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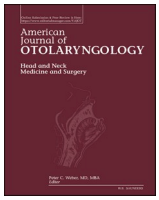

Vertigo/dizziness following COVID-19 vaccination

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ABSTRACT

Purpose: This study assessed the vertigo/dizziness in patients following COVID-19 vaccination.
Patients and methods: From July 2021 to June 2022, totaling 50 patients with dizzy spells following COVID-19 vaccination by AZ (AstraZeneca-Oxford University, AZD1222), BNT (Pfizer-BioNTech, BNT162b2) or Moderna (Moderna, mRNA-1273) vaccine were enrolled in this study. The interval from vaccination to the onset of vertigo/dizziness was compared with inter-episodic interval of vertigo/dizziness in the same patients, but without vaccination, during past one year (2020).
Results: The incidences of severe systemic complication per 10^6 shots were 0.86 for Moderna vaccine, 1.22 for AZ vaccine, and 1.23 for BNT vaccine. Conversely, rate of post-vaccination vertigo/dizziness was noted in the Moderna group (66 %), followed by the AZ group (20 %) and the BNT (14 %) group, meaning that type of COVID-19 vaccine may affect various organ systems. The median time to the onset of vertigo/dizziness following vaccination is 10d, which is consistent with the onset of IgG production, and significantly less than inter-episodic interval (84d) in the same patients without vaccination.
Conclusion: Post-vaccination vertigo/dizziness can manifest as exacerbation of previous neurotological disorder. The median time to the onset of vertigo/dizziness following COVID-19 vaccination is 10d. Since the outcome is fair after supportive treatment, the immunomodulatory effect of the vaccines does not undermine the necessity of the COVID-19 vaccination.

1. Introduction

The global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since November 2019 led the World Health Organization (WHO) to declare a pandemic infection of "Coronavirus disease 2019 (COVID-19)". A newly developed vaccine termed ChAdOx1 nCoV19 (AstraZeneca-Oxford University, Vaxzevria, AZD1222), briefly AZ vaccine, was approved for emergency use at the end of 2020 [1]. Thereafter, several types of vaccines against COVID-19 infection have been released for controlling the pandemic and its socioeconomic impact [2], including Elasomeran (Moderna, Spikevax, mRNA-1273), briefly Moderna vaccine [3]; Tozinameran (Pfizer-BioNTech, Comirnaty, BNT162b2), briefly BNT vaccine [4]; Ad26.COV2.S (Janssen, COVID-19 Vaccine Janssen), briefly Janssen vaccine [5], and so on.

Vaccination against COVID-19 started in Taiwan in March 2021. Initially, the AZ vaccine was administered to the elderly aged >65 years, followed by the Moderna vaccine since June 2021, and the BNT vaccine since September 2021, according to a decreasing sequence of 10-year age bands among adults based on the policy of the Centers for Disease Control (CDC) in Taiwan. By the end of June 2022, overall 15,294,226, 17,926,798 and 21,860,972 shots of the AZ, BNT and Moderna vaccines were administered in Taiwan, respectively [6].

During the pandemic period of COVID-19, the annual new cases of audiovestibular disorders at our neurotological clinic of a university hospital decreased from 2068 (2019) to 1829 (2020), likely because patients with inner ear disorders did exist, yet they just never presented for medical care. Opposed to the declining numbers of a neurotological clinic, more patients with autonomic dysfunction visited our clinic. The incidence of autonomic dysfunction in 2020 (15.3 %) was significantly higher than 8.5–13.1 % during 2016–2019, probably because of increased psychological stress, panic, anxiety, or depression associated with social isolation in time of a pandemic COVID-19 period [7].

On the other hand, many patients came to the neurotological clinic due to episodic vertigo/dizziness after receiving COVID-19 vaccine, which warrants further investigation. Hence, this study assessed the episodic vertigo/dizziness following COVID-19 vaccination.

