Original Article:

Novel Messenger RNA Coronavirus Vaccination: A Study of Adverse Skin Reactions

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Abstract

Background: Anecdotal reports regarding novel formulations of messenger RNA (mRNA)-based vaccines are being inflated by social media, generating alarming misconceptions about vaccination. **Objectives:** To evaluate the morphology and timing of cutaneous reactions after messenger RNA virus vaccination and to calculate the number and frequency of each of those eruptions. **Methods:** This prospective observational study was conducted on a total of 183 people who reported cutaneous reactions after vaccination with Food and Drug Administration-approved Pfizer or Moderna mRNA vaccines, at Kuwait Bangladesh Friendship Government Hospital, Dhaka. Statistical analyses were done by using SPSS 26 and descriptive analysis and association of variables were seen by frequency distribution and Chi-square analysis with p-value ≤0.005. **Results:** Adverse skin eruption was found among 60.7% of study participants after the booster dose, among 31.1% of participants after 2nd dose and only among 8.2% of participants after 1st dose. The latency between getting vaccine and onset of skin eruption was <7 days among 29.5% of participants, 7 to 14 days among 34.4% of participants and >14 days among 36.1% of participants and the average duration of skin lesion was 19.54±21.50 days. Fifty nine percent of the study participants developed generalized pruritus, 65.6% developed urticaria, 13.1% developed morbilliform eruption, 3.3% developed vasculitic reaction, dermatophytosis, chilblain-like reactions and local injection site reactions respectively and 1.6% developed facial swelling, diffuse hair loss respectively. **Conclusion:** The low rate of reactions and favourable course observed in our study would be helpful to reassure patients as well as healthcare providers that the vaccination program is safe and affordable even in allergic patients.

Key word: Corona virus, vaccination, mRNA vaccine, skin reactions.

Introduction:

Vaccines are the most effective strategy to control the COVID-19 spread and reduce mortality, but adverse reactions can occur. Skin involvement with novel messenger RNA coronavirus vaccines seems frequent but is not completely characterized.In December 2020, the Food and Drug Administration issued Emergency Use Authorizations for Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccines. Clinical trials for both vaccines reported local injection site reactions and systemic symptoms after both the 1st and 2nd doses.[1,2]

The novel messenger RNA (mRNA) technology vaccines are a crucial part of the worldwide fight against coronavirus disease 2019 (COVID-19), and the Pfizer-BioNTech vaccine has been the first issued in Italy for the health care workers' vaccination program. Reported adverse effects in clinical trials include minimal local skin reactions, especially following the required second dose of the vaccine, without systemic adverse reactions.[3,4] The BNT162b2 vaccine is based on lipid nanoparticles and other substances to enable the transport of messenger RNA (mRNA) molecules into the cells, which can be potential allergens. In Pfizer-BioNTech

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COVID-19 vaccine approval clinical trials, injection site pain was frequently reported (84.1% of recipients), followed by swelling (10.5%) and erythema (9.5%).[5]In case of the Moderna vaccine, reactions, thought to be mediated by T cells, have been attributed to ingredients such as neomycin or thimerosal and have not been considered as a contraindication to subsequent vaccination.[5]Although the aetiology of these delayed large local reactions due to the Moderna vaccine is unclear, a delayed-type hypersensitivity reaction to the excipient polyethylene glycol is[1] potential aetiology.[6]

Severe allergic reactions to vaccines are rare but can be life-threatening. However, the Centers for Disease Control and Prevention (CDC) recommends avoiding a second dose if a severe or immediate allergic reaction to the first dose of an mRNA COVID-19 vaccine has occurred.[7] Mucocutaneous reactions, such as pruritus, urticaria, and angioedema, may occur after COVID-19 messenger RNA (mRNA) vaccination. The incidence of these reactions and recurrence with subsequent vaccination has not been described. Cutaneous reactions may contribute to unnecessary avoidance of future vaccination doses.[8]

According to WHO, Bangladesh became the largest recipient of U.S. COVID-19 Vaccine donations and shared with over 61 million total doses of Pfizer and Moderna Vaccines by February 2022[9]. As there is no prevailing data in our country, we aimed to collect cases of cutaneous side effects to the messenger RNA (mRNA) COVID-19 vaccines (1) to describe the morphology and timing of cutaneous reactions to the Pfizer and Moderna vaccines and (2) to understand differences in cutaneous reactions between the 2 vaccine doses to guide vaccine counselling.

