Original Article

An Analysis of Perioperative Anesthetic Adverse Events in Thailand [PAAd Thai]: Allergic Reaction/Anaphylactoid/ Anaphylaxis

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Background: Perioperative anaphylaxis or anaphylactoid reaction is an uncommon event and difficult to diagnose. Clinical symptoms range from mild with skin lesion to serious life-threatening conditions.

Objective: To describe characteristics of patients who developed anaphylaxis or anaphylactoid reaction during anesthesia including signs, symptoms, treatment, outcome, and suggestive strategies for perioperative anaphylaxis or anaphylactoid reaction in Thailand.

Materials and Methods: A prospective descriptive study was conducted by using data from first 2,000 incident reports of the Perioperative and Anesthetic Adverse Events in Thailand [PAAd Thai] study. Patient characteristic and detail of anaphylaxis including signs, symptoms, probable causes, treatment, and immediate outcome were recorded. All data were reviewed by three experienced anesthesiologists. Descriptive statistics was used.

Results: After reviewed, 70 incidents were identified as perioperative anaphylaxis or anaphylactoid reaction. Anaphylaxis occurred more commonly in female. Most (98.5%) were ASA I-III with mean age 42.6±2.5 years. Seventy-two-point-nine percent of events occurred during general anesthesia. By using clinical severity, patients were classified as grade I, II, III, in 38, 4, and 28 patients, respectively. Suspected causes were identified in 41 cases. The most common causes were antibiotic, blood component, and colloid, in 13, 9, and 6 cases, respectively. Clinical manifestations of grade III were hypotension, rash or urticarial, bronchospasm, tachycardia, and angioedema, in 21, 18, 15, 11, and 5 patients, respectively. Only 19 from 28 patients in grade III received adrenaline treatment. All patients in grade I and II recovered completely. In grade III, surgery was postponed in five cases and two cases were admitted to ICU. Only one patient received serologic test and skin test.

Conclusion: To improve outcome, guidelines for perioperative anaphylaxis management should be followed. After anaphylaxis event, proper investigation to identify definite cause should be done at proper time.

Keywords: Anaphylaxis, Anaphylactoid reactions, Allergic reactions, Perioperative, Adverse event, Drug allergy

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Anaphylaxis is a clinical syndrome that involves skin, mucous membrane, gastrointestinal tract, respiratory, and cardiovascular system. Anaphylaxis is an uncommon adverse event during anesthesia. Perioperative anaphylaxis can present from mild symptoms involving only the skin or cutaneous to serious systemic life-threatening conditions. The exact incidence is difficult to determine. Some studies reported the incidence between 1/10,000 to 1/20,000[1-3]. In 2005, The Royal College of Anesthesiologists of Thailand hosted the Thai Anesthesia Incidents Study [THAI study]. It revealed the incidence of drug allergy, anaphylactoid, and anaphylaxis to be 1:5,500[4]. The subsequent study of the Thai Anesthesia Incidents Monitoring Study [Thai AIMS] in 2007 using incident reports among fifty-one hospitals across Thailand in

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the concepts of "from routine to research and from research to routine practice", reported 43 anaphylaxis events from 2,537 incident reports[5]. Neuromuscular blocking agents [NMBAs] were suspected as the main causative agents, similar to the other studies[1,5-9]. Perioperative and Anesthetic Adverse events in Thailand [PAAd Thai] incident reporting study in 2015 demonstrated the incidence of drug allergy, anaphylaxis, or anaphylactoid reaction as 2.37:10,000[10]. Even the incidence of anaphylaxis did not change. In current practice, usage of perioperative antibiotic prophylaxis is increasing. Various drugs such as new NMBAs and reversal, and non-steroidal anti-inflammatory drugs [NSAIDs] have been introduced into clinical practice. Perioperative anaphylaxis can be changed. The present study aimed to describe characteristics of patients who developed allergic reaction and anaphylaxis during anesthesia including common signs, symptoms, treatment, outcome, and suggestive strategies for prevention.

