The management of general anesthesia in a case with polyethylene glycol and polysorbate allergy: a case report

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Abstract
Polyethylene glycol (PEG) and polysorbate 80 are ingredient in various medical products including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine. However, little is known about the relationship between these allergy and general anesthesia. We present a case of a 41-year-old woman who successfully underwent surgery under general anesthesia without any major problems.

1. Introduction
Polyethylene glycol (PEG) is a widely used excipient in cosmetics, foods and medical products. PEG allergic reactions were infrequently reported prior to the widespread implementation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine to prevent against coronavirus disease 2019 (COVID-19). The SARS-CoV-2 vaccines, BNT162b2 (Corrinaty, Pfizer-BioNTech, New York, NY, USA) and mRNA-1273 (Spikevax, Moderna, Cambridge, MA USA), are messenger RNA (mRNA)-based vaccines that contain numerous excipients and lipids, one of which is based on PEG [1, 2].

As the number of people receiving SARS-CoV-2 vaccines increased, a large number of allergic reactions to PEG were reported, ranging from mild reactions to life-threatening anaphylaxis [3–5]. PEG has been reported as a high-risk hidden allergen, which is widely included in medicine and food items, is difficult to detect, and may be underdiagnosed by healthcare providers [6]. Polysorbate 80 has cross-reactivity with PEG due to their shared chemical moiety: –(CH2CH2O)n [7]. However, there is limited understanding of the relationship between PEG and polysorbate 80 allergy and general anesthesia. Here, we report a case of an individual with PEG and polysorbate 80 allergy who successfully underwent surgery under general anesthesia without any major problems.

2. Case presentation
A 41-year-old woman (height, 153 cm; body weight, 56 kg) visited the anesthesiology department for preoperative evaluation. She was scheduled to undergo left partial mastectomy after sono-guided needle localization for a breast mass. The patient had a past medical history of asthma diagnosed 6 years ago and was treated with an inhaler once a month. No specific findings were observed on her pulmonary function test. The preoperative laboratory, electrocardiogram and chest X-ray showed no abnormal findings, and she had no notable family history.

The patient had a history of allergy to cosmetics. Three years prior, she had undergone an allergic test that had revealed an allergy to PEG and polysorbate. As a result, she was warned to be cautious when taking drugs given that PEG and polysorbate are included in many medical treatments. Additionally, she was advised not to receive a SARS-CoV-2 vaccine due to the presence of PEG and polysorbate. She had a history of sneezing and an itchy nose when she took an acetaminophen tablet, but couldn’t recall the product name of the medication. However, when she took a different type of acetaminophen tablet due to fever caused by a COVID-19 infection, she didn’t
experience any specific symptoms. She reported no issues with taking Advil (ibuprofen).

Following a preoperative consultation with the department of allergic medicine, the anesthesiologist confirmed that the drugs planned for surgery, including propofol (Fresofol MCT 1% inj., Fresenius Kabi, Graz, Austria), remifentanil (Remiva inj. 1 mg, Hana Pharm Co., Ltd., Seoul, South Korea), fentanyl (Fentanyl citrate Hana inj., Hana Pharm Co., Ltd., Seoul, South Korea), rocuronium (Rocaron inj. 5 mL, Reyon Pharm Co., Ltd., Reyon Pharm Co, Seoul, South Korea), and sugammadex (Bridion inj. 2 mL, MSD Korea Ltd., Seoul, South Korea), do not contain PEG or polysorbate. In consideration of the short operation time, supraglottic airway devices were considered for the patient’s airway management. However, the plan was changed to perform tracheal intubation because of the possibility of increased airway pressure due to an allergic reaction leading to bronchospasm or asthma.

To prevent a possible pseudoallergic reaction, the patient was pretreated with 4 mg of chlorpheniramine (Peniramin inj., Yuhan Corp., Seoul, South Korea) and 40 mg of methylprednisolone (Disolrin inj., Gu Ju Pharm, Seoul, South Korea) intravenously. Additionally, pretreatment with a salbutamol nebulizer (Ventolin nebulizer, GlaxoSmithKline, Brentford, United Kingdom) was performed due to her asthma history. Intravenous cefazolin (Cefazoline CKD Inj., Chong Kun Dang Pharmaceutical Corp., Seoul, South Korea) was injected as a preoperative antibiotic after performing an allergen skin test.