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2. Patients and methods

2.1. Participants

From July 2021 to June 2022, totaling 50 patients with episodic vertigo/dizziness following COVID-19 vaccination visited our neurotological clinic of the university hospital. Fifteen were males and 35 females, with a mean age of 56 ± 14 years. All patients received otoscopy first, followed by an inner ear test battery including audiometry, cervical vestibular-evoked myogenic potential (cVEMP) test, ocular VEMP (oVEMP) test, and caloric test, then diagnosis was established. Details of vaccination were obtained *via* face-to-face interview including types and shots of the vaccine, time from date of vaccination to the onset of vertigo/dizziness. Additionally, inter-episodic interval of vertigo/dizziness in the same patients, but without vaccination, during past one year (2020) was also recorded for comparison.

Diagnosis of vestibular migraine (VM) was jointly formulated and recently updated by the Barany Society and International Headache Society [8], including a cardinal symptom of at least 5 episodes of vestibular symptoms (lasting 5 min to 72 h) with migraine features, but normal hearing and vestibular function tests between attacks. Diagnosis of Meniere disease (MD) was based on the guidelines proposed by the American Academy of Otolaryngology-Head and Neck Surgery in 1995 and the Barany Society in 2015 [9,10].

Exclusion criteria comprised concurrent middle or inner ear anomaly/infection and head injury. Those patients with vertigo/dizziness beyond one month after vaccination, those without complete 3-month medication previously, or those without vaccination were also excluded.

This study was approved by the institutional review board of the university hospital and each subject signed the informed consent to participate.

2.2. Inner ear test battery

Audiometry was used for assessing the cochlear function. Bithermal caloric test was performed for checking the semicircular canal function. The detailed procedures of the oVEMP and cVEMP tests were described elsewhere [11], which were utilized for assessing the utricular and saccular function, respectively.

2.3. Statistical methods

The gender ratio among three types of vaccine was compared by 2 × 3 Chi-square test. Comparisons of the age between three groups were analyzed by one-way repeated measures ANOVA test, followed by Bonferroni-adjusted test. Incidence of severe systemic complication among three groups was compared by 2 × 3 Chi-square test. The interval among the three groups was compared by Kruskal-Wallis test. The interval from date of vaccination to the onset vertigo, and inter-episode interval without vaccination, was compared by Wilcoxon signed-rank test.

In the time-to-event analysis, an event was defined as the presence of vertigo, while length of time was determined by either inter-episode interval without vaccination or time to vertigo onset after vaccination. Kaplan-Meier curve and Cox regression were utilized to compare the interval between two groups. The effect size is delineated with hazard ratio with 95 % confidence interval (CI). A significant difference indicates $p < 0.05$.

3. Results

3.1. Demographic study

Totaling 50 patients with vertigo/dizziness following COVID-19 vaccination were enrolled. These patients had been vaccinated with any of three major COVID-19 vaccines, namely AZ, BNT, and Moderna vaccines. Thirty-three (66 %) patients had vertigo/dizziness after Moderna vaccination, followed by 10 (20 %) who received AZ vaccine and 7 (14 %) who received BNT vaccine. Twenty-nine patients had received two shots (58 %) of vaccines, 16 patients (32 %) had 3–4 shots, and 5 patients (10 %) had one shot only. However, people who were given multiple shots did not necessarily receive the same type of vaccine each time.

The mean ages in the Moderna, AZ and BNT groups were 60 ± 10, 53 ± 16, and 38 ± 7 years, respectively, showing a significantly younger age in the BNT group ($p < 0.001$, one-way repeated measures ANOVA test, followed by Bonferroni-adjusted test, Table 1). This is likely due to the policy of vaccination in Taiwan. The COVID-19 vaccination started from the elderly first, followed by a sequence of administration *via* a 10-year age band from those aged 55–64 years to young adults. In addition, AZ vaccine was initially available, then Moderna and BNT vaccine. That is why most young people received BNT vaccine. However, there was no significant difference in gender ratio among the three groups ($p > 0.05$, 2 × 3 Chi-square test, Table 1).