Materials and Methods

As part of the PAAd Thai study, a multicentered observational study using incident reporting system in 22 government hospitals (eight university and fourteen service-based hospitals) across Thailand[10]. After approval of ethical consideration by each institutional ethical committee, informed consent was waived due to observational data collection fashion. During the 12 months period between January 1 and December 31, 2015, structured data collection form was requested to be filled by the anesthesia attending and/or the site managers. Anesthesia personnel in 22 participating hospitals voluntarily reported adverse events that occurred during anesthesia and within 24 hours postoperatively on an anonymous basis. From the first 2,000 adverse events, patient demographic data, detail of operation, anesthetic technique, drug, and use of surgical safety checklists were recorded. The perioperative anaphylaxis, anaphylactoid, or allergic reaction was defined as a severe hypersensitivity reaction with angioedema, unexplained hypotension, bronchospasm, erythema, rash, or urticaria that happen during anesthesia. The detail of the allergic events including signs, symptoms, probable causes, treatment, immediate outcome, factors contributing, factors minimizing, and suggested preventive strategies were recorded. All data were reviewed by a group of three experienced anesthesiologists. SPSS for windows version 23 were used for data analysis. Continuous variables will be shown as mean ± SD. Categorical data will be shown as number and percentages.

Results

From first 2,000 incident reports, 75 adverse events were reported from 17 hospitals as allergic events. Seventy relevant incidents were identified as perioperative anaphylaxis, anaphylactoid reaction, or allergic events. The demographic data including age, sex, the American Society of Anesthesiologists [ASA] physical status, urgency and type of surgery, anesthetic technique, and timing of event are shown in Table 1.

Most of the events were found in patients that received general anesthesia and occurred during induction and maintenance phase. By using clinical severity[11], patients were divided to four groups as shown in Table 2.

Grade I reaction occurred in 23 females, 15 males. Twenty-nine patients (76.3%) were ASA I and II. The culprit agents were identified by clinical and timing of event in 22 cases. Rash or urticaria appeared after receiving blood components in eight cases, pethidine in four cases, and morphine in three cases equal to antibiotic (two from cefazolin and one from clindamycin). Each of haemaccel, thiopental, and propofol caused skin reaction in one case, same

Table 1. Patient demographic, surgical and anesthetic data (n = 70)

Age (year), mean ± SD	42.64±2.46
ASA, n (%)	
1	20 (28.6)
2	28 (40.0)
3	21 (30.0)
4	1 (1.4)
Emergency, n (%)	14 (20.0)
Type of surgery, n	
Orthopaedic	20
General	11
Gynecological	8
Cesarean section	6
Urological	5
Intervention/endoscopic	5
Otorhino laryngological & opthalmological	5
Cardiothoracic & vascular	5
Neurosurgery	4
Plastic	1
Anesthetic technique, n (%)	
General anesthesia alone	51 (72.9)
Spinal anesthesia	18 (25.7)
Monitored anesthesia care	1 (1.4)
Timing of events, n (%)	
Induction	24 (34.3)
Maintenance	25 (35.7)
Emergence	15 (21.4)
Post anesthesia care unit	6 (8.6)

ASA = American Society of Anesthesiologists physical status

as micropore tape. Six patients received no treatment. Twenty-two patients received only H1 antihistamine. Nine patients received H1 blocker and steroid. Only one case received H1, H2 blocker, and steroid.

Grade II reaction were reported in two females and two males. Two patients developed rash and nausea after received cefazolin. H1, H2 blocker and steroid were given in the first case and H1 blocker with steroid for the other. The third patient had tachycardia followed by rash five minutes after ceftriaxone. Only H1 antihistamine was given. The last patient had mild hypotension after received ampicillin. Blood pressure was restored to normal after given steroid and intravenous colloid infusion.

Twenty-eight cases were classified into grade III. The suspected causes of grade III allergic reaction were identified in 15 cases. Antibiotics were the most common causative agents, involved in six patients (ceftriaxone 3, cefazolin 2, cloxacillin 1), followed by colloids, radiocontrast media, blood component and bone cement, in five, two, one, and one patient, respectively. The clinical presentation varied from severe hypotension, rash or urticarial, bronchospasm, tachycardia, bradycardia, stridor, and angioedema. The detail of clinical presentation are shown in Table 3.

The first symptom was severe hypotension in 16 cases followed by rash or urticaria, increased airway pressure or wheezing, angioedema, and dyspnea, in six, four, and two cases, respectively. Twenty-seven (96.4%) cases presented with at least two symptoms. Only one cases presented with hypotension alone.

Seven patients presented with bronchospasm and urticaria or angioedema, without hypotension and received H1 antihistamine and steroid. Beta 2 agonist nebulized and H2 antihistamine were given, in five and two patients, respectively. Adrenaline was given in two normotensive patients that presented with angioedema and stridor.

