Hydroxyethyl starch (HES) is a colloid commonly used to treat perioperative hypovolemia. HES belongs to a class of synthetic colloid solutions that are modified natural polysaccharides and are similar to glycogen [1]. The physicochemical characteristics of HES are determined by the concentration, mean molecular weight ($M_w$), degree of molar substitution (MS), and $C_2/C_6$ ratio.

The risk of an anaphylactic reaction, which may be a side effect of HES, is very low [2]. In a clinical trial, the use of HES was associated with a low incidence of anaphylactic reactions, similar to that observed with the use of albumin. This risk was lower than that associated with the use of other colloids [3]. As the allergic reaction appears to be induced by the substance itself (starch), all generations of HES may exhibit anaphylactic potency. There have been several cases of anaphylactic reaction induced by first- and second-generation HES and only one case of such a reaction with the third-generation HES. The HES used in the present case was balanced tetrashtarch, which is a third-generation HES. We present a patient who developed an intra-operative anaphylactic reaction immediately after the initiation of HES 130/0.4 infusion, along with a review of the literature.

**CASE REPORT**

An 83-year-old man (weight: 65 kg, height: 167 cm) was scheduled to undergo open reduction and internal fixation of a pertrochanteric fracture of the right femur. His past medical history was nonspecific. He had no history of allergy to drugs or food. Preoperative assessment including blood biochem-
Anaphylaxis with hydroxyethyl starch

Clinical signs including hypotension, tachycardia, and mild hypoxemia, as well as the appearance of a skin rash were consistent with the clinical criteria for an anaphylactic reaction. Other antibiotics or blood components were not administered during the surgery, and the anaphylactic reaction occurred within 5 min of HES exposure. The infusion of HES was terminated within 10 min, as it was considered the cause of the anaphylactic reaction. Subsequently, 5 mg of IV dexamethasone was administered. The total amount of IV injected phenylephrine was 400 μg. The patient received 1 L of the crystalloid (plasma solution) and 50 ml of the colloid (HES). Estimated blood loss and urine output were 100 ml and 200 ml, respectively. The total anesthesia time was 2 hours and the operation time was 46 min.

In the recovery room, laboratory tests including immunoglobulin E (IgE) levels and tryptase assessment were performed. The patient was taken chest X-ray due to observation of mild hypoxemia; however, the radiologist interpreted no unusual findings compared with the preoperative examination. The skin rash on the entire body persisted while the patient stayed in the recovery room; hence, IV dexamethasone 7.5 mg and chlorpheniramine 6 mg were administered along with 800 ml of crystalloid fluid for symptom relief.

The patient was transferred to the general ward with stable vital signs (BP: 111/78 mmHg, HR: 96 beats/min, SpO₂: 100%) after close observation in the recovery room for 75 min. The patient’s urine output was sufficient (1–2 ml/kg/h) for 24 h after operation.

The result of the skin test to detect a reaction against HES performed on the next day was negative. Testing of a blood sample drawn in the operating room revealed the presence of 13.9 ng/ml of tryptase (normal range: < 11.4 ng/ml) and 211 IU/ml of total IgE, as determined using paper radioimmunosorbent test (PRIST) (normal range: 0–100 IU/ml). On the twenty-first day after the surgery, the patient was discharged without any complications.

**DISCUSSION**

HES is derived from amylpectin of maize or potato. HES solutions can be classified by their Mₘ or MS. Volulyte is a third generation HES with balanced 130 (Mₘ, kDa)/0.4 (MS) or 130 (Mₘ, kDa)/0.42 (MS).

An anaphylactic reaction is defined as a serious allergic...
reaction that is rapid in onset and may cause death [4]. Symptoms are variable, ranging from minor clinical changes such as agitation, urticaria to cardiopulmonary collapse.

The diagnosis of an anaphylactic reaction is usually obvious and is made based on the symptoms. If the symptoms are mild, the diagnosis can be confirmed using a blood or urine test, which provide a measure the levels of substances produced during an allergic reaction [1]. Traditionally, in addition to the clinical features, serum tryptase, plasma histamine, and 24-h urinary histamine metabolites have been clinically used to confirm the diagnosis of anaphylactic reactions. Skin tests and allergen-specific IgE tests can provide confirmatory evidence of sensitization to a specific allergen.

In the present case, severe and widespread skin rash and agitation were the first signs of the reaction. Tachypnea, mild hypoxemia, and hypotension were the subsequent signs that confirmed the suspicion of an anaphylactic reaction. All of the clinical signs were detected within a few minutes after the infusion of HES. Fortunately, bronchospasm did not develop in the current case.

Treatment of an anaphylactic reaction consists of both short and long-term management. The immediate goal is to maintain an airway with oxygen supply and support the blood pressure. Intravenous epinephrine diluted with 1:10,000 is administered slowly, the dose is usually limited to 3 ml for an average sized (70 kg) adult. Hypotension should be treated by expanding the intravascular volume. When a prolonged course with urticarial or a late phase response is suspected, antihistamines and corticosteroids are useful as second line therapy. Methylprednisolone sodium succinate is usually given every 6 h. Inhaled beta 2 agonist and intravenous atropine are also recommended for refractory bronchospasm.