Upon entering the operating room, the patient’s blood pressure, electrocardiogram and oxygen saturation were monitored. Her vital signs were stable and she was preoxygenated with 100% oxygen for 5 min. After the administration of propofol 100 mg, bag-mask ventilation was performed with 4% sevoflurane. Continuous intravenous infusion of remifentanil was started at a rate of 0.05 mcg/kg/h. Before the injection of rocuronium, redness around the patient’s face and neck was noted. However, there were no other signs of allergy, such as wheezing or spasm and her vital signs were still stable. Another 4 mg of chlorpheniramine was injected and the skin lesion disappeared spontaneously within a few minutes. After the injection of rocuronium, tracheal intubation was performed and anesthesia was maintained with 2.5% sevoflurane. Sterile skin preparation was performed with Povidone-iodine solution and chlorhexidine 2%-ethanol solution (Hexi-Al solution, Huons Meditech, Seoul, South Korea). The surgery took 35 min. At the end of surgery, sugammadex 0.5 mg/kg was injected as a test dose. After confirming that there was no allergic reaction, the remaining dose of sugammadex 1.5 mg/kg was injected. The patient was extubated and moved to the post anesthesia care unit (PACU). In the PACU, 50 mcg of fentanyl and 0.3 mg of ramosetron (Nasea inj., Daichi Sankyo Korea Co., Ltd., Seoul, Korea) were administered as a rescue analgesic and antiemetic, respectively.

After being transferred from the PACU to the ward, patient’s total serum IgE level was measured. The total serum IgE level was 117.09 KU/L, which was confirmed within the normal range (<150 KU/L). For postoperative management, the surgeon prescribed propacetamol IV (Denogin inj., YUNGIN PHARM, Seoul, South Korea), acetaminophen PO (Tacenol Tablet, Bukwang Pharm, Seoul, South Korea) and ambroxol PO (Mucopext Tablet, Opela HealthCare Korea, Seoul, South Korea), which were confirmed to contain no PEG or polysorbate. She showed no signs of allergic reaction to any of the medications.

3. Discussion

Perioperative hypersensitivity reactions are rare but serious complications that can contribute significantly to the morbidity and mortality of surgical patients [8]. As prevention is better than cure, in allergic patients, anesthesiologists should identify allergens through preoperative evaluation of the patient’s clinical history and the suspected agents should be avoided [9].

PEG is suspected as one of the possible culprits of anaphylactic reaction after SARS-CoV-2 vaccines, and following the emergency use approval of the mRNA SARS-CoV-2 vaccines on December 2020, allergy to PEG and polysorbate has been increasingly recognized [10]. In Moderna (mRNA-1273) and Pfizer/BioNTech mRNA vaccines (BNT162b2), mRNA is packaged in lipid nanoparticles in combination with PEG 2000 molecules to protect the mRNA after injection and increase its water-solubility and bioavailability. Allergic reactions to PEGylated lipids can be IgE-mediated, but may also be derived from non-IgE-mediated reactions such as complement activation-related pseudoallergy (CARPA) [11]. The Oxford/AstraZeneca and Johnson and Johnson COVID-19 vaccines do not contain PEG, but instead, they contain polysorbate 80 as an excipient. Cross-reactivity between PEG and polysorbate has been suggested due to their structural similarities (Fig. 1) [4].

Diagnosis of allergy to PEG is challenging. PEG allergy should be suspected in patients presenting with history of allergy to multiple unrelated drugs with anaphylaxis or severe systemic reactions with immediate onset. Such patients may have mild skin reactions to cosmetics, toothpaste, shower gels and moisturizers with lower PEG molecular weights [4]. The current patient, who was previously diagnosed as being allergic to PEG and polysorbate, also had a history of allergies to cosmetics, and inconsistent allergic reaction to multiple drugs, even those with the same active ingredient.

