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Perioperative anaphylaxis: a potential hazard to the safety of surgical patients

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Anaphylaxis is a rare, but severe, potentially life-threatening allergic reaction, which most commonly presents with multi-system involvements, such as cutaneous, cardiovascular, respiratory, gastrointestinal and central nervous system signs and symptoms. It can hardly be recognized when occurring in the perioperative period due to the many influencing factors, for example, the cutaneous changes concealed by sterile drapes, inability to describe their symptoms when patients are sedated or anesthetized, and the application of anesthetics leading to sympathetic blockade which presents with blood pressure decrease. All of the above reasons make the identification and immediate treatment of perioperative anaphylaxis difficult and are partially attributable to high mortality.

The overall incidence rate of anaphylaxis during general anesthesia varies greatly worldwide, ranging from 1:20,000 to 1:381.[1,2] The mostly common cause of perioperative anaphylaxis is the use of the neuromuscular blocking agents (NMBAs), antibiotics, antiseptics (such as chlorhexidine), gelatin, latex, and others.[3]

The use of NMBAs, a major cause of perioperative anaphylaxis, has already aroused the attention of anesthesiologists worldwide. Among the NMBAs used commonly in clinical practice, rocuronium is one of the most common culprits in the United Kingdom[3] and Western Australia,[4] while succinylcholine is responsible for over half of the cases of anaphylaxis caused by NMBAs in the France.[5] The big difference in the published incidences of anaphylaxis to NMBAs among studies is mainly due to the variations in local practice, official sales, NMBA exposure, and drug preferences. There have been few reported cases of anaphylaxis triggered by pancuronium or cisatracurium.[3,4] Analysis of recent data on anaphylaxis to NMBAs is shown in Table 1.

Several epidemiologic investigations show that antibiotics are common among the top three culprits of perioperative anaphylaxis and the proportion of anaphylactic episodes related to antibiotics significantly increases in recent years.[3,6-8] β-Lactam antibiotics have been identified as a common cause of perioperative anaphylaxis.[9] Immediate hypersensitivity reactions to β-lactam antibiotics may be because of reactivity to the β-lactam moiety or the side chain. Penicillin, amoxicillin, and cephalosporins, which share the β-lactam ring, have been reported as the leading antibiotic triggers for perioperative anaphylaxis.[6,10]

Anaphylaxis to chlorhexidine is an emerging concern. Routes of exposure to chlorhexidine can be divided into three categories: topical cutaneous (such as surgical skin preparation), mucous membrane (such as lubricant gels for urethral catheterization, and vaginal and rectal examination), and parenteral administration (such as a coated central venous catheter). However, it is an easily overlooked trigger due to the atypical presentation of chlorhexidine. It is reported that only 28% of allergies to chlorhexidine are suspected by anesthesiologists.[3] If this potential trigger (eg, coated central venous catheter) is not recognized as the source of the problem and removed, prolonged and intractable anaphylaxis may occur.

The clinical symptoms and signs of anaphylaxis during anesthesia do not vary from those of anaphylaxis in general. The classic clinical features of anaphylaxis are symptoms of the skin and mucous membranes, respiratory system, cardiovascular system, central nervous system, and gastrointestinal system.[11]

For anesthetized patients, the cardiovascular symptoms of anaphylaxis often comprise hypotension and tachycardia, which may rapidly progress into cardiovascular collapse if

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Table 1: The incidences and proportions of anaphylactic reactions to different NMBAs in several epidemiologic surveys.

NMBAs	United Kingdom[3] (2016)		Western Australia[4] (2002–2011)		French[5] (2000–2012)	
	Incidence per 100,000 administrations	Proportion (%)	Incidence per 100,000 administrations	Proportion (%)	Incidence per 100,000 administrations	Proportion (%)
Rocuronium	5.9	41.5	8.0	71.0	11.8	9.6
Atracurium	4.2	35.5	4.0	11.0	1.1	15.9
Succinylcholine	11.1	21.5	ND	ND	14.8	64.0
Mivacurium	3.3	1.5	ND	ND	1.2	0.9
Vecuronium	0	0	2.8	14.0	0.6	2.1
Pancuronium	0	0	0	0	0.6	0.9
Cisatracurium	0	0	0	0	15.9	6.6
Total NMBAs	5.3	100	NM	100	3.0	100

NMBAs: Neuromuscular blocking agents; ND: No detail mentioned.

