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Original Article

Safety of SARS-CoV-2 Vaccination in Patients with Vascular Malformations: Patient-Reported Adverse Vaccine Reactions

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Objectives: Concerns among susceptible individuals, especially those with vascular malformations, have been raised by reports of thromboembolism following the administration of the SARS-CoV-2 vaccination against coronavirus disease 2019 (COVID-19). This study's goal was to assess any negative side effects that patients with vascular malformations who received the SARS-CoV-2 vaccine reported after receiving it.
Materials and Methods: Through the three patient groups for vascular malformations in Japan in November 2021, a questionnaire was distributed to patients with vascular malformations who were 12 years of age or older. Multiple regression analysis was used to find relevant variables.
Results: A total of 128 patients responded, representing a response rate of 58.8%. Ninety-six participants (75.0%) had received at least one dose of SARS-CoV-2 vaccine. In total, 84 (87.5%) and 84 (89.4%) subjects experienced at least 1 general adverse response following dose 1 and dose 2, respectively. Adverse reactions related to vascular malformations were reported by 15 participants (16.0%) after the 1st dose and 17 (17.7%) after the 2nd dose. Notably, no case of thromboembolism following vaccination was reported.
Conclusion: The rate of vaccine-related adverse reactions in patients with vascular malformations is not different from that reported in the general population. There is no report of life-threatening responses in the research population.

Keywords: vaccination, adverse reactions, vascular malformations, vascular anomalies, COVID-19

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Introduction

Vascular malformations include a broad spectrum of vascular pathology, including proliferating vascular tumors and vascular malformations.[1–3] Patients with venous malformations, lymphatic venous malformations, and Klippel–Trenaunay syndrome are at risk of developing life-threatening hematological complications like venous thrombosis.[4–6]

As of December 2021, 101 million people in Japan (79.2% of the population) had received the SARS-CoV-2 vaccine 1st dose, and 98 million (77.9%) had received the 2nd dose.[7] Several reports of thromboembolic events following SARS-CoV-2 vaccination have been published[8,9] with large-scale meta-analyses showing the ChAdOx1 vaccine (Oxford-AstraZeneca) is strongly associated with thromboembolic events.[10–12] This has raised concerns about the safety of the vaccines in patients with vascular malformations who are already at risk of such adverse vascular reactions. Furthermore, the Japanese Ministry of Health, Labor and Welfare (MHLW) recently reported the death of a 26-year-old female from intracranial hemorrhage 4 days after receiving her first dose of SARS-CoV-2 vaccination with autopsy reports pointing to intracranial arteriovenous malformations.[13] These reports may have further worsened vaccine anxiety in patients with vascular malformations and highlight the need for study of the vac-

cine safety in this unique population.

Although vascular malformations are strongly associated with thromboembolism,[4–6] the association between vascular malformations and side effects of SARS-CoV-2 vaccines particularly thrombotic problems has not previously been studied and remains unclear. This study aims to evaluate the patient-reported adverse reactions and associated factors of SARS-CoV-2 vaccines in patients with vascular malformations and to assess their opinions on the vaccines.

Patients and Methods

Participants and experimental design

A cohort of 249 patients with vascular anomalies in Japan was recruited. Eligibility criteria included (1) diagnosis of vascular malformations, (2) 12 years of age or older, (3) access to the Internet and ability to complete surveys in Japanese, and (4) willingness to participate in the study. Children younger than 12 years old were excluded because the Japanese government had not yet approved SARS-CoV-2 vaccination in this age range at the time of the trial. An electronic self-reported survey was sent via the three patient societies of vascular malformations in Japan: Patients Association of Vascular Anomalies, *Kekkan-kikei* Network, and *Kongo-gata Myakkann-kikei no Kai*. Reminders were sent 2 weeks and 1 week prior to survey deadline on November 30, 2021. All study procedures were approved by the local research ethics committee (Mie University Hospital IRBMED Number H2021-212) and were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Data collection and measurements

Data collected included demographic data, age and sex, type of vascular malformations, medical and drug history, details of SARS-CoV-2 vaccination, and adverse reactions. Adverse reactions analyzed were further divided as general adverse reactions such as pain, swelling, induration, itching of the injected site, fever (37.5°C or above), muscle soreness, arthralgia, headache, fatigue, and thromboembolism and adverse reactions related to vascular malformations including pain, redness, swelling, enlargement, and thrombosis of the lesion. Participants who had not been vaccinated were optionally asked for reasons.