Treatment for twenty-one hypotensive patients composed with intravenous fluid infusion, antihistamine H1, H2, beta-2 agonists, ephedrine, adrenaline, norepinephrine, and dopamine. The details of treatment are shown in Table 4.

Adrenaline was given in a wide range of dosage from 10 to 500 micrograms. Different routes such as intramuscular, intravenous, subcutaneous, and nebulized were used, in five, nine, three, and two patients respectively. Intravenous bolus of norepinephrine in different doses were used as first line drug in seven cases. They all received intravenous adrenaline later due to unsuccessful resuscitation. Steroid used was dexamethasone, except in one case, where hydrocortisone 100 mg intravenously was used. Doses and interval of dexamethasone given varied. No patient got cardiac arrest.

The suspected causes were identified in 41 cases, 22 cases (57.9%) of grade I, 4 cases (100%) of grade II, and 15 (53.5%) of grade III. The most common causes were antibiotic, blood component, and colloid in 13, 9, and 6 cases, respectively. Antibiotics related to allergic reaction were cefazolin in six cases, ceftriaxone in four cases, clindamycin, cloxacillin and ampicillin in one case each. For blood component group, fresh frozen plasma were given in six cases, packed red cell

Table 2. Grading of anaphylaxis reaction in patients with peri-operative anaphylaxis and suspected causes of reactions identified

Clinical severity	Perioperative anaphylaxis (n = 70) n (%)	Suspected causes of reactions identified (n = 41) n (%)
Grade I: mucocutaneous signs only	38 (54.3)	22 (53.7)
Grade II: multi-organ manifestations	4 (5.7)	4 (9.7)
Grade III: severe life-threatening multi-organ manifestations	28 (40.0)	15 (36.6)
Grade IV: cardiac arrest	0 (0.0)	0 (0.0)

Table 3. Clinical presentations of patients with grade III reaction (n = 28)

Symptoms	n (%)
Hypotension	21 (75.0)
Rash, urticaria, itching	18 (64.3)
Bronchospasm	15 (53.6)
Tachycardia	11 (39.3)
Angioedema	5 (17.9)
Bradycardia	2 (7.1)
Nausea/vomiting	2 (7.1)
Stridor	1 (3.6)

Table 4. Treatment for patients with grade III reaction (n = 28)

Treatment	n (%)
Intravenous fluid infusion	13 (46.4)
Antihistamines H1	25 (89.3)
Antihistamines H2	9 (32.1)
Steroid	25 (89.3)
Beta-2 agonist nebulized	7 (25.0)
Ephedrine	11 (39.3)
Adrenaline	19 (67.8)
Norepinephrine	10 (35.7)
Dopamine	7 (25.0)

Table 5. Drug given during induction compare between grade I and grade III reactions

Drug	Grade I (n = 11)	Grade III (n = 7)
Thiopenthal	8	1
Propofol	3	5
Atracurium	7	2
Cisatracurium	0	4
Rocuronium	1	1
Succinylcholine	0	2
Morphine	4	3
Fentanyl	4	3

in two cases and platelet in one case. The six colloids used were gelatin, five were haemaccel and one was gelofusine.

Twenty-nine cases were considered as unknown cause and divided into two categories. The first group were eighteen events, eleven cases in grade I and seven cases in grade III. They occurred during induction while at least two drugs such as induction, narcotic, NMBAs were given simultaneously. Antibiotic were given in three cases. The detail of drugs given during induction are shown in Table 5.

Thiopental and atracurium were the most common drugs used during induction. Anaphylaxis or anaphylactoid reaction to these two drugs mostly were classified as grade I reaction. While reactions related to cisatracurium or succinylcholine were more severe, all were classified into grade III reactions. One patient got severe hypotension and bronchospasm after receiving thiopental, morphine, cisatracurium, and cefazolin during induction. Operation was cancelled. Resuscitation with ephedrine, H1 antihistamine, steroid, and norepinephrine was successful. Ten days later this patient got severe anaphylaxis or anaphylactoid reaction again after receiving clindamycin followed by morphine, propofol, and cisatracurium during induction. Severe hypotension was successfully treated by ephedrine, H1 antihistamine, steroid, adrenaline, and norepinephrine. Surgery was done uneventfully. Rash was found in the second group during maintenance or just after the operation was finished in 11 cases. Then other symptoms such as bronchospasm and hypotension were discovered and considered as part of allergic reaction.

