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Cutaneous Adverse Reaction After COVID-19 Vaccination

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As coronavirus disease 2019 (COVID-19) spreads worldwide, various vaccines are being developed against the SARS-CoV-2 virus. These vaccines had to be developed in a relatively short period; therefore, they had to be manufactured using a method different from that of conventional vaccines. In addition, many people were vaccinated in a short period, and various side effects related to vaccination have been reported. In this article, we describe the injection site reactions and some unique skin reactions associated with COVID-19 vaccination, such as drug eruptions, bullous lesions, and foreign body reactions, with their possible causes.

Key Words: COVID-19 vaccine, Cutaneous adverse reactions, mRNA vaccine

INTRODUCTION

As coronavirus disease 2019 (COVID-19) spreads worldwide, various vaccines are being developed against the SARS-CoV-2 virus. Of these, five vaccines are currently available in Korea. BNT162b2 (Comirnaty, Pfizer-BioNTech) and mRNA-1273 (Moderna) are messenger RNA (mRNA) vaccines. In addition, ChAdOx1SnCoV-19 (Covishield, Vaxzevria, AZD1222, Oxford-AstraZeneca) and Ad26.COV2.S (JNJ-78436735, Janssen) are adenoviral vector vaccines. The most recently released NVX-CoV2373 (Novavax) vaccine is a protein subunit vaccine[1]. These vaccines had to be developed in a relatively short period; therefore, they had to be manufactured via a method different from that of conventional vaccines. In addition, many people were vaccinated in a short period, and various side effects related to vaccination have been reported[2]. In this article, we describe the injection site reactions, some unique skin reactions associated with COVID-19 vaccination, and their possible causes.

MAIN TEXT

Tan et al.[3] reviewed the cutaneous side effects reported from January 2020 to September 2021. According to their review, cutaneous side effects related to vaccines have been commonly reported as local injection site reactions, delayed local reactions, urticaria, angioedema, and morbilliform eruptions. In addition, there were herpes zoster, bullous eruptions, filler reactions, chilblains, Sweet syndrome, pityriasis rosea, erythema multiforme, dermal hypersensitivity reactions, lichen planus, pityriasis rosea-like eruptions, papulovesicular eruptions, severe cutaneous reactions, facial pustular neutrophilic eruptions, and generalized annular eruptions. The study demonstrated that mRNA vaccines had more cutaneous side effects because these vaccines were more frequently injected. Cutaneous side effects typically occur during the first inoculation.

1. Inoculation site reaction

Although reports on skin side effects after COVID-19 vac-

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cination are continuously being published, the criteria for categorizing them vary from study to study. Interestingly, inoculation site reactions have been described separately from other skin reactions in almost all studies because they are the most common cutaneous side effect, and they can be further classified into immediate and delayed types. Inoculation site reactions in a phase-III clinical study have been reported for all the COVID-19 vaccines used in Korea[4]. This study reported that among those injected with the BNT162b2 vaccine, 66~83% experienced pain, and 5~7% experienced erythema and edema. Among those injected with the mRNA-1273 vaccine, inoculation site pain was reported in 88.2~83.7%, and erythema and edema in 2.8~12.2%. Among those injected with the ChAdOx1SnCoV-19 vaccine, pain was reported in 50~67%, and erythema and edema in 2~4%. For the Ad26.COV2.S vaccine, 48.6% of the participants complained of injection site pain, and 5.3~7.3% complained of erythema and edema[4]. Lastly, among those injected with the NVX-CoV2373 vaccine, 29.3~51.2% reported pain[5].

2. Whole-body skin reactions

Cutaneous adverse reactions, excluding the inoculation site reaction, may cause a skin rash similar to the one induced by COVID-19. Various types of drug eruptions may also occur[6], including urticaria, morbilliform rash, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. The detailed classification and description of skin reactions differ depending on the researcher. This is because there are many non-specific rashes that are difficult to differentiate clearly, and the criteria for classifying them have not been established. The heterogeneity of the classification method may become an obstacle to further analyses through systematic literature reviews or meta-analyses. It is also difficult to ascertain the causal relationship between skin rash and vaccination[6].