Based on the website of vaccine adverse event reporting system (VAERS) established by the CDC in Taiwan [6], severe systemic complication of vaccination was defined as: 1) thrombosis with thrombocytopenia syndrome; 2) cerebral venous sinus thrombosis without thrombocytopenia; 3) idiopathic thrombocytopenic purpura; 4) myocarditis and/or pericarditis; 5) Guillain–Barre´ syndrome; and 6) anaphylaxis. By the end of June 2022, COVID-19 vaccination rates for the first, second and third shots have reached to 91 %, 83 % and 70 % in the general population of Taiwan, respectively. Accordingly, the incidences of severe systemic complication in relation to overall shots comprised 189/21,860,972 for the Moderna vaccine, 186/15,294,226 for the AZ vaccine, and 221/17,926,798 for the BNT vaccine, accounting for 0.86, 1.22 and 1.23 per 10^6 shots, respectively, exhibiting a significant difference among the three types of vaccine ($p = 0.001$, 2 × 3 Chi-square test, Table 1). Restated, the highest incidence of the severe systemic complication occurred in the BNT group, followed by the AZ and Moderna groups.

Opposed to this declining sequence of severe systemic complication, the highest rate of post-vaccination vertigo/dizziness was observed in the Moderna group (66 %), followed by the AZ group (20 %) and BNT group (14 %), indicating that the type of COVID-19 vaccine may affect various organ systems. Hence, disease distribution in patients with post-vaccination vertigo/dizziness was subsequently analyzed.

3.2. Disease distribution

All 50 patients had received an inner ear test battery coupled with a complete course of three-month medication at our clinic previously.

Table 1
Comparison of various types of COVID-19 vaccine.

Types of vaccine	Cases of vertigo	Age (Y)	Sex (M/F)	Incidence of severe complication
Moderna	33 (66 %)	60 ± 10[a,c]	12/21	189/21,860,972 (0.86/10^6)
AZ	10 (20 %)	53 ± 16[a,b]	1/9	186/15,294,226 (1.22/10^6)
BNT	7 (14 %)	38 ± 7[b,c]	2/5	221/17,926,798 (1.23/10^6)
p value		<0.001*	>0.05#	0.001#

AZ: AstraZeneca-Oxford University, Vaxzevria, AZD1222 vaccine.
BNT: Pfizer-BioNTech, Comirnaty, BNT162b2) vaccine.
Moderna: Spikevax, mRNA-1273 vaccine.
* One-way repeated measures ANOVA test, followed by Bonferroni-adjusted test.
[a] $p > 0.05$.
[b] $p = 0.026$.
[c] $p < 0.001$.
2 × 3 Chi-square test.

Clinical manifestation in these patients included vertigo/dizziness in all 50 patients (100 %), followed by tinnitus (70 %), headache (66 %), nausea/vomiting (62 %), hearing loss (46 %), and fullness sensation (42 %).

Disease distribution comprised Meniere's disease (MD) in 13 patients (26 %), followed by vertebrobasilar artery insufficiency (VBI) (18 %), vestibular migraine (16 %), benign paroxysmal positional vertigo (16 %), autonomic dysfunction (12 %), and others in 6 patients (12 %) including acoustic trauma 3, sudden deafness 1, downbeat nystagmus 1, and cerebellar encephalitis 1 (Table 2). Comparing types of vaccine at last shot in relation to each neurotological disorder revealed non-significant difference ($p > 0.05$, 3 × 6 Chi-square test), indicating that type of COVID-19 vaccine is unrelated to the neurotological disorders.

3.3. Interval to the onset of vertigo/dizziness

The median time to the onset of vertigo/dizziness following vaccination was 12d (range, 1-30d) for Moderna group, 6d (range, 0-16d) for AZ group, and 6d (range, 0-30d) for BNT group. Since significant difference in time to the onset of vertigo/dizziness was not shown among the three groups ($p = 0.290$, Kruskal-Wallis test, Table 3), data of 50 patients were thus pooled together, which revealed that the median time to the onset of vertigo/dizziness was 10d (range, 0-30d) following vaccination (Table 3).