All patients in grade I and II got complete recovery. In grade III reaction, surgery was cancelled in five cases which two patients were unplanned admitted to ICU for 24 hours. Pharmacist, internal medicine physician, and dermatologist were consulted in nine, two, and one case, respectively. From 12 cases with blood component related events, blood was sent back to blood bank for reevaluated in only two cases.

Investigation was carried out in one case only. Skin test for cefazolin, serum tryptase, specific IgE to latex, and basophil activation were done. All tests were negative except skin test for cefazolin was positive.

Surgical safety checklists were completely done in 13 cases. History of drug allergy were asked in 67 cases, which were positive in five cases (7.5%). Most of the events were considered as unpreventable, even some related to patient and anesthetic factors. Inexperience and improper decision were considered as the main contributing factor of the reactions. Factors minimizing event were considered as experienced in allergic reaction before, vigilance, and experienced assistant. Suggested preventive strategies were guidelines practice, improved supervision, and additional training.

Discussion

The present sub-study revealed the recent case series of perioperative anaphylaxis, anaphylactoid, or allergic reaction in Thailand. In the present study, perioperative allergic reactions were common in female adult similar to other studies[1,4,6,9]. Skin or cutaneous lesion was the most common presentation followed by hypotension, bronchospasm, and tachycardia, comparable to other studies[5,6,12]. The diagnosis of anaphylaxis without skin lesion is difficult or even missed. Cardiovascular symptoms as hypotension, tachycardia, or bronchospasm during anesthesia occur more often than other causes. However, the diagnosis of anaphylaxis should be considered in unexplained hypotension, especially in case that does not respond well with common vasopressor use in clinical practice. In the present study, most of the severe anaphylaxis reaction presented with at least two symptoms. Only one patient presented with lone hypotension, which severe sudden decrease in blood pressure occurred just after colloid was given without any other cause. According to guidelines from the European Academy of Allergy and Clinical Immunology [AACI], the diagnosis of anaphylaxis in this case was made[13]. Most of the anaphylaxis events were diagnosed mainly by history, timing from allergen given to signs and symptoms started. Therefore, only 41 cases (58.6%) were identified as known suspected causes. In this group, antibiotic was the most common cause followed by blood components, and colloids. In the antibiotic group, cefazolin was the most common

causal agent followed by ceftriaxone. These two drugs are most commonly used as antibiotic prophylaxis before procedure. In the present study, six cases were recognized as reaction to colloid. All colloid used were gelatin. Gelatin reports a higher incidence as compare to starch. Five out of the six cases were haemaccel and reported from only one institute. Our finding differs from previous study that mostly reported NMBAs was the most common cause of perioperative allergic reaction or anaphylaxis[1,5-9]. In 18 cases, anaphylaxis occurred a few minutes after induction while many drugs including NMBAs were given. Even anaphylaxis to intravenous anesthetic agent and opioids are less common than NMBAs[14]. In the present study, because NMBAs was not given separately, without any serologic and skin test, NMBAs were not concluded as a sole causative agent.

In less severe cases with cutaneous lesion only, guidelines from various countries suggest combined H1 and H2 antihistamine may be more effective than H1 antihistamine alone. There is no evidence that given steroid improve outcome. However, steroid may be effective in biphasic reactions. Therefore, steroid is recommended as secondary treatment after the immediate acute treatment is completely done. In the present study, treatment in grade I reaction was not consistent. Twenty-Two from 38 patients (57.8%) got H1 antihistamine only. One patient received H1 and H2 antihistamine with steroid. Adrenaline is recommended as the first line drug for treatment of anaphylaxis reaction, especially in more severe cases[13-15]. Most of anaphylaxis guidelines suggest that adrenaline should be given without delay, before antihistamine and steroid. Even when adrenaline is given early, mortality is still high. Dose and route regimens of adrenaline vary between country and situation. Intramuscular adrenaline is the most suggested route[13,15-17]. However, in perioperative anaphylaxis intravenous is preferable. Subcutaneous or inhaled adrenaline for anaphylaxis shock is not recommended, except in case with stridor and laryngeal edema, nebulized adrenaline can be used. Garvey et al reported that during perioperative anaphylaxis, anesthetists chose to give antihistamine and steroid before adrenaline in 16.8%, and did not give adrenaline at all in 17.2% of patients having grade III and IV reaction[18]. In the present study, only 19 patients (67.8%) in grade III reaction received adrenaline. Most of them got adrenaline after other rescue drugs such as H1, H2 blocker, steroid, ephedrine, dopamine, and norepinephrine were given. Even when the diagnosis of anaphylaxis was made, adrenaline administration was delayed. Subcutaneous adrenaline were given in three severe hypotensive cases, which intramuscular or intravenous adrenaline may be more appropriated. Norepinephrine was given as the first line drug in seven cases without any improvement. Standard dose of adrenaline for cardiac arrest are used worldwide[17]. Because adrenaline has narrow therapeutic gap and can cause serious side effect, numerous practice guidelines for perioperative anaphylaxis suggested different routes and doses of adrenaline, making anaphylaxis treatment with adrenaline more difficult[13,15,16,19]. Gompels et al did a questionnaire study about the knowledge of using adrenaline in anaphylaxis. They found that even 100% of doctors would use adrenaline for anaphylaxis, but only 5% administrated adrenaline in correct route and doses[20]. The finding from the present study suggests that standardize practice guideline for perioperative anaphylaxis management in Thailand is urgently needed. This is similar to additional training for anesthesia personnel. According to anaphylaxis management guidelines, patients that experienced moderate to life threatening reaction should be admitted to an intensive care unit for 24 hours for close observation and monitoring[13-16,19]. In the present study, only two of the 28 patients with grade III reaction were admitted to intensive care unit. The reason may be due to unavailable intensive care bed, lack of knowledge, or unaware of potential biphasic or other adverse events.