Methodology:

From November 2021 to April 2022, a prospective observational study was conducted on a total of 1,95, 654 people who underwent the COVID-19 vaccination with Moderna and Pfizer vaccines at Kuwait Bangladesh Friendship Government Hospital. Most people (134818) were vaccinated with Moderna and of them 38,009 people were immunized with the 1st dose, 37,518 with the 2nd dose and 59,291 with the 3rd dose. 60,836 people took Pfizer and of them 25,616 people were immunized with the 1st dose, 22,271 with the 2nd dose and 12,949 with the 3rd dose of vaccine. In this study, we only included people who reported cutaneous adverse reactions (CAR) following vaccination with Food and Drug Administration-approved Pfizer or Moderna mRNA vaccines. During these 6 months of the study period, no one developed immediate hypersensitivity reactions. In the following days of successive vaccination, 183 subjects were referred to the outdoor, Dermatology department with Vaccine-related CARs. All of them were provided with informed written consent to the use of their details. A thorough skin examination was performed by dermatologists to specify the cutaneous eruptions. In addition, patients were asked to complete a written questionnaire on the type and dose of the COVID-19 vaccine, the time of onset of cutaneous reactions, and the dates of administration. Comorbidities, pre-existing dermatoses, and concomitant therapies were also investigated. Routine blood tests were carried out to investigate the inflammatory and allergic status and the status of co-morbidities; Histology was not carried out due to unavailable facilities during that Covid period.

Data Management and Statistical Analysis: Data were collected through face-to-face interviews and physical examinations and laboratory investigation by using a pre-tested questionnaire. Data were entered in SPSS 26 and descriptive analysis and association of variables were seen by frequency distribution and Chi-square analysis with p-value ≤ 0.005.

Result:

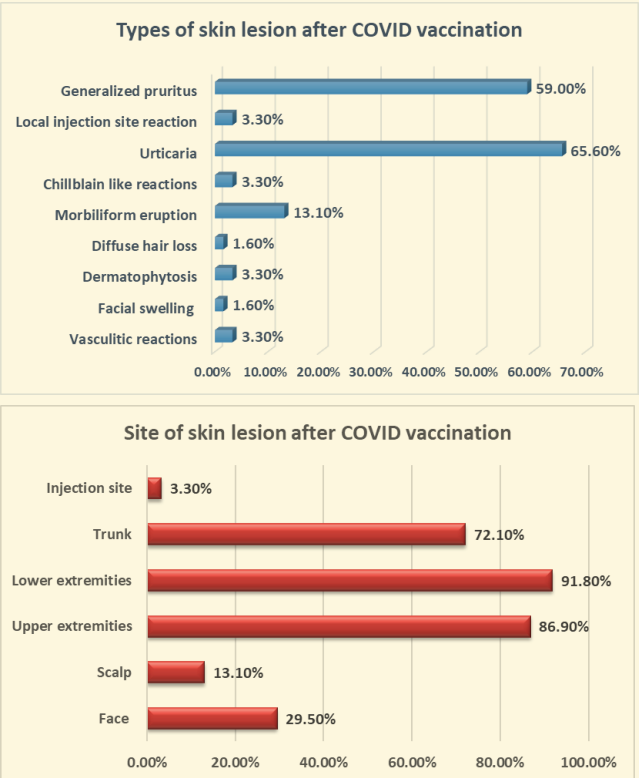
Table 1: Socio-demographic characteristics and vaccine profile of study participants (n=183)

