical characteristics and anti-allergy premedication outcomes in cases of high-risk perioperative anaphylaxis

A total of 93 patients with high-risk of perioperative anaphylaxis were identified, and their clinical characteristics were summarized in Table 4. 35 (37.6%) patients had definite culprits, of these patients, 34 patients had previous antimicrobial allergic reaction and one patient was allergic to antipyretic analgesics. Fourteen patients completely avoided the trigger during the operation and 21 patients changed to another antibacterial. None of the 35 patients developed an allergic reaction during their surgical procedures. 58 (62.4%) patients had been administrated anti-allergy premedication prior to the operation due to previous anaphylaxis with unidentified culprits, in which 36 patients had previous perioperative anaphylaxis. The surgical procedures were uneventful for the 58 patients.

Factors associated with anti-allergy premedication options in high-risk perioperative anaphylaxis patients

Risk factors for perioperative anaphylaxis between premedication regimen A and regimen B (Table 1) were compared by univariate and multivariate logistic analysis and the results were presented in Table 5. In univariate analysis, the characteristics associated with premedication regimen B were history of allergic diseases, more than two allergens to food or other substances, history of grade II or grade III perioperative anaphylaxis, orthopedic surgery, using ACE-inhibitors. In multivariate model, after adjustment for the other variables, only history of grade II or grade III perioperative anaphylaxis (OR 9.09; 95% CI, 1.34–61.55; $P = 0.02$) was associated with anti-allergy premedication options in high-risk perioperative anaphylaxis patients.

Table 4 Clinical characteristics of patients with high-risk perioperative anaphylaxis

Characteristics	*N* (%) (*n* = 93)
Age (mean ± SD[a])	49.7±18.3
Sex	
Female	35 (37.6)
Allergic histories	
Allergic diseases	14 (15.1)
Drug allergy	69 (74.2)
Allergies to food or other substances	24 (25.8)
Previous perioperative anaphylaxis	
Yes	36 (38.7)
Anesthesia methods	
Local/regional	23 (24.7)
General	70 (75.3)
Surgery approaches	
Abdominal	31 (33.3)
Cardiothoracic	10 (10.8)
Orthopedic	22 (23.7)
Neurologic	5 (5.4)
Otolaryngological	15 (16.1)
Vascular	3 (3.2)
Other	7 (7.5)
Concomitant diseases	
Hypertension	15 (16.1)
Anti-hypertensive agents	
ACE-inhibitors[b]	7 (7.5)
Beta-blockers	2 (2.2)

[a]SD: standard deviation

[b]ACE-inhibitors: Angiotensin converting enzyme inhibitors

Discussion

Perioperative anaphylaxis is a potential life-threatening reaction and has a higher mortality than anaphylaxis occurring in other settings. In this nested case-control study, we found that several risk factors were associated with perioperative anaphylaxis and allergy evaluation followed by anti-allergy premedication played a crucial role in preventing perioperative anaphylaxis.

In our study, although no grade IV perioperative anaphylaxis was identified, 24% of patients experienced a life-threatening grade III allergic reaction. Therefore, identifying the risk factors and establishing preventing protocols are of crucial importance. The identified causes and risk factors for perioperative anaphylaxis were reported by a large number of documents [6–11]. However, unless there is a validated provocation test, identifying culprit allergens can be quite difficult in a significant number of cases. In this study, we identified risk factors through univariate and multivariate logistic analysis. In univariate analysis, history of allergic diseases, drug allergy, allergies to food or other substances, surgery approaches were associated with increased risk for perioperative anaphylaxis; but history of allergic diseases (OR 3.88; 95% CI, 0.67–22.47; $P = 0.13$) did not show significant difference in multivariate logistic model. However, prior studies [1, 17, 20] described asthma as a moderate risk factor for anaphylaxis during general anesthesia; It was found by Faitelson et al. [21] asthma (OR, 0.12; 95% CI, 0.017–0.869; $P = 0.03$) was significantly associated with Amoxicillin allergy in multivariate logistic regression model; asthma had been shown to aggravate allergic reactions in previous studies [22, 23]. In our study, asthma was not isolated from allergic diseases, while other allergic diseases had not been found to be risk factors for allergic reaction in published studies. Meanwhile, a recent study [24] has also shown that history of asthma may not be associated with anaphylactic bronchospasm since it has different mechanisms for increased airway resistance. These could be the reasons why in our study history of allergic diseases turned out not to be a significant risk factor for perioperative anaphylaxis.

