

Injection site reactions after COVID-19 mRNA vaccination

Dear Editor,

The Pfizer-BioNTech (BNT162b2 mRNA) and Moderna (mRNA-1273) COVID-19 vaccinations were approved for use in Singapore in December 2020 and February 2021, respectively. To date, over 10 million doses of mRNA vaccines have been administered for the primary series and booster doses.¹ Initial studies have shown that 0.8% of individuals who received Moderna mRNA vaccine developed delayed injection-site reactions. These reactions were characterised as tender erythematous, indurated plaques and were commonly misdiagnosed as cellulitis or allergic reactions.²⁻⁵ Such reactions to the Moderna mRNA vaccine are thought to be generally benign and not a contraindication to further doses. On the other hand, injection-site reactions associated with the Pfizer-BioNTech mRNA vaccine are less clearly defined. In this current study, we report the characteristics of mRNA COVID-19 injection-site reactions, comparing the clinical features between Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) reactions in the Singapore adult population.

We retrospectively reviewed patients referred to the Dermatology Service/Allergy Centre at the Singapore General Hospital for reactions post COVID-19 vaccination from 10 January to 26 August 2021. Inclusion criteria were adult patients who developed a localised injection-site reaction after either Moderna or Pfizer-BioNTech mRNA COVID-19 vaccination. Patients who developed non-injection site reactions or had reactions assessed as unrelated to vaccination were excluded. Patient's demographics, clinical history, management and recurrence of subsequent reactions were collected and analysed. Data are presented as median for discrete data, and counts or percentages for categorical data. Fisher's Exact test was performed in comparison of categorical variables between groups, and Mann-Whitney U test was performed for discrete variables. *P* value of ≤ 0.05 was considered statistically significant. The data were analysed using SPSS Statistics version 22 (IBM Corp, Armonk, US).

During the study period, there were 322 patients referred for post-COVID-19 vaccine cutaneous reactions. Of these, 21 developed post-vaccination injection-site reactions. Eleven (52%) had received the Moderna mRNA vaccine while the remaining 10 (48%) received the Pfizer-BioNTech mRNA vaccine. The median age (range) was 55 years (24–80), with 17 (81%) being

female. Twenty (95%) cases developed after the first dose of vaccine.

In the group receiving the Moderna mRNA vaccines, median duration to onset of the reaction (range) was 8 days (1–9). These patients developed pruritic, erythematous plaques with varying degrees of induration and swelling at or near the site of vaccination.

In the group receiving the Pfizer-BioNTech vaccine, median duration to onset of the reaction (range) was 1 day (1–8). These patients developed similar injection-site reactions that were pruritic, mildly erythematous and mildly oedematous.

Patients receiving the Moderna mRNA vaccine had a longer median latency period ($P=0.001$) and were more likely to have a latency duration of >5 days ($P=0.009$) as compared to patients receiving the Pfizer-BioNTech vaccine.

Two patients developed injection-site reactions with secondary dissemination. The reactions started from the injection-site and sequentially spread to the rest of the body (Table 1). One patient required admission for treatment of the symptoms. A skin biopsy performed on the lesions showed focal interface dermatitis with moderate superficial and deep chronic inflammation.

Eleven (52%) of these reactions resolved without treatment, while the remaining 10 (48%) required symptomatic treatment with topical corticosteroids, antihistamines, or a combination of both. Patients who developed an injection-site reaction post Moderna mRNA vaccine were more likely to receive symptomatic treatment ($P=0.03$).

All 21 patients went on to receive the second vaccine dose. Of these, 2 patients experienced recurrence of the reaction. These reactions developed earlier and were less intense in terms of pain, erythema and oedema. They were self-limited and did not require treatment. Table 1 summarises the characteristics of the cases.

Localised injection-site reactions are uncommon side effects that can develop after either Moderna or Pfizer-BioNTech mRNA COVID-19 vaccination.^{6,7} From our series, we demonstrate phenotypic differences between the injection-site reactions following the 2 different mRNA vaccines.