For comparison, the interval between two vertigo/dizziness episodes in the same patients during past one year (2020), but without vaccination, was served a control group. As a result, the median intervals were 86d (range, 28-287d) for the Moderna group, 96d (range, 16-245d) for the AZ group, and 70d (range, 28-210d) for the BNT group. Again, significant difference was not identified among the three groups ($p = 0.911$, Kruskal-Wallis test, Table 3). Thus, data of the three groups were pooled together for analysis. Accordingly, the median inter-episodic interval in patients without vaccination was 84d (range 16-287d), which was significantly longer than 10d (range 0-30d) in the same patients with vaccination ($p < 0.001$, Wilcoxon singed-rank test, Table 3).

Additionally, in the time-to-event analysis, an event was defined as the presence of vertigo/dizziness, while length of time was determined by either time to vertigo/dizziness onset after vaccination, or inter-episodic interval without vaccination. Accordingly, patients with vaccination had significantly shorter interval for episodic vertigo/dizziness than same patients without vaccination ($p < 0.001$, log-rank test, Fig. 1). Furthermore, Cox regression demonstrated that vaccination was associated with significantly higher risk of recurrent vertigo/dizziness, with a hazard ratio of 15.4 (95 % CI, 7.0–34.2; $p < 0.001$).

All patients underwent supportive treatment. Relief of vertigo without untoward effect was achieved after one-month medication in all patients.

Table 2
Disease distribution in 50 patients with post-vaccination vertigo/dizziness.

Neurotological diseases	Case no.	Moderna	AZ	BNT
Meniere's disease	13 (26 %)	10	1	2
Vertebrobasilar artery insufficiency	9 (18 %)	7	2	0
Vestibular migraine	8 (16 %)	4	2	2
Benign paroxysmal positional vertigo	8 (16 %)	7	1	0
Autonomic dysfunction	6 (12 %)	2	2	2
Others	6 (12 %)	3	2	1
p value		(NS)		

AZ: AstraZeneca-Oxford University, Vaxzevria, AZD1222 vaccine.
BNT: Pfizer-BioNTech, Comirnaty, BNT162b2) vaccine.
Moderna: Spikevax, mRNA-1273 vaccine.
NS: non-significant difference, $p > 0.05$, 3 × 6 Chi-square test.

Table 3
Comparison of interval to the onset of vertigo/dizziness between patients with and without vaccination.

Vaccine	N	Interval to the onset of vertigo/dizziness following vaccination (d)	N	Inter-episode interval without vaccination (d)
Moderna	33	12 (1−30)	23	86 (28–287)
AZ	10	6 (0–16)	5	96 (16–245)
BNT	7	6 (0−30)	6	70 (28–210)
p value[a]		0.290		0.911
Total	50	10 (0–30)[#]	34	84 (16–287)[#]

Data are expressed as median (range).
AZ: AstraZeneca-Oxford University, Vaxzevria, AZD1222 vaccine.
BNT: Pfizer-BioNTech, Comirnaty, BNT162b2) vaccine.
Moderna: Spikevax, mRNA-1273 vaccine.
[a] Kruskal-Wallis test.
[#] $p < 0.001$, Wilcoxon signed-rank test.

4. Discussion

4.1. Types of COVID-19 vaccine

Four types of COVID-19 vaccine with different mechanisms have been released, namely, whole virus vaccine (live attenuated, inactivated *i.e.* Sinovac vaccine), viral vector vaccine (non-replicating, replicating, *i.e.* AZ vaccine), nucleic acid vaccine (mRNA, DNA *i.e.*, BNT or Moderna vaccine), and protein-based vaccine (subunit, virus-like particle *i.e.* Navavax vaccine). Of them, AZ, BNT and Moderna are three major types of vaccine utilized in Taiwan.