In the present case, a skin test for a reaction against HES was performed on the next day of the surgery. The result of this test was negative. High doses of systemic corticosteroids and antihistamines may interfere with the results of skin tests, and it is important to avoid these drugs for up to 7 days before the test [5]. We had already administered an antihistamine and corticosteroids due to the allergic reaction. The administration of these drugs may thus have induced the negative results. The elevated values of total IgE and tryptase measured during the surgery support the diagnosis of an anaphylactic reaction due to HES. One day after the surgery, the patient was delirious and uncooperative. The patient’s family refused additional tests for the patient because of the difficulty of nursing and old age of the patient. They thought that the patient would not have another surgery in the future due to his old age. Therefore, the confirmatory tests such as plasma histamine, 24-h urinary histamine metabolites, and allergen-specific IgE evaluations could not be performed.

There have been several case reports of anaphylactic reactions against HES. However, a majority of these reactions were against 6% dextran 60 [6] and first-generation (hetastarch) [7–10], or second-generation (pentastarch) [11–13] HES. Only one case involving a third-generation HES (tetrastarch)-induced anaphylactic reaction has been reported. A 42-year-old man experienced a severe intra-operative anaphylactic reaction soon after the initiation of HES 130/0.4 (Volvren®, Fresenius Kabi, Germany) infusion. Within minutes of HES administration, facial erythema, hypotension, and bronchospasm developed, however the measurement of serum tryptase, plasma histamine, or allergen-specific IgE or skin tests were not performed [14].

All colloids used for intravascular volume replacement, including the natural colloid albumin, have the potential to induce anaphylactic reactions [15]. In a large clinical trial that included approximately 20,000 patients, it was demonstrated that the use of HES was associated with a low incidence of anaphylactic reactions similar to that with albumin, and significantly less than that with other colloids [3]. Data on the incidence of anaphylactic reactions after IV administration of the HES 130/0.4 are not available.

Fortunately, anaphylactic reactions induced by HES are uncommon, and life-threatening anaphylaxis is rare. The diagnosis of anaphylactic reaction could be difficult while the patient is under anesthesia and when various types of medications are used simultaneously. Therefore, it is essential to know the past medical history of the patient’s allergic reactions, be aware of the criteria for the diagnosis, and provide prompt treatment for anaphylactic reactions.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.
REFERENCES

1. Jungheinrich C, Neff TA. Pharmacokinetics of hydroxyethyl starch. Clin Pharmacokinet 2005; 44: 681-99.
2. Boldt J. Modern rapidly degradable hydroxyethyl starches: current concepts. Anesth Analg 2009; 108: 1574-82.
3. Laxenaire MC, Charpentier C, Feldman L. Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanisms. A French multicenter prospective study. Ann Fr Anesth Reanim 1994; 13: 301-10.
4. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis--a practice parameter update 2015. Ann Allergy Asthma Immunol 2015; 115: 341-84.
5. Kränke B, Aberer W. Skin testing for IgE-mediated drug allergy. Immunol Allergy Clin North Am 2009; 29: 503-16.
6. Lehmann G, Asskali F, Förster H. Severe adverse event following iv administration of 10 ml 6% Dextran60 (0.6 g) in a healthy volunteer. Anaesthesist 2002; 51: 829-4.
7. Takada M, Tomatsu T, Harada T, Murakami N, Shimonaka H, Dohi S. Bronchospasm due to anaphylactic reaction to Hydroxyethyl starch (HESPAUNDER). Masui 1997; 46: 397-400.
8. Hall BA, Frigas E, Matesic D, Gillett MD, Sprung J. Case report: intraoperative anaphylactoid reaction and hydroxyethyl starch in balanced electrolyte solution (Hextend). Can J Anaesth 2006; 53: 989-93.
9. Cullen MJ, Singer M. Severe anaphylactoid reaction to hydroxyethyl starch. Anaesthesia 1990; 45: 1041-2.
10. Porter SS, Goldberg RJ. Intraoperative allergic reactions to hydroxyethyl starch: a report of two cases. Can Anaesth Soc J 1986; 33(3 Pt 1): 394-8.
11. Vercauteren MP, Coppejans HC, Sermeus L. Anaphylactoid reaction to hydroxyethylstarch during cesarean delivery in a patient with HELLP syndrome. Anesth Analg 2003; 96: 859-61.
12. Kannan S, Milligan KR. Moderately severe anaphylactoid reaction to pentastarch (200/0.5) in a patient with acute severe asthma. Intensive Care Med 1999; 25: 220-2.
13. McHugh GI. Anaphylactoid reaction to pentastarch. Can J Anaesth 1998; 45: 270-2.
14. Kim HJ, Kim SY, Oh MJ, Kim JM. Anaphylaxis induced by hydroxyethyl starch during general anesthesia -a case report-. Korean J Anesthesiol 2012; 63: 260-2.
15. Franz A, Bräunlich P, Gamsjäger T, Felfernig M, Gustorff B, Kozek-Langenecker SA. The effects of hydroxyethyl starches of varying molecular weights on platelet function. Anesth Analg 2001; 92: 1402-7.