PEG- or polysorbate-containing products that may be encountered in perioperative environment include corticosteroid formulations, ultrasound gels, disinfectants, bowel laxatives, antiepileptics, antiemetics, anticoagulants, antidepressants, analgesics, antibiotics, anti-inflammatory drugs and even wound dressing bandages [12–15]. Furthermore, PEG/polysorbate may or may not be included in the same active drug depending on the brand names or formulations of the product [14]. Therefore, careful confirmation, including discussion with an allergist, is necessary. As these products are closely related not only to anesthesia but also to operating field and perioperative management, it is essential to share the matter with the surgeon and other medical staffs in the operating room. In previous case reports related to PEG allergy, the suspected etiologies included povidone-iodine gel (containing PEG 400, PEG 4000 and PEG 6000), chlorhexidine solution (containing polysorbate 80), Hesponder® plasma expander infusion (Hydroxyethylated starch), and Mepilex bandage.
When establishing the patient’s anesthetic plan, we had to be suspicious of all medications administered to the patient and all medical equipment that came into contact with the patient. It was challenging to determine the safety of a particular agent or medical products due to inadequate description of the excipients and the lack of standardization in the nomenclature of PEG. For medications to be administered during anesthesia including propofol, remifentanil, fentanyl, rocuronium and sugammadex, we checked whether they contained PEG/polysorbate through the product information and by contact with manufacturers and distributors. The face mask and endotracheal tube made of latex-free polyvinyl chloride (PVC) were also confirmed to be PEG-free. Considering that PEG is mainly included in gel-type products, a non-adhesive sterile cloth was used for the surgical area drape, and surgical paper tape was used to secure the endotracheal tube intubated and the patient’s eyes closed.

In this case, we did not perform a skin prick test preoperatively due to the following reasons: (1) the skin prick test itself has limited sensitivity and specificity, (2) the reaction to PEG can vary depending on the molecular weight and concentration, and (3) the patient had no history of drug intolerance due to the absence of previous general anesthesia exposure. Referring to the preoperative consultation with the allergist, we administered antihistamine and corticosteroid before surgery as pre-treatment considering the possibility of pseudoallergy in addition to avoiding exposure to PEG/polysorbate. Although redness around the patient’s face and neck occurred immediately after propofol administration, it resolved soon without any other symptoms after injection of antihistamine. The patient underwent surgery safely and was discharged from the hospital with no major issues.

The limitations of this case report include the unclear causal relationship of the transient erythema following propofol administration. At that time, additional antihistamine was administered suspecting an allergy to propofol itself [17] or the potential for cross-reactivity. However, despite the low negative predictive value, the normal total serum IgE level measured immediately after surgery indicates a low likelihood of IgE-mediated allergic reaction accounting for the observed symptoms [18]. Furthermore, the patient had no history of previous general anesthesia and propofol exposure. It is possible that the contact and physical pressure with the PVC face mask and the anesthesiologist’s hands wearing latex gloves might have caused acute irritant contact dermatitis, but the skin lesion was not limited to the contact surfaces of the face mask and gloves and the onset was too rapid to suspect contact dermatitis. Otherwise, it could be the flushing or erythema that occurred as a side effect of propofol administration.

Although further laboratory test to evaluate anaphylaxis or mast cell activation were not conducted due to the patient’s symptoms not progressing to severe allergic reactions, performing such tests would have provided a clearer understanding of the situation. Instead, the patient was informed to undergo specific tests for anesthetic and analgesic agents if she plans to undergo surgeries requiring general anesthesia in the future.

4. Conclusions

This case report is significant in that it provides considerations and suggestions for safe surgical management in patients with a history of PEG and polysorbate 80 allergies; this is particularly relevant given that the number of reported cases of such allergies has increased in conjunction with the COVID-19 pandemic and associated vaccination. Here, we describe a successful surgical procedure and anesthesia in a patient with a history of these allergies. Patients with a history of allergies to these ingredients should be suspected during preoperative evaluation, and the allergen should be identified by conducting a thorough evaluation of the patient’s past medical history. This report aims to review the relevant patient population and provide guidance for safe surgical management.
ABBREVIATIONS
PEG, polyethylene glycol; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.

AVAILABILITY OF DATA AND MATERIALS
The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS
EJA and J JL—designed the study. J JL, SYC and MKK—contributed to manuscript writing and data collection. EJA—contributed to editing and supervision. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
This study has been approved by the Institutional Review Board of Gwang-Myung Chung-Ang University Hospital (IRB n. 2303-067-024). Written informed consent was waived for the publication of this case report.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

REFERENCES

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