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Editorial

Does Cephalosporin Skin Test Predict Immediate Hypersensitivity to Cephalosporin?

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Cephalosporins are the most commonly used β-lactam antibiotics for treatment of various infections and prevention of infections in patients undergoing surgery.[1] Immediate hypersensitivity to penicillin is well known, and its diagnostic skin test has been extensively validated for predicting and diagnosing immediate hypersensitivity to penicillin, such as anaphylaxis; however, the cephalosporin skin test has not been well validated. Furthermore, the cephalosporin intradermal skin test (IDT) has not been standardized considering optimal concentration, injection volume, use of negative control, and interpretation of positive response.[2] Currently, cephalosporins have been widely and safely used in individuals with a history of penicillin allergy, despite concerns regarding immune cross-reactivity with both drugs. Even individuals allergic to cephalosporin can tolerate other cephalosporins with different R1 side chain because immunoglobulin E-mediated allergic reactions to β-lactams are mainly attributed to R1 side chains and not to the β-lactam ring itself.[1]

However, most hospitals in Korea are still performing routine cephalosporin IDT before administering the antibiotics to prevent immediate hypersensitivity regardless of patients' histories of antibiotic allergy, which may cause waste of time and labor as well as patients' discomfort. Furthermore, false-positive reactions to cephalosporin IDT have led to an increase in the use of alternative antibiotics, usually broader-spectrum antibiotics, which promote the development multiple drug-resistant bacteria.[3]

Two large-scale studies on the clinical efficacy of screening IDTs for cephalosporins in Korea have recently been published.[4,5] Yoon et al.[4] conducted a prospective study to investigate the predictive value of cephalosporin IDTs, which included 1,421 patients who did not have previous histories of drug allergy and required preoperative cephalosporins. They conducted IDTs for four cephalosporins including first-, second-, third-, and fourth-generation cephalosporin and penicillin G. Seventy-four patients (74/1,421, 5.2%) of them were tested positive for at least one cephalosporin. None of the responders had immediate hypersensitivity reactions after a challenge dose of the same or different cephalosporin, which was positive in the skin test, whereas four patients among those with negative skin test results developed generalized urticaria and itching after drug administration. The

cephalosporin IDT had 0% sensitivity, 97.5% specificity, 99.7% negative predictive value, and 0% positive predictive value, suggesting that routine cephalosporin IDTs are not useful for predicting immediate hypersensitivity reactions. Yang et al.[5] performed a large multicenter retrospective cohort study using the electronic medical records of 12 general hospitals, of which 8 conducted routine screening cephalosporin IDTs (intervention group) and four did not conduct routine screening cephalosporin IDTs (control group). The authors compared cephalosporin-induced anaphylaxis between the intervention and control groups. The total incidence of cephalosporin-induced anaphylaxis was 6.8 per 100,000 exposures, and the incidence of fatal anaphylaxis was 0.1 per 100,000 exposures. The clinical effectiveness of routine screening IDT was not significant ($P = 0.06$). The authors concluded that routine screening IDT has no clinical efficacy in general. They also suggested that routine screening IDT may be useful for certain cephalosporins showing the highest incidence of anaphylaxis, including ceftizoxime (13.0 per 100,000 exposures) and cephalosporins with a specific side-chain group such as cefepime, cefotaxime, ceftizoxime, ceftriaxone, and cefuroxime (9.3 per 100,000 exposures).

In the current issue of the *Journal of Korean Medical Science*, Kwon et al.[6] provided more evidence on the efficacy of routine cephalosporin IDT. They reported that 184 (1.45%) of 13,153 cases had positive response to preoperative IDTs for cefazolin, a first-generation cephalosporin, and 8 of 12,969 cases (0.06%) who had negative response to cefazolin IDTs had immediate hypersensitivity reactions. In addition, 15% (6/40) patients with a history of β-lactam allergy showed a positive response to cefazolin IDTs, while 1.36% (178/13,113) cases without a history of β-lactam allergy had positive response to cefazolin IDTs. Although this study had several limitations, including a relatively lower concentration of cefazolin IDT (0.3 mg/mL), lack of negative control, a broader definition of positive response to IDTs (flare ≥ 15 mm or wheal ≥ 5 mm), and use of retrospective review of medical records to find immediate adverse reactions, these results further support that routine cephalosporin IDTs are not useful for predicting immediate hypersensitivity to cephalosporins.

In conclusion, routine use of cephalosporin IDTs seems inefficient for predicting immediate hypersensitivity reactions such as anaphylaxis. The cephalosporin skin test may be useful for patients with a previous history of β-lactam allergy. Prospective, large-scale, multicenter studies are needed to confirm the clinical efficacy of routine use of cephalosporin IDTs.

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