Variables			
Age (in years)	Mean±SD	34.00±14.78	
Duration of skin lesion (in days)	Mean±SD	19.54±21.50	
		Frequency	Percentage
Sex	Male	87	47.5
	Female	96	52.5
Type of Covid Vaccine	Moderna	138	75.4.5
	Pfizer	45	24.6
Onset of eruption after vaccine dose	After 1st dose	15	8.2
	After 2nd dose	57	31.1
	After Booster dose	111	60.7
Latency (in days)	<7 days	54	29.5
	7 to 14 days	63	34.4
	>14 days	66	36.1

A total of 183 study participants had messenger RNA virus vaccines. The average age of the study participants was 34.00±14.78 years and among them 47.5% were male and 52.5% were female. There were two messenger RNA vaccines: Moderna and Pfizer. Majority (75.4%) of the study participants had

Moderna and 24.6% had the Pfizer vaccine. Adverse skin eruption was found among 60.7% of study participants after the booster dose, among 31.1% of participants after 2nd dose and only among 8.2% of participants after 1st dose. The latency between getting vaccine and onset of skin eruption was <7 days among 29.5% participants, 7 to 14 days among 34.4% participants and >14 days among 36.1% participants and the average duration of skin lesion was 19.54±21.50 days. (Table 1)

Figure 1: Types and site of skin lesion after COVID vaccination (n=183)



A spectrum of skin lesions was found among the study participants who had messenger RNA vaccines and the sites of skin lesions were also different. Fifty nine percent of the study participants developed generalized pruritus, 65.6% developed urticaria, 13.1% developed morbilliform eruption, 3.3% developed vasculitic reaction, dermatophytosis, chilblain-like reactions and local injection site reactions respectively and 1.6% developed facial swelling, diffuse hair loss respectively. Skin lesions involved the lower extremities (91.8%), upper extremities (86.9%), trunk (72.1%), face (29.5%), scalp (13.1%) and injection site (only 3.3%). (Figure 1)

Table 2: Distribution of skin lesion according to types of COVID vaccine (n=183)

	Moderna	Pfizer	Pearson Chi square P value
Generalized pruritus	84 (60.9)	24 (53.3)	0.388
Local injection site reaction	0 (0.0)	6 (13.3)	0.000*
Urticaria	96 (69.6)	24 (53.3)	0.070
Chilblain like reactions	3 (2.2)	3 (6.7)	0.160
Morbilliform eruption	21 (15.2)	3 (6.7)	0.203
Diffuse hair loss	0 (0.0)	3 (6.7)	0.014*
Dermatophytosis	6 (4.3)	0 (0)	0.339
Facial swelling	3 (2.2)	0 (0)	1.000
Vasculitic reaction	3 (2.2)	3 (6.7)	0.160

*Statistically significant

Between the two types of COVID vaccines, namely Moderna and Pfizer, adverse skin reactions varied. Generalized pruritus (60.90%), urticaria (69.60%), morbilliform eruption (15.20%), dermatophytosis (4.30%) were more common in Moderna vaccine recipients and facial swelling (2.20%), vasculitic reaction (2.20%) and chilblain like reactions (2.20%) were less common. On the other hand, those who received the Pfizer vaccine had generalized pruritus (53.30%), urticaria (53.30%), local injection site reaction (13.30%), morbilliform eruption (6.70%), chilblain-like reactions (6.70%), diffuse hair loss (6.70%) and vasculitic reaction (6.70%). (Table 2)

Table 3: Latency of skin lesion (n=183)

	Latency			
	<7 days	7 to 14 days	>14 days	Pearson Chi square P value
Generalized pruritus	21 (19.4)	36 (33.3)	51 (47.2)	0.000*
Local injection site reaction	3 (50.0)	3 (50.0)	0 (0)	0.063
Urticaria	33 (27.5)	36 (30.0)	51 (42.5)	0.040*
Chilblain like reacions	0 (0)	3 (50.0)	3 (50.0)	0.117
Morbilliform eruption	15 (62.5)	6 (25.0)	3 (12.5)	0.001*
Diffuse hair loss	0 (0.0)	3 (100.0)	0 (0)	0.039*
Dermatophytosis	0 (0)	3 (50.0)	3 (50.0)	0.117
Facial swelling	3 (100.0)	0 (0)	0 (0)	0.024*
Vasculitic reaction	3 (50.0)	3 (50.0)	0 (0)	0.063

