Supplementary text

Perioperative Hypersensitivity Reactions in Children: A 12-Year Retrospective Cohort Study from a Japanese Tertiary Center

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Methods

Data extraction and evaluation

Detailed clinical information was extracted from the medical records, including patient demographics (age and sex), relevant medical history (such as atopic conditions and previous drug or food allergies), characteristics of the surgical procedure and anesthetic management, features of the hypersensitivity reaction (including onset, type, and severity of symptoms), and the therapeutic interventions provided.

Anaphylaxis was defined in accordance with established clinical diagnostic criteria.[1] Anaphylaxis was considered likely if any one of the following three conditions was met:

(1) An acute illness developing within minutes to hours, involving

1. skin or mucosal tissue (e.g., urticaria, generalized pruritus or flushing, swelling of the lips, tongue, or uvula),

and either

2. airway compromise (e.g., dyspnea, wheezing or bronchospasm, stridor, or reduced peak expiratory flow),

or

3. hypotension or related symptoms (e.g., hypotonia or syncope).

(2) The occurrence of two or more of the following symptoms within minutes to hours after exposure to a known allergen for that patient:

1. a history of severe allergic reactions,

involvement of the skin or mucosal tissue (e.g., urticaria, generalized itching or flushing, or swelling of the lips, tongue, or uvula),

2. airway compromise (e.g., dyspnea, wheezing or bronchospasm, stridor, or reduced peak expiratory flow),

3. hypotension or associated symptoms (e.g., hypotonia or syncope),

(3) Hypotension occurring within minutes to hours after exposure to a known allergen, defined as:

1. in infants and children, a low age-specific systolic blood pressure or a decrease of

more than 30% from baseline; Low systolic blood pressure in children was defined as <70 mmHg for those aged 1 month to 1 year; <70 mmHg + (2 × age in years) for those aged 1 to 10 years; and <90 mmHg for those aged 11 to 17 years.
2. in 18 years (in accordance with adults), a systolic blood pressure below 100 mmHg or a decrease of more than 30% from baseline.

The clinical scoring system using the Items contributing to the clinical score for suspected perioperative immediate hypersensitivity reactions (IHRs)

Patient symptoms were evaluated using a standardized clinical scoring system designed to assess suspected perioperative immediate hypersensitivity reactions (IHRs). The definitions of individual items are provided below.
The scoring framework consists of five domains—cardiovascular, respiratory, dermal/mucosal, combined manifestations, and timing—in which findings indicative of an IHR are assigned positive scores, whereas findings arguing against an IHR receive negative scores. Each item within these domains is weighted according to its assigned point value. The total clinical score represents the sum of the net scores across all five categories.
1. Cardiovascular
(Select hypotension, severe hypotension, or cardiac arrest where applicable, followed by any additional relevant items)
Hypotension: 4; Severe hypotension: 6; Cardiac arrest: 9; Tachycardia: 2.
Poor or transient response of hypotension to standard doses of sympathomimetic agents administered for anesthetic-related hypotension (e.g., ephedrine, phenylephrine, metaraminol): 2.
Point-of-care echocardiography demonstrating a hyperdynamic and underfilled heart: 2.
Recurrence or deterioration of hypotension after administration of an additional dose of a drug given before the initial reaction: 1.

Cardiovascular confounders (in cases with hypotension or cardiac arrest, select all that apply)

Excessive dosing of anesthetic agents: −2.
Surgically induced hypovolemia or relative hypovolemia due to prolonged fasting or dehydration: −1.
Acute illness predisposing to hypotension: −1.
Use of medications that alter cardiovascular responses during anesthesia: −2.
Neuraxial regional anesthesia (epidural or spinal): −1.
Development of hypotension following an increase in peak airway pressure during mechanical ventilation: −2.

2. Respiratory
(Select bronchospasm or severe bronchospasm where appropriate, followed by any additional applicable items)
Bronchospasm: 2; Severe bronchospasm: 4.
Recurrence or worsening of bronchospasm after administration of an additional dose of a drug given before the initial event: 1.
Bronchospasm occurring prior to airway instrumentation (after excluding airway obstruction): 2.

Respiratory confounders (in the presence of bronchospasm)
Underlying respiratory disease with reactive airways: −1.
Prolonged or repeated attempts at tracheal intubation: −1.
Inadequate dosing of drugs to blunt airway reflexes before airway instrumentation: −1.

3. Dermal/Mucosal
(Select all applicable items)
Generalized pruritic rash in an awake patient not receiving epidural or spinal opioids: 1.
Angioedema: 3.
Generalized erythema: 3.
Generalized urticaria: 4.