The AZ vaccine comprises the replication-deficient adenovirus vector ChAdOx1, which contains genes that express spike protein of SARS-CoV-2 in human cells. Adaptive immunity produces antibody against the spike protein on SARS-CoV-2, thus reducing the incidence of symptomatic disease in vulnerable populations [1].

Both the BNT and Moderna vaccines consisted of lipid nanoparticles filled with mRNA. These nucleic acid vaccines introduced mRNA into the cells for producing antibodies against the SARS-CoV-2 spike protein. The BNT and Moderna vaccines differs on the mRNA content [12]. One dose of BNT vaccine contains 30 μg of mRNA, while that of Moderna vaccine delivers 100 μg. Hence, the Moderna vaccine triggers stronger immune response than the BNT vaccine, which may account for the higher rate of post-vaccination vertigo/dizziness in the former than the latter.

4.2. Disease distribution

Although the vaccine type received by patients with post-vaccination vertigo/dizziness was in a declining sequence from the Moderna vaccine (66 %), AZ vaccine (20 %) to BNT vaccine (14 %), the incidence of severe systemic complication in general population opposed to this sequence, *i.e.*, running from the BNT vaccine (1.23 per 10^6), AZ vaccine (1.22 per 10^6), to the Moderna vaccine (0.86 per 10^6), based on the VAERS by the CDC in Taiwan (Table 1). Hence, the type of vaccine that produces more adverse effects is difficult to determine, likely because the vaccine type may affect various organ systems. Thus, post-vaccination vertigo/dizziness could be noted in various neurotological disorders regardless of the type of vaccine given.

Most patients with post-vaccination vertigo/dizziness were referred to MD, followed by VBI, vestibular migraine, benign paroxysmal positional vertigo, autonomic dysfunction, *etc.* (Table 2). This heterogenous group of post-vaccination vertigo/dizziness indicates that immunological factor may play a key role for exacerbating pre-existing neurotological disorders, originating from a spike of disease-specific IgG. More than 60 % of patients with post-vaccination vertigo/dizziness experienced tinnitus, headache, nausea/vomiting, hearing loss, and fullness sensation, meaning that these non-specific inner ear symptoms