Statistical analysis

A multiple linear regression model was created to determine the variables connected to adverse reactions in individuals with vascular malformations. $P<0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS v.27.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 147 participants completed the questionnaire survey, with a survey response rate of 58.8%. Nineteen were disqualified due to being under 12 years of age, leaving a total of n = 128 eligible responses (**Supplementary Fig. 1**).

The demographics of the overall participants are described in **Table 1**. The most prevalent age group was 12–19 years (n = 31, 24.2%) closely followed by 20–29 years (n = 27, 21.1%) and 40–49 years (n = 27, 21.1%). Female participants accounted for 67 (52.3%) of the total and males 61 (47.7%). The most prevalent vascular malformations included 56 (43.8%) venous malformation (VM), 47 (36.7%) arteriovenous malformation (AVM), and 32 (25.0%) hemangiomas. The most common sites were the lower extremities (n = 74, 57.8%) and head and neck (n = 32, 25.0%) followed by the upper extremities (n = 22, 17.2%) and trunk (n = 19, 14.8%). Participants with Klippel–Trenaunay (KT) syndrome and Parkes–Weber (PW) syndrome were investigated together despite having separate etiology, since some participants were unable to discern between the two and referred to their anomaly as KT/PW spectrum.

Regarding the SARS-CoV-2 vaccination, 96 participants (75.0%) had received at least 1 dose of the vaccine, whereas 32 participants (25.0%) were unvaccinated. Vaccine distribution comprised 75 (78.1%) BNT162b2 (Pfizer-BioNTech), 19 (19.8%) mRNA-1273 (NIH-Moderna), and 2 (2.1%) unknown. No participant reported receiving ChAdOx1. Comparison between vaccinated and unvaccinated participants (**Supplementary Table S1**) showed that the rate of younger vaccinated participants was considerably lower than those of older participants ($p = 0.005$). The percentage of vaccinated participants was 54.8% (n = 17) participants aged under 20 years and 81.4% (n = 79) in those aged 20 or above. All the patients registered in this study with blue rubber bleb nevus syndrome (BRBNS) (n = 2), systemic vascular malformations (n = 2), and a history of heart disease (n = 3) were all unvaccinated.

Of the 32 unvaccinated participants, 31 (96.9%) shared their reasons for not receiving the vaccination (**Supplementary Table S2**). The most common reason was personal concerns regarding the vaccine side effects (n = 24, 77.4%) with n = 4 (12.9%) explicitly worried about embolism or venous thrombosis following vaccination. The second leading reason was due to concerns raised by others, for instance, family members or their doctors about the vaccine (n = 4, 12.9%). Other justifications were mistrust of political authorities and conflicting media messages about vaccinations.

The proportion of participants who reported at least

Table 1 Demographics of the study population

Item	Total (N=128)	
	n	Percent
Age		
12–19	31	24.2%
20–29	27	21.1%
30–39	17	13.3%
40–49	27	21.1%
50–59	23	18.0%
60–	3	2.3%
Sex		
Female	67	52.3%
Male	61	47.7%
Type of vascular malformations		
Hemangioma	32	25.0%
VM	56	43.8%
CM	8	6.3%
AVM	47	36.7%
LM	16	12.5%
KT/PW	10	7.8%
BRBNS	2	1.6%
Location of vascular malformations		
Head and neck	32	25%
Upper extremities	22	17.2%
Trunk	19	14.8%
Lower extremities	74	57.8%
Viscera	3	2.3%
Systemic	2	1.6%
Medical history		
COVID-19 infection	2	1.6%
Hypertension	7	5.5%
Diabetes mellitus	3	2.3%
Asthma	19	14.8%
Seizure	4	3.1%
Stroke	3	2.3%
Heart disease	3	2.3%
Thromboembolism	12	9.4%
Coagulation abnormalities	4	3.1%
Malignancy	4	3.1%
Others	8	6.3%
None of the above	74	57.8%
Medication		
Antithrombotic drug	12	9.3%
Sirolimus	6	4.7%
Immunosuppressor	6	4.7%
Beta blocker	3	2.3%
Others	2	2.3%
None of the above	101	78.9%
Dose number		
0	32	25.0%
1	2	1.6%
2	94	73.4%
Vaccine company (among vaccinated subjects)		
Pfizer	75	78.1%
Moderna	19	19.8%
AstraZeneca	0	0%
Unknown	2	2.1%