3. Bullous lesions

Bullous pemphigoid and linear IgA bullous dermatosis due to COVID-19 vaccination have been reported[7]. It is well known that both conditions can occur after drug administration, and when a monoclonal antibody for the spike protein and nucleoprotein of COVID-19 reacts with human antigens, it is confirmed to cross-react with various antigens such as transglutaminases 2 and 3, collagen, and S100B[8].

4. Vascular lesions

It has been reported that some patients infected with COVID-19 develop bluish-reddish macules on the tips of the hands and toes that worsen when exposed to cold, similar to chilblain[1]. This is caused by damage to blood vessels due to viral infections, resulting in coagulation disorders and infections of vascular endothelial cells. Similar symptoms appear even after vaccination. Vaccines do not directly penetrate endothelial cells; however, viral proteins damage these cells. Moreover, immune complexes accumulate in blood vessels, activating the complement system and causing vascular damage similar to that caused by the SARS-CoV-2 infection. Leukocytoclastic vasculitis (LCV), which is characteristic of Henoch-Schönlein purpura, has been reported to result from such blood vessel damage. Vasculitis is a side effect that can appear even after the administration of other vaccines, such as the influenza vaccine, and is known to occur mainly within 10 days (range: 1~56 days) after vaccination. Most cases of LCV after COVID-19 vaccination occur between 4 hours and 5 days after vaccination[9].

5. Foreign body reaction (filler reaction)

Delayed hypersensitivity reactions to foreign substances such as fillers have also been observed in previous vaccinations (such as those for influenza). However, there have been many reports related to COVID-19 vaccination, as many of them have been injected within a short time. Most of the reported cases involve hyaluronic acid fillers because they are more commonly used; however, reactions to collagen synthesis promoters such as polycaprolactone have also been reported[10]. The reaction occurs 1~10 days after vaccination. Hyaluronidase, corticosteroids, and lisinopril are used for treatment, and their prognoses are good. Lisinopril is an angiotensin-converting enzyme inhibitor used to treat delayed-type hypersensitivity reactions. Angiotensin 2 in skin tissue has a pro-inflammatory effect and promotes aldosterone secretion. Normally, angiotensin-converting enzyme 2 (ACE-2) converts angiotensin 2 to angiotensin 1~7, which has an anti-inflammatory effect. During COVID-19, the spike protein of the virus binds to ACE-2. As a result, tissue angiotensin 2 levels increase, intensifying inflammation and edema. In this case, the use of lisinopril prevents the conversion of angiotensin 1 to angiotensin 2, which can be expected to reduce inflammation and edema[11-13].

Table 1. Vaccine-specific excipients

Vaccine	Excipients
BNT162b2	(4-hydroxybutyl) azanediyl) bis (hexane-6,1-diyl) bis (2-hexyldecanoate)
	2-[(polyethylene glycol) 2000]-N,N-ditetradecylacetamide
	1,2-distearoyl-sn-glycero-3-phosphocholine
	Cholesterol
	Potassium chloride
	Potassium dihydrogen phosphate
	Sodium chloride
	Disodium hydrogen phosphate dihydrate
	Sucrose
	Water for injections
mRNA-1273	SM-102
	1,2-dimyristoyl-rac-glycero-3-methoxy polyethylene glycol-2000 [PEG2000-DMG]
	1,2-distearoyl-sn-glycero-3-phosphocholine
	Cholesterol
	Tromethamine
	Tromethamine hydrochloride
	Acetic acid
	Sodium acetate
	Sucrose
AZD1222	L-Histidine
	L-Histidine hydrochloride monohydrate
	Magnesium chloride hexahydrate
	Polysorbate 80
	Ethanol
	Sucrose
	Sodium chloride
	Disodium edetate dihydrate (EDTA)
	Water for injections
JNJ-78436735	Citric acid monohydrate
	Trisodium citrate dihydrate
	Ethanol
	2-Hydroxypropyl-B-cyclodextrin
	Polysorbate-80
	Sodium chloride