Dermal/mucosal confounder

Angioedema in a patient treated with an ACE inhibitor: −3.

4. Combined systems

(Select no more than one item)

CVS > 2 and RS > 2: 5.

CVS > 2 and D/M > 2: 5.

RS > 2 and D/M > 2: 5.

CVS > 2, RS > 2, and D/M > 2: 8.

5. Timing

(Select no more than one item)

Onset of cardiovascular or respiratory manifestations within 5 minutes of a possible intravenous trigger: 7.

Onset within 15 minutes of a possible intravenous trigger: 3.

Onset within 60 minutes of a possible non-intravenous trigger: 2.

Onset more than 60 minutes after a possible non-intravenous trigger: −1.

For an organ system score—cardiovascular (CVS), respiratory (RS), or dermal/mucosal (D/M)—to be eligible for inclusion in a combination score, the net score for that system must exceed 2. The net score is calculated as the total of positive feature scores minus the total of confounder scores within that system.

The Clinical Grading Scale used to interpret the Clinical Score for suspected perioperative immediate hypersensitivity reactions (IHRs) is shown below.

Interpretation Total (net) score

Almost certain to be an IHR: >21

Very likely to be an IHR: 15 to 21

Likely to be an IHR: 11 to 14

Possible IHR: 8 to 10

Unlikely to be an IHR: < 8

We also recorded the results of diagnostic investigations to identify the causative agent(s). Diagnostic evaluation included serum tryptase measurement (when available), skin prick tests, intradermal tests, and total IgE testing. Total serum IgE was measured using a fluorescent enzyme immunoassay and ImmunoCAP (Thermo Scientific Inc., Uppsala, Sweden). Skin testing was performed in accordance with established procedures at least 4–6 weeks after the allergic episode to minimize false-negative results due to refractory periods.[2, 3] Even when SPT was positive and the causative drug was confirmed, intradermal testing was sometimes performed on drugs that were SPT-negative to verify that other drugs truly had no IHR.

Skin Prick Test

【Items to Prepare】

Lancet needle, allergen extract for pricking, saline solution, 1% dihydrochloride histamine solution, disinfectant cotton (e.g., 0.2% chlorhexidine digluconate), tissue paper or gauze

① Disinfect the flexor side of the forearm and mark the placement guide for allergens. Ensure approximately 3 cm spacing between allergens.
② Apply one drop of saline solution. Prick the skin with the lancet needle. Wipe off any remaining allergen extract on the skin with tissue paper, then wipe the lancet needle with disinfectant swabs.
③ Repeat step ② with each allergen extract and the 1% histamine dihydrochloride solution.
④ Perform the evaluation after 15 to 20 minutes.

Intradermal Test

【Items to Prepare】

Tuberculin syringe needle or 27G needle + 1mL syringe, intradermal allergen extract, saline

solution, 200,000-fold diluted histamine dihydrochloride solution, disinfectant cotton (e.g., 0.2% chlorhexidine digluconate)

[Method]

① Disinfect the flexor side of the forearm and mark the sites for allergen injection. Ensure an interval of approximately 3–5 cm between allergen sites.

② Inject 0.02 mL of intradermal allergen extract (dilute highly antigenic allergens at least 10-fold) intradermally without causing bleeding, forming a wheal approximately 5 mm in diameter.

③ Repeat step ② with various allergen extracts, physiological saline, and a 200,000-fold diluted solution of histamine dihydrochloride.

④ Perform evaluation 15–30 minutes later.

Prick Test/Splano Test Evaluation Criteria

When using histamine

Wheal Diameter

(1) Equivalent to saline

1+ Smaller than half the histamine wheal, larger than saline

2+ Half the histamine wheal

3+ Equivalent to histamine

4+ Twice the histamine wheal

※A reaction of 2+ or greater is considered positive.

When not using histamine

Negative: Wheal diameter 0-4mm, erythema 0-14mm

Positive: Wheal diameter ≥5mm or ≥2× control solution, erythema ≥15mm or ≥2× control solution

Non-irritating concentrations for ST were based on a previous publication.[4] Intradermal

tests were performed for those with negative skin prick tests. DPT to antibiotics, sedative drugs, and NMBAs were performed when skin tests were negative. Suspected drugs were tested based on the perioperative drug exposure profile, and included neuromuscular blocking agents (NMBAs), antibiotics, anesthetics, analgesics, latex, and disinfectants. Causative agents were identified based on a combination of clinical history, timing of exposure, and diagnostic test results. Importantly, latex products are not used in routine clinical practice at NCCHD; however, the patients referred from external facilities were also considered, and latex evaluation was performed when it was considered a possible cause.

References

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