not recognized and treated in time. The respiratory symptoms, such as oxygen desaturation, difficult ventilation, bronchospasm, airway angioedema, are also common. The cutaneous symptoms, such as erythema, flushing, urticaria and/or angioedema, are common but easily ignored because these features are usually hidden by surgical drapes. Gastrointestinal symptoms (such as crampy abdominal pain, vomiting) and central nervous symptoms (for example, confusion, agitation, and loss of consciousness) can be observed only when patients are conscious in the perioperative period.[6,11,12]

Perioperative anaphylaxis is not always easy to recognize. It requires two elements. (a) Acute onset of anaphylactic reactions: the majority of perioperative anaphylaxis occur within minutes after exposure to triggers, which are often administered intravenously. However, some triggers (eg, latex, chlorhexidine, and the dye patent blue) administered via other routes (eg, skin and mucosa, urethra, peritoneum, or subcutaneous) may cause reactions after more than 15 min. (b) Typical symptoms occur in two or more systems: skin and mucous membranes, respiratory, cardiovascular, gastrointestinal, and central nervous systems.[11] Many anesthesiologists to diagnose anaphylaxis in time as they believe there should be cutaneous signs. However, cutaneous signs can be subtle or absent in up to 20% of reactions.

The grading system of anaphylaxis is important for guiding initial management and facilitating case reports and clinical research.[13] As the clinical manifestations of perioperative anaphylaxis show striking variations of severity ranging from mild to catastrophic, the severity-grading of anaphylactic reactions mainly depends on clinical signs and symptoms of patients. In the available literature, a number of grading systems with three, four, or five scales have been developed as ways of stratifying the severity of anaphylactic reactions. The most quoted grading system is developed by Ring and Messmer,[14] which includes the four grades: grade 1 (mild) is generalized cutaneous signs (erythema, urticaria with or without angioedema); grade 2 (moderate) is moderate multi-organ involvement with cutaneous signs, hypotension, and tachycardia, bronchial hyperreactivity (cough, ventilatory impairment); grade 3 (life-threatening) is severe life-threatening multi-organ involvement requiring specific treatments (circulatory collapse, tachycardia or bradycardia, cardiac arrhythmias, bronchospasm), but the cutaneous signs may be absent or occur only after the arterial blood pressure recovers; and grade 4 (arrest) is circulatory or respiratory arrest. The Scandinavian clinical practice guidelines on anaphylaxis add a fifth severity category, where grade 5 is death due to a lack of response to cardiopulmonary resuscitation.[12] The members of the Australian and New Zealand Anesthetic Allergy Group (ANZAAG) have proposed a new grading system of the Perioperative Anaphylaxis Grading System (PAGS).[13] It defines three grades of anaphylaxis: A, moderate; B, life-threatening and C, cardiac arrest with or without respiratory arrest. The grading system of PAGS removes grade 1 (mild) reactions as only the appearance of cutaneous symptoms in a stable patient should not prompt the use of epinephrine and the initiation of resuscitative treatments.

The cornerstones of treatments for perioperative anaphylaxis are intravenous epinephrine and fluid resuscitation. In managing perioperative anaphylaxis, there are actually no contraindications for the use of epinephrine. It must be emphasized that failure to inject epinephrine promptly is potentially associated with fatal outcomes. The available evidence that fatal anaphylaxis is significantly associated with delayed epinephrine administration and epinephrine is often under-used during anaphylaxis treatment.[11] However, potentially serious adverse effects by an overdose of epinephrine, such as ventricular arrhythmias, hypertensive crisis, and pulmonary edema, should not be ignored. Thus, it is best that epinephrine is intravenously tailored according to clinical severity. In addition, aggressive fluid resuscitation should immediately be initiated to treat the intravascular volume depletion. However, fluid administration is not always sufficient.[3] To date, several guidelines or consensus recommendations on the management of perioperative anaphylaxis about the intravenous epinephrine dose and fluids in adults are shown in Table 2.[6,12,15-19] In particular, in 2014, the Anesthesiology Branch of the Chinese Medical Association issued an expert consensus on the diagnosis and treatment of perioperative anaphylaxis, in which clinical symptoms, diagnosis, and treatments of perioperative anaphylaxis

Table 2: Summary of immediate management of perioperative anaphylaxis in adults in different guidelines or consensus recommendations.