Table 1. Vaccine-specific excipients (Continued)

Vaccine	Excipients
NVX-CoV2373	Disodium hydrogen phosphate heptahydrate
	Sodium dihydrogen phosphate monohydrate
	Sodium chloride
	Polysorbate 80
	Sodium hydroxide
	Hydrochloric acid
	Water for injections
	Cholesterol
	Phosphatidylcholine (including all-rac-α-Tocopherol)
	Potassium dihydrogen phosphate
	Potassium chloride
	Disodium hydrogen phosphate dihydrate
	Sodium chloride

6. Exacerbation of existing skin diseases

The exacerbation of psoriasis, atopic dermatitis, lupus, dermatomyositis, chronic urticaria, leukocytoclastic vasculitis, erythema multiforme, and radiation recall dermatitis, inflammation at the Bacillus Calmette-Guerin vaccine inoculation site, and the reactivation of the herpes simplex virus/varicella-zoster virus have been reported. Lupus, or dermatomyositis, is a Th1 polarizing disease. Immune response by vaccination activates the Th1 response, including IFN-ɣ, similar to what occurs during viral infection; thus, the exacerbation of Th1 polarizing diseases may occur. There has been a case of subacute cutaneous lupus erythematosus (CLE) that worsened after the first dose of BNT162b2, and another case of Rowell's syndrome, a type of CLE with erythema multiforme-like symptoms. In addition, a lupus-like reaction by PEGylated liposomal doxorubicin has previously been reported; similarly, the aggravation of the lesion by polyethylene glycol (PEG) is possible. Studies have demonstrated that the COVID-19 vaccine increases the number of IL-6 and Th17 cells and activates plasmacytoid dermal myeloid dendritic cells. It is thought that the exacerbation of psoriasis after vaccination may be caused by this mechanism[14,15].

7. Skin reactions to excipients

Vaccines contain various excipients aside from the mRNA and protein of the virus that can trigger an immune response[16]. Representative examples of such substances known to cause immediate or delayed hypersensitivity reactions in the skin include PEGs, polysorbate 80 (polyoxyethylene-80-sorbitan monooleate), and trometamol (Table 1). PEGs are hydrophilic polymers of ethylene oxide, which allows them to bind to drugs to deliver them to a desired site and control their molecular weight to prevent their degradation. PEGs are widely used not only in medicine but also in cosmetics and food; thus, they have many opportunities for sensitization. Polysorbates are surfactants that are used in food and medicine that can cross-react with PEGs. The number following "polysorbate" represents the number of ethylene oxide groups that are attached. Such polysorbates are used in hepatitis B, human papillomavirus, and influenza vaccines. Trometamol is a substance present in gadolinium-based contrast media. According to a report by the Center for Disease Control and Prevention, 20% of patients who developed anaphylaxis from the administration of mRNA-1273 have a history of anaphylaxis with the contrast media[17,18].

CONCLUSION

The vaccine-related cutaneous side effects identified so far are mild and mostly self-limiting. In many studies, cutaneous side effects have been reported to be more common

in women. This may be due to a reporting bias since many nurses were vaccinated in the early stages of the pandemic, which increased the proportion of women. In addition, because more women have autoimmune diseases, the possibility that side effects may occur frequently in women is increased[19,20].

In the future, it will be necessary to establish a standard for classifying cutaneous side effects through additional research. In addition, in the event of cutaneous side effects, an agreement must be reached on how to perform subsequent booster vaccinations. Lastly, confirming the causal relationship between the vaccine and skin reactions is also a possible area of future research.

CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

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