*Statistically significant

The latency of different types of skin lesions was not the same. Most of the study participants (47.2%) developed generalized pruritus after >14 days, 33.3% developed between 7-14 days and only 19.4% developed within <7 days. Urticaria developed in

42.5% of participants after >14 days, 30.0% developed between 7-14 days and only 27.5% developed within <7 days. The morbilliform eruption mostly developed within <7 days (62.5%) and between 7-14 days (25.0%). Local injection site reaction and the vasculitic reaction developed mostly between 7-14 days (50.0%) and within <7 days (50.0%). 100% of the facial swelling developed within <7 days. 100% of the diffuse hair loss developed between 7-14 days. Chilblain-like reactions and dermatophytosis was developed mostly between 7-14 days (50.0%) and after > 14 days (50.0%).

Discussion

Recently, delayed skin reactions have been reported in 1% of individuals following mRNA vaccination against SARS-CoV-2. The exact pathophysiology and the risk factors remain unclear.[10] The probable mechanism may be (1) the host immune response to the virus is being replicated by the vaccine and (2) some components of these dermatologic manifestations of the virus are likely to be from an immune response to the virus rather than direct viral effects.[11,12]

In this study, we have explored the cutaneous reactions after vaccination with Food and Drug Administration-approved Pfizer or Moderna mRNA vaccines, irrespective of doses (1st, 2nd and booster).In a registry-based study of 414 cases, a spectrum of cutaneous reactions after mRNA COVID-19 Moderna (83%) and Pfizer (17%) vaccines was reported.[13] Similarly in our study of 183 cases, Moderna vaccine induced cutaneous reaction (75.9%) was more common than Pfizer induced reactions(24.6%). No serious adverse events developed in any of the patients, thus not discouraging vaccination.

In previous studies, cutaneous reactions were more commonly reported among women after mRNA COVID vaccinations.[14,15] The underlying cause for this difference is not yet known, although drug allergies are more common in women.[16] Our study also showed the female predominance of cutaneous reaction. Here, we have characterized the morphology and timing of cutaneous reactions for the novel Moderna and Pfizer mRNA COVID-19 vaccines. We observed a broad spectrum of reported reactions after vaccination like urticarial reaction, generalized pruritus, morbilliform eruption, pain and swelling of the injection site and flare of dermatophytic infection. In other studies, common cutaneous reactions were local injection site reactions, delayed large local reactions, urticarial and morbilliform eruptions. Some unusual reactions were erythromelalgia, chilblain-like reactions, filler reactions, and pityriasis-rosea-like eruptions to Moderna and Pfizer vaccines. 67 patients with cutaneous findings after the first dose and only 29 showed cutaneous symptoms after the second.[17-19] On the contrary, our study shows 60.7% reactions after the booster dose, then 1st dose and less commonly after the 2nd dose.

We additionally observed facial swelling, vasculitic reaction, chilblain-like reaction and hair loss among the reported patients.McMahon et al reported that vasculitis accounted for 2.9 and 0.7% of the cutaneous side effects in patients receiving Pfizer-BioNTech and Moderna vaccines respectively.[20] The incidence of alopecia following COVID-19 vaccination has also risen significantly.[21]In the study 6.7% patients developed vasculitic reaction by the Pfizer and 2.2% by the Moderna vaccine. Here we have noticed facial swelling in three patients following the Moderna vaccine. There was no history of injectable filler substances. The swelling was a non-anaphylactic type, associated with erythema and pruritus and subsided within 7 to 10 days with antihistamine and short course steroids. Similar type of facial swelling was also described in the earlier study following the Pfizer vaccine[22]

Conclusion

We report a spectrum of cutaneous reactions after mRNA COVID-19 vaccines. As per our knowledge, there is no prior study on this background in our country. Hopefully, this study would support the Vaccine Adverse Event Reporting System (VARES) and augment the ongoing safety monitoring of vaccination.

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