Guidelines	Treatments	Grade 1	Grade 2	Grade 3	Grade 4
International[16] (2019)	IV EP	ND	• 20 μg bolus • Inadequate response at 2 min, escalate to 50 μg • Repeat every 2 min	• 50 μg bolus or 100 μg bolus if inadequate response to other vasopressors or bronchodilators • Inadequate response at 2 min, escalate to 200 μg • Repeat every 2 min	• 1 mg • Repeat as per ALS guidelines • ECM if: SBP < 50 mmHg or $P_{ET}CO_2$ < 20 mmHg
	IV fluids	ND	• Rapid bolus crystalloid fluid 500 mL • Review responses • Repeat as needed	• 1 L rapid bolus • Review responses • Repeat as needed up to 30 mL/kg	Following ALS guidelines
SEAIC and SEDAR[15] (2018)	IV EP	ND	20–30 μg	100–200 μg	1 mg
	IV fluids	ND	ND	ND	ND
ANZCA and ANZAAG[17] (2017)	IV EP	ND	• 20 μg bolus • Repeat every 1–2 min • Increase dose if unresponsive • > 3 boluses of epinephrine start infusion	• 100–200 μg bolus • Repeat every 1–2 min • Increase dose if unresponsive	• 1 mg (Repeat 1–2 min) • ALS guidelines • Immediately start CPR
	IV fluids	If hypotensive: elevate legs; bolus crystalloid fluid 2L, repeat as needed; large-bore IV access, and warm IV fluids if possible.			
SFAR and SFA[18] (2011)	IV EP	ND	• 10–20 μg bolus • Repeat every 1–2 min • Increase dose if unresponsive	• 100–200 μg bolus • Repeat every 1–2 min • Increase dose if unresponsive • IV infusion at a dose of 0.05–0.1 μg/kg/min removes the need for a repetitive bolus of epinephrine	• 1–2 mg bolus • Repeat every 1–2 min • Initiate cardiac message
	IV fluids	Elevate the lower limbs; rapid infusion of isotonic crystalloid solutions; colloids are substituted when the volume of crystalloids administered exceeds 30 mL/kg.			
AAGBI[6] (2009)	IV EP	• Initial dose: 50 μg bolus • Several doses may be required if there is severe hypotension or bronchospasm • Starting infusion if several doses are required			
	IV fluids	If hypotensive: elevate legs; administer 0.9% saline or lactated Ringer's solution at a high rate.			
SSAI[12] (2007)	IV EP	ND	10–50 μg bolus	• 100 μg–1 mg bolus • Infusion: start at 0.05–0.1 μg/kg/min • If no IV access, 500–800 μg IM	ND
	IV fluids	0.9% saline 9 mg/mL, Ringer's acetate or colloids; bolus fluid 20 mL/kg, more may be needed			
China[19] (2014)	IV EP	• Initial dose: 30–50 μg bolus • Repeat every 5–10 min • IV infusion at a dose of 1–10 μg/min as needed			
	IV fluids	ND	ND	ND	ND

SEAIC and SEDAR: The Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology and the Spanish Anesthesia Society; ANZCA and ANZAAG: The Australian and New Zealand College of Anesthetists and the Australian and New Zealand Anesthetic Allergy Group; SFAR and SFA: The French Society for Anesthesia and Intensive Care and the French Society of Allergology; AAGBI: The Association of Anesthetists of Great Britain and Ireland; CPR: Cardiopulmonary resuscitation; SSAI: The Scandinavian Society of Anesthesiology and Intensive Care Medicine; ND: No details mentioned; ALS: Advanced life support; ECM: External cardiac massage; IV: Intravenously; IM: Intramuscularly; EP: Epinephrine.

were described in detail, and a warning card of perioperative anaphylaxis was provided.[19] Recently, Zong and Hu[20] again reviewed the etiology, diagnosis, prevention, and treatment of perioperative anaphylaxis, in order to improve clinicians' awareness of this life-threatening event and reduce the related morbidity and mortality.

In conclusion, perioperative anaphylaxis is often a life-threatening clinical condition involving multiple organ systems, with the severity ranging from mild to catastrophic. As the incidence of perioperative anaphylaxis is relatively low and clinical features are most changeful, it is difficult for anesthesiologists to accurately recognize and properly respond within a short time, which may significantly reduce the mortality rate. Therefore, both the mastery of clinical features of perioperative anaphylaxis and immediate initiation of effective management are very important for successful treatment.

Conflicts of interest

None.

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