It has been revealed by our study that history of drug allergy (OR 6.78; 95% CI, 2.35–19.54) was a high-risk factor for perioperative anaphylaxis probably because of cross-reactivity between different drugs. There were cross-reactivity, for example, among iodinated contrast agents, NMBAs, penicillin and fist-generation cephalosporin [4, 17, 20] and also between NMBAs and other drugs containing quaternary or tertiary ammonium ions such as pholcodine, choline, morphine, neostigmine and pentolinium etc [16]. Also, cross-reactivity between drugs and food was often quoted in studies, for example, eggs, peanuts and soybean oil are in cross-reactivity with propofol, seafood with protamine, and certain fruits (banana, kiwi, avocado and others) with latex [14, 17, 25]. In our study, we found that history of allergies to food or other substances (OR 40.56; 95% CI, 8.12–202.52) was associated with significantly higher odds ratios of perioperative anaphylaxis. Whereas, some studies [20, 25] had shown that there was no contraindication for the use of propofol with patients allergic to soybean oil or peanuts, eggs. Pascale et al. [20] also proposed there was no sufficient evidence to prove protamine was likely to provoke allergic reaction in subjects with fish allergy. The results of our study showed that there was probably cross-reactivity between drugs and food, but we did not classify food allergy in our study, so the cross-reactivity among propofol, soybean oil, peanuts and eggs and between protamine and fish food should be further studied in case control study.

Interestingly, multivariable analysis found that orthopedic surgery (OR 3.03; 95% CI, 1.06–8.63) and vascular surgery (OR 16.56; 95% CI, 2.95–92.90), relative to abdominal surgery, could increase the risk of perioperative anaphylaxis, which had never been reported in previous studies. The

Table 5 Logistic regression analysis for factors associated with anti-allergy premedication options

Variables	Premedication regimens		Univariate analysis			Multivariate analysis		
	Regimen A ($n=42$)	Regimen B ($n=16$)	ORs[a]	95% CI	*P* value	ORs[a,b]	95% CI	*P* value
Age (mean ± SD)	52.2 ± 14.8	57.5 ± 17.3	1.02	0.98–1.06	0.25			
Sex, *n* (%)								
Female	28 (66.7)	10 (62.5)	0.83	0.25–2.76	0.77			
Allergic histories, *n* (%)								
Allergic diseases								
No	37 (88.1)	10 (62.5)		Reference			Reference	
Yes	5 (11.9)	6 (37.5)	4.44	1.12–17.60	0.03	3.99	0.48–33.53	0.20
Number of allergenic drugs								
≤ 1	24 (57.1)	8(50.0)	reference					
≥ 2	18 (42.9)	8 (50.0)	1.33	0.18–2.06	0.63			
Number of allergenic food or other substances								
≤ 1	37 (88.1)	9(56.3)		Reference			Reference	
≥ 2	5 (11.9)	7 (43.7)	5.76	1.48–22.41	0.01	7.65	0.95–61.40	0.06
Severity of previous perioperative anaphylaxis, *n* (%)								
No + I	33 (78.6)	7 (43.8)		Reference			Reference	
II + III	9 (21.4)	9(56.3)	4.71	1.38–16.17	0.01	9.09	1.34–61.55	0.02
Anesthesia methods, *n* (%)								
General	35 (83.3)	14 (87.5)	1.40	0.26–7.58	0.70			
Surgery approaches, *n* (%)								
Abdominal	20 (47.6)	5 (31.3)		Reference			Reference	
Cardiothoracic	6 (14.3)	1 (6.3)	0.67	0.07–6.87	0.73	1.01	0.07–15.59	0.99
Orthopedic	5 (11.9)	7 (43.8)	5.60	1.24–25.33	0.03	4.79	0.64–35.71	0.13
Neurologic	3 (7.1)	0 (0.0)	–	–	–	–	–	–
Otolaryngological	4 (9.5)	2 (12.5)	2.00	0.28–14.20	0.49	1.87	0.19–18.32	0.59
Vascular	3 (7.1)	0 (6.7)	–	–	–	–	–	–
Other	1 (2.4)	1 (6.3)	4.00	0.21–75.66	0.36	3.41	0.09–132.52	0.51
Concomitant diseases, *n* (%)								
Hypertension	4 (9.5)	4 (25.0)	3.17	0.69–14.63	0.14			
Anti-hypertensive agents, *n* (%)								
ACE-inhibitors[c]	1 (2.4)	4 (25.0)	13.67	1.39–134.12	0.03	7.44	0.20–281.24	0.28
Beta-blockers	0 (0.0)	2 (12.5)	–	–	–			