VM: venous malformation; CM: capillary malformation; AVM: arteriovenous malformation; LM: lymphatic malformation; KT/PW: Klippel–Trenaunay syndrome/Parkes–Weber syndrome; BRBNS: blue rubber bleb nevus syndrome

one general adverse reaction following vaccination was 87.5% (n=84) after dose 1 and 89.4% (n=84) after dose 2 (**Fig. 1A**). The vast majority of the participants reported pain at the injected site, 71.9% (n=69) and 75.5% (n=71); swelling at the injected site, 27.1% (n=26) and 35.1% (n=33); and fever, 21.9% (n=21) and 54.3% (n=51), after dose 1 (**Supplementary Table S3**) and dose 2, respectively (**Supplementary Table S4**). Adverse reactions related to the vascular anomaly lesions were reported by 17.7% of the participants (n=17) after dose 1 and 16.0% (n=15) after dose 2 (**Fig. 1B**). All of the participants who disclosed adverse reactions related to vascular anomaly lesions also reported at least one other negative effect. Notably, none of the participants reported anaphylaxis, thromboembolism, or thrombosis at lesion site after vaccination (**Fig. 1**).

Regression analysis found no factors connected to adverse reactions to dose 1 (**Table 2**). Older age (p=0.03), a history of COVID-19 infection (p=0.04), asthma (p=0.03), and thromboembolism (p=0.03) were negatively associated with general adverse reactions to dose 2. A higher population of KT/PW 42.9% (n=3) experienced at least one adverse event associated with vascular abnormality lesions to dose 2 (p=0.04).

This study had too few vaccinated participants with systemic complications like rare systemic vascular malformations and a history of heart disease, coagulation abnormalities, and antithrombotic drug use. Consequently,

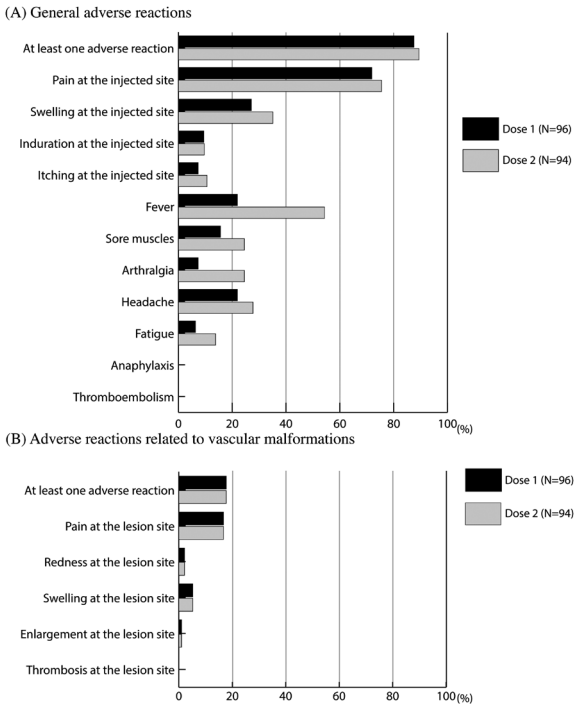

Fig. 1 Reported adverse reactions of each type of vascular malformations following SARS-CoV-2 vaccine.

Table 2 Multiple regression analysis of factors associated with adverse reactions following SARS-CoV-2 vaccination