In injection-site reactions following Pfizer-BioNTech vaccination, the latency between vaccination and onset of cutaneous lesions is significantly shorter. While

Table 1. Characteristics of patients and injection-site reaction

	Moderna (n=11)	Pfizer-BioNTech (n=10)	P value
Sex, no. (%)			
Male	3 (27)	1 (10)	0.586
Female	8 (73)	9 (90)	
Median age (range), years	56 (24–77)	51 (29–80)	0.691
Prior allergies, no. (%)			
NSAID	1 (9)	2 (20)	0.499
Penicillin	0 (0)	1 (10)	
Contrast	1 (9)	0 (0)	
Tetracycline	1 (9)	1 (10)	
Sulfonamide	1 (9)	0 (0)	
Onset of reaction			
Median (range), days	8 (1–9)	1 (1–8)	0.001
Latency >5 days, no. (%)	9 (82)	2 (20)	0.009
Disseminated lesions, no. (%)	1 (9)	1 (10)	1
Other symptoms, no. (%)			
Headache	0 (0)	1 (10)	0.476
Axillary swelling	1 (9)	0 (0)	1
Urticaria	0 (0)	1 (10)	0.476
Pre-referral diagnosis, no. (%)			
Possible allergy	7 (64)	10 (100)	0.09
Cellulitis/erysipelas	2 (18)	0 (0)	0.476
Treatment, no. (%)			
No treatment	3 (27)	8 (80)	0.03
Topical steroids	7 (64)	0 (0)	
Antihistamines	5 (45)	2 (20)	
Need for admission, no. (%)	1 (9)	0 (0)	0.524
Recurrence, no. (%)	1 (9)	1 (10)	0.738

NSAID: non-steroidal anti-inflammatory drug



Fig. 1. (A) Injection-site reaction over the left deltoid with secondary dissemination of lesions. Sites of dissemination on (B) right elbow and (C) right knee.

swelling and redness within 7 days of Pfizer-BioNTech mRNA vaccine have been reported in up to 7% of patients, the true incidence of injection-site reactions is unknown.⁸ Our study has also confirmed the benign nature of the delayed local injection-site reactions to Moderna mRNA and Pfizer-BioNTech mRNA vaccines. All the patients went on to receive the second dose despite the initial first dose reactions. None of the patients developed severe allergic reactions, even in those who had disseminated lesions. These findings are consistent

with Singapore studies evaluating the safety profile of mRNA vaccines.⁹

Histologically, reactions that develop after Moderna mRNA vaccine demonstrate a superficial to mid perivascular inflammatory infiltrate composed of lymphocytes and eosinophils with vacuolar interface dermatitis.^{4,7,10} These features support a drug-mediated delayed hypersensitivity reaction. Histological evaluation of Pfizer-BioNTech mRNA vaccine reactions are less well characterised, and features of epidermal hyperplasia with spongiosis and an eosinophil rich infiltrate have been reported.⁷ It remains unclear if pathogenic mechanisms behind injection reactions across the 2 vaccines differs.

Although uncommonly reported with Moderna mRNA vaccine, our study has shown that dissemination of lesions can be seen in Pfizer BioNTech mRNA vaccine as well. Nonetheless, these reactions appear self-limited, with none recurring after vaccine challenge. The mechanism of dissemination of these lesions is unclear, but we postulate that these may arise as interface dermatitis

reactions where a secondary immunologic host response develops after the initial primary reaction.

Our study's limitations include its small sample size and retrospective nature. We also acknowledge the presence of a referral bias, where included patients are only those referred to our centre. Mild cases may have consequently been missed.

With the call for booster vaccinations globally, it is important to recognise that these reactions are mild, self-limited and should not deter one from subsequent vaccines. Ongoing surveillance is necessary to better characterise the behaviour of such reactions with subsequent booster vaccination.

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