[a]ORs: odds ratios

[b]Adjusted for the other variables in the table apart from age, sex, number of allergenic drugs, anesthesia methods, hypertension and Beta-blockers

[c]ACE-inhibitors: Angiotensin converting enzyme inhibitors

underlying reason for these findings was probably that most orthopedic and vascular surgeries require the implantation of foreign materials whether it is prosthesis or a stent which could cause an allergic reaction. However, the real reason why some surgeries carry a higher allergic reaction risk requires further investigation in future research.

Medication with Beta-blockers and ACE-inhibitors had been reported to increase the risk of allergic reaction [26–28]. It was supposed that ACE-inhibitors could increase the concentration of bradykinin in circulation by inhibiting its degradation and Beta-blockers and ACE-inhibitors also could be associated with direct mast cell priming effects [28]. In our study, Beta-blockers and ACE-inhibitors medication were not found to be associated with increased risk for perioperative anaphylaxis in both univariate and multivariate analysis.

In an ideal situation, patients suffering from perioperative anaphylactic shock would be tested and re-challenged to identify culprits. Unfortunately, it is almost impractical for patients who required anesthesia for emergency surgery and at times when information regarding the history of allergy is unavailable, coupled with the lack of reliable

and validated tests for drug allergy [19, 29]. Therefore, for these patients, effective prevention strategies are essential, involving avoidance of high-risk agents responsible for perioperative anaphylaxis and adherence to the general precautions in future anesthesia procedures. In our study, 35 patients whose surgical procedures were uneventful had avoided definite culprit agents during the operation, which proved that avoiding culprits was essential to prevent allergic reaction. Fiftyeight patients who previously experienced anaphylaxis with unidentified culprits had been given anti-allergy premedication and did not develop an allergic reaction during their surgical procedures. So we believed that preoperative anti-allergy premedication was efficient for preventing perioperative anaphylaxis. Similar to our study, Jelena et al. [17] suggested anti-allergy premedication regimens for non-emergency surgery and emergency surgery. Laguna et al. [30] recommended that patient with a suggestive clinical allergy history should be pre-treated with antihistamines. Some studies [17, 19] pointed out that although premedication with antihistamines and corticosteroids would not probably prevent anaphylactic shock, it was able to prevent or alleviate reactions caused by non-specific histamine release. Other studies proposed that except avoiding culprits, there were no premedication strategies that can effectively prevent an allergic reaction in the operative setting [3, 31]. Different from these studies, anti-allergy premedication regimens were applied and stratified in our research according to the degree of risk and severity of anaphylaxis and their preventative effect was quite promising.

We further evaluated factors associated with the anti-allergy premedication options. with history of grade II or grade III perioperative anaphylaxis (OR 9.09; 95% CI, 1.34–61.55) should be recommended stronger anti-allergy premedication regimen. The result was consistent with a previous study which suggested the severity of previous perioperative anaphylaxis was a crucial factor affecting physicians' evaluation of their patients [15].

There were limitations of this present study. As this was a single-center retrospective cohort of surgery patients, the results may be influenced by clinical practices that were different from other institutions; there was the potential for selection bias. Our clinical evaluation of anaphylaxis, grading of severity, acquisition of allergy histories and allergies diseases of patients were based on the anesthesia notes and medical records, there was the potential for information bias. In addition, the sample size of this study was comparatively small since perioperative anaphylaxis was rare. So a prospective, multi-centre study should be conducted in the future to further explore risk factors and rational anti-allergy premedication in high-risk surgical patients and provide a more precise view of general precautions.

Conclusion

In conclusion, few studies had examined risk factors and anti-allergy premedication outcomes for perioperative anaphylaxis based on nested case-control study. Our study identified the history of drug allergy and history of allergies to food or other substances as the risk factors of perioperative anaphylaxis. Therefore, thorough evaluation to identify culprits and risk factors are necessary to guide future management and prevention approaches. We also found avoiding culprit drugs or taking rational anti-allergy premedication was critical to prevent perioperative anaphylaxis for surgical patients with high risk factors.

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