Independent variable	General adverse reactions				Adverse reactions related to lesions of vascular malformations			
	Dose 1		Dose 2		Dose 1		Dose 2	
	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value
Age	−0.09	0.58	−0.30	0.03*	0.12	0.41	−0.03	0.84
Sex								
Female	Reference		Reference		Reference		Reference	
Male	0.20	0.13	−0.03	0.81	0.13	0.27	−0.01	0.99
Type of vascular malformations								
Hemangioma	−0.09	0.57	−0.10	0.43	0.08	0.59	0.19	0.15
VM	−0.24	0.91	−0.17	0.35	0.14	0.47	0.18	0.33
CM	0.10	0.46	0.16	0.18	0.001	1.00	0.04	0.70
AVM	0.08	0.72	−0.01	0.94	0.33	0.08	0.28	0.12
LM	0.21	0.23	0.28	0.05	0.29	0.06	0.13	0.36
KT/PW	0.11	0.57	0.18	0.25	0.18	0.27	0.34	0.04*
Location of vascular malformations								
Head and neck	0.14	0.72	0.21	0.51	0.43	0.21	0.32	0.33
Upper extremities	−0.13	0.73	0.16	0.61	0.21	0.52	0.11	0.71
Trunk	−0.10	0.55	−0.04	0.77	−0.18	0.21	0.11	0.45
Lower extremities	0.07	0.87	−0.05	0.89	0.42	0.27	0.16	0.67
Viscera	−0.01	0.95	0.07	0.59	−0.12	0.38	−0.03	0.81
Medical history								
COVID-19 infection	−0.17	0.19	−0.23	0.04*	−0.02	0.89	0.23	0.40
Hypertension	−0.17	0.41	−0.29	0.09	−0.14	0.43	−0.19	0.27
Diabetes mellitus	0.24	0.90	0.07	0.61	0.06	0.69	0.33	0.03
Asthma	−0.16	0.47	−0.41	0.03*	0.10	0.59	0.19	0.32
Seizure	−0.01	0.95	−0.14	0.33	0.15	0.36	−0.06	0.68
Stroke	−0.22	0.20	−0.10	0.47	−0.26	0.08	−0.10	0.48
Thromboembolism	−0.14	0.56	−0.43	0.03*	−0.30	0.15	−0.22	0.27
Coagulation abnormalities	−0.02	0.91	−0.08	0.55	0.04	0.77	−0.02	NA
Malignancy	−0.01	0.97	−0.31	0.02*	−0.15	0.28	−0.05	0.71
Others	−0.19	0.37	−0.30	0.08	−0.13	0.48	0.03	0.87
Allergy								
Hay fever	−0.19	0.47	−0.03	0.09	0.33	0.14	0.25	0.26
Contrast agents	−0.15	0.54	0.07	0.74	0.09	0.69	−0.11	0.61
Others	−0.14	0.74	0.13	0.72	0.62	0.10	0.32	0.40
Medication								
Antithrombotic drug	−0.78	0.73	−0.30	0.14	0.42	0.04	0.53	NA
Sirolimus	−0.07	0.79	−0.12	0.55	0.15	0.47	0.17	0.39
Immunosuppressor	0.07	0.71	0.04	0.80	0.09	0.60	−0.06	0.70
Beta blocker	−0.06	0.68	−0.01	0.95	−0.01	0.95	0.09	0.47
Others	0.08	0.79	0.03	0.91	0.39	0.16	0.51	0.09

VM: venous malformation; CM: capillary malformation; AVM: arteriovenous malformation; LM: lymphatic malformation; KT/PW: Klippel–Trenaunay syndrome/Parkes–Weber syndrome; NA: not available *p<0.05

a detailed analysis of these conditions was not possible for these.

Discussion

The 75.0% SARS-CoV-2 vaccination rate in patients with vascular malformations found in this study was slightly lower than the overall national vaccination rate across Japan which was 77.9% as of December 2021.[7] Regarding the general adverse reactions following SARS-CoV-2 vaccines, the frequency of reported reactions was generally similar with the findings observed in clinical trials across the general population with discomfort at the injection site being the most common adverse reaction.[14–16]

The Ministry of Health, Labor and Welfare (MHLW) of Japan general population study of over 19,000 participants working at hospitals who received BNT162b2 vaccines reported pain at the injected site in 92.5% after the 1st dose and 89.5% following the 2nd dose, while fever was observed in 3.3% after the 1st dose and 38.1% following the 2nd dose.[17] With regard to mRNA-1273 vaccine, 84.4% developed the pain at the injection site after the 1st dose and 83.2% after the 2nd, and the incidence of fever was 7.0% after the 1st dose and 76.8% after the 2nd dose in more than 11,000 participants investigated.[18] The incidence of pain at the injection site in our study was consistent with the MHLW results for both the BNT162b2 and mRNA-1273 vaccines. This implies that the presence of vascular abnormalities might not be a risk factor for general severe reactions for these vaccinations.