In the present study, the diagnosis of anaphylaxis was done by using clinical sign and symptoms. Only one patient received test for IgE, tryptase, and skin test, which was positive for cefazolin. Repeated anaphylaxis reaction occurred in one patient who got two anaphylaxis reactions in the same admission, within 10-day interval. Cefazolin, thiopental, morphine, and cisatracurium were given during induction at the first event. At the second episode antibiotic was changed to clindamycin, induction agent was changed from thiopental to propofol while morphine and cisatracurium were still used. Maybe at the beginning, cefazolin was blamed as causative agent of anaphylaxis. Without any tests to diagnose or identify the cause of the reaction, a second anesthesia was done. Serious life-threatening reaction occurred again. The resuscitation was successful, and the surgery was done uneventfully. However, this event could have been avoided or modified to reduce the risk by identifying the causative agent before the second attempt of anesthesia. Guidelines for management anaphylaxis suggest that all patient experienced anaphylaxis perioperatively should be evaluated or tested to identified causal allergen[15,16,19]. In Thailand,

serologic tests and skin test are not available in all hospitals. Additionally, immunologist are not available in all hospitals. Some university hospital might have the tests available. However, most of anaphylaxis patients did not get any tests. The reason was the cost of those tests, lack of knowledge, or not aware about cross reaction between antibiotic or NMBAs. Therefore, it is important to identify the allergen to avoid some drugs at the next anesthesia. Anesthesiologist should be encouraged to take responsibility in history taking, physical examination, observe and record clinical symptoms related to anaphylaxis, provide effective acute management, and refer to appropriated center.

There are some limitations to the present study. First, the present study is based on voluntary reporting of incidents. Anaphylaxis is difficult to diagnose, especially during anesthesia. The present reports came from 17 of 22 participated hospitals. Forty cases (57%) were reported from four institutes. It might be underreported. Second, because of the lack of serologic test and skin test, the real causative agents of anaphylaxis reaction during induction were not identified.

Conclusion

Seventy perioperative anaphylaxis or anaphylactoid events were reported. The most common clinical presentation was urticaria, followed by hypotension, bronchospasm, tachycardia, and angioedema. Suspected causes were identified by using clinical presentation and timing of when the event happened in only 41 events. The most common causes were antibiotic, blood component, and colloid. In severe case, early adrenaline administration was recommended. To improve outcome, guidelines for perioperative anaphylaxis management should be followed. After anaphylaxis event, proper investigation at proper time should be done, to identify definite cause.

What is already known on this topic?

Perioperative anaphylaxis is an uncommon adverse event but was more common in female adult. Skin lesion was the most common presentation, followed by hypotension, bronchospasm, and tachycardia.

What this study adds?

As treatment of anaphylaxis, adrenaline is recommended as the first line drug. This study showed that adrenaline was not given early or prior to the other drugs. Dose and route of adrenaline are varied. The treatment is not standardized.

Very few patients received investigation after anaphylaxis event.

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Potential conflicts of interest

The authors declare no conflict of interest.

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