According to our results, no enormous increase in thrombotic complications was observed in patients with vascular malformations after vaccination. Several studies have documented vaccine-induced immune thrombotic thrombocytopenia (VIIT) following SARS-CoV-2 vaccination[19–26] particularly after ChAdOx1 or Ad26.COV2.S (Janssen/Johnson & Johnson) vaccines.[10,21–26] MHLW reported that the incidence rate of VIIT in the general population was 0.1–0.2 cases among 100,000 recipients after BNT162b2 and mRNA-1273, whereas 18–24 cases per 100,000 recipients after ChAdOx1.[27] In our group, participants only received BNT162b2 or mRNA-1273 vaccines, which may account for the lack of thrombotic side effects following vaccination. Both of the vaccines are approved for those aged over 12 years old at the research period. In Japan, vaccines of BNT162b2, mRNA-1273, and ChAdOx1 are authorized for use as SARS-CoV-2 vaccines as of December 2020. More careful surveillance is still needed.

Multiple regression analysis in our study revealed that younger age was one of the risk factors of general adverse reactions after second dose of the vaccination ($p = 0.03$) in line with several studies in the general population that reported a higher frequency of adverse reactions following SARS-CoV-2 vaccination in younger individuals than in older.[16, 28, 29] In addition, our multiple regression analysis showed that KT/PW was associated with a higher incidence rate of adverse reactions related to vascular anomaly lesions following dose 2 of SARS-CoV-2 vaccine in our study. Symptoms of KT/PW are often severe.[6] However, there are few reports that suggest the relationship between these medical conditions and adverse reactions following SARS-CoV-2 vaccine. Furthermore, the number of participants with uncommon abnormalities and concomitant medical problems was relatively low in our cohort. Thus, further studies dealing with a larger number of participants are still required to validate our findings.

The merits of this study are that it is one of the earliest studies on the effects of SARS-CoV-2 vaccination on patients with vascular malformations. The study group was also relatively large with a good response rate and included patients from multiple centers.

Limitations

We admit a number of limitations in this study. Firstly, due to the nature of the retrospective survey design, potential recall bias and self-selection bias may have been present. Secondly, every single participant was Japanese; therefore, regional and ethnical differences could not be evaluated. Future research involving a bigger and more diverse population is necessary. Third, due to the nature of the retrospective patient-reported questionnaire, the recall bias can affect the result, and the evaluation by the patient report can be lack of precision. Lastly, the actual incidence of lethal events in patients with vascular abnormalities cannot be assessed precisely because the severe events are uncommon in the general population. Our cohort included relatively small case number of participants as prevalence of vascular malformations is not so high. Thrombotic events, for example, are also noted in the modest number of vaccine recipients.[27] Actually, we also could not assess the effects of SARS-CoV-2 vaccination on patients with these medical conditions with rare systemic vascular malformations and a history of heart disease due to little data. However, our results showed that there is not a noticeably higher rate of fatal consequences following vaccinations among patients with vascular abnormalities.

Conclusion

Based on our results, patients with vascular malformations have a similar SARS-CoV-2 vaccination rate. This study reveals that there is no difference in the rate of patient-reported adverse effects between patients with vascular abnormalities and the general population. Notably, there was no case of thromboembolism in our study group. Our findings overall imply that SARS-CoV-2 vaccination may be equally safe in patients with vascular malformations as in the broader public.

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Ethics Statement

The Mie University Hospital Institutional Review Board

examined and approved the study's use of human subjects, and it was carried out in compliance with institutional and national research committee ethical standards (Mie University Hospital IRBMED Number H2021-212). The publication of this original research has informed consent.

Disclosure Statement

Declaration of Conflicting Interests: The authors declared no conflicts of interest. No funding was received for conducting this research.

Author Contributions

Study conception: MS, MN, MK, SY, MO
Data collection: MS, MN, CHB, KM, KD, RI
Analysis: MS, MN, CHB
Investigation: MS, MN, CHB, MK, SY, MO
Writing: MS
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

Supplementary Materials

Supplementary materials are available at the online article sites on J-STAGE and PMC.

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