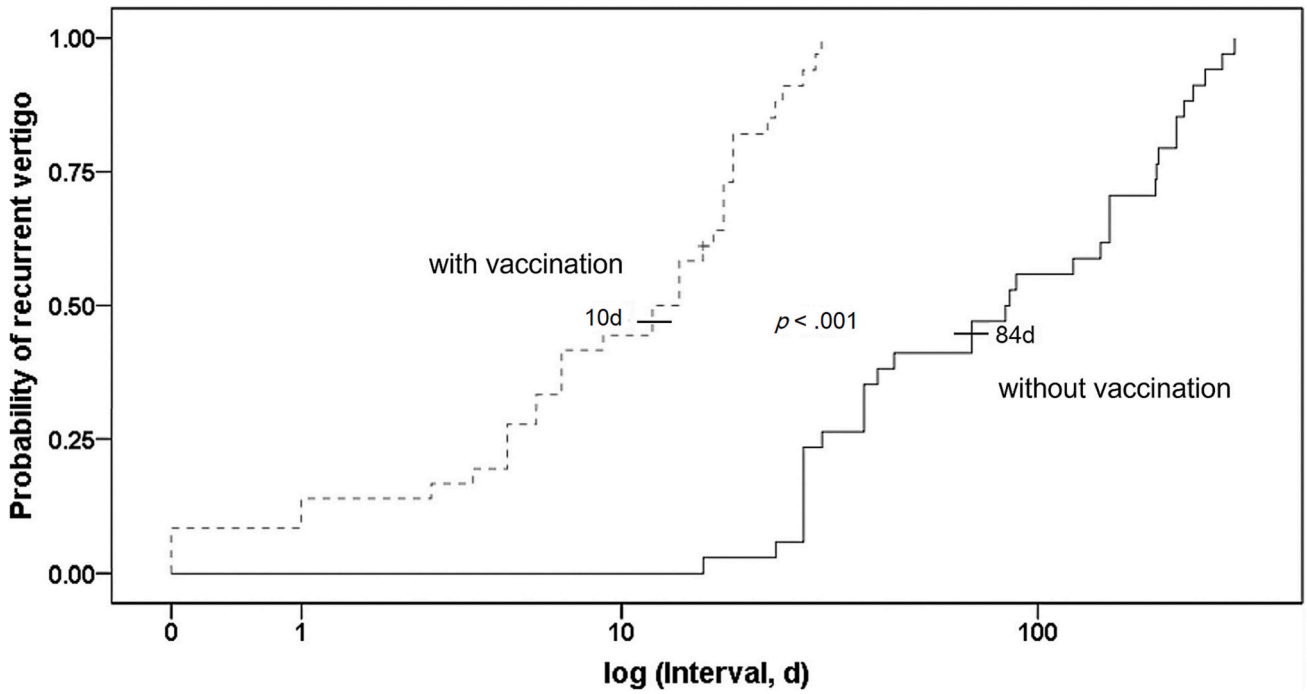

Fig. 1. The Kaplan-Meier curve demonstrates probability of recurrent vertigo/dizziness over time in patients with *vs.* without vaccination. The median intervals of recurrent vertigo/dizziness are 10d and 84d in patients with and without vaccination, respectively.

could be part of the clinical spectrum of COVID-19 vaccine side effects.

4.3. Interval to the onset of vertigo/dizziness

The median time to the onset of vertigo/dizziness was 12d, 6d, and 6d after Moderna, AZ and BNT vaccination, respectively, showing a non-significant difference among the three groups (Table 3). Hence, all three groups were pooled together, revealing that a median time to the onset of vertigo/dizziness of 10d after vaccination, consistent with the onset of IgG production, because IgG antibodies to the vaccine protein antigens first appear at 10-14d after priming [13]. Since IgG binds efficiently to the antigen and aids in opsonization, it is likely to generate an aggressive systemic response, leading to exacerbation of a previous neurotological disorder manifesting as recurrent vertigo/dizziness episode.

Additionally, comparing the inter-episodic interval of vertigo/dizziness in the same patients during past one year (2020), but without vaccination, median intervals were 86d, 96d and 70d for the Moderna, AZ, and BNT groups, respectively (Table 3). Since all three groups did not significantly differ in the inter-episodic interval, data of the three groups were also pooled together, which revealed a median inter-episodic interval of 84d (range, 16-287d). The latter (84d) was significantly longer than 10d of post-vaccination vertigo/dizziness (Table 3). Further, Cox regression also indicated that vaccination is associated with significantly higher risk of recurrent vertigo/dizziness, with a hazard ratio of 15.4 (Fig. 1).

4.4. Post-vaccination vertigo/dizziness in relation to immunological reaction

Most patients with post-vaccination vertigo/dizziness were referred to MD (Table 2), which is a multifactorial disorder and has immunological factors that exacerbate the endolymphatic hydrops [14]. Additionally, increased osmolality in the inner ear may boost pro-inflammatory cytokines and activate the immune cells [15]. Thus, a potential systemic immune response and a spike of disease-specific IgG could intensify disease activity, as shown by vertiginous attack in a stable MD patient following vaccination [16].

Next to MD, VBI represents second commonest cause of post-vaccination vertigo/dizziness. Dysregulation of the blood flow due to altered plasma viscosity, platelet aggregation, red blood cell deformability, and endothelial function may induce vertigo in patients with VBI. Although the AZ vaccine provides effective immunization against SARS-COV-2 in the general population, increased risk of thrombotic event has led to a halt of AZ vaccination by many countries [1]. Yet, the benefits of immunization by AZ vaccine far outweigh the risk of potential side effects.

Finally, an immunization anxiety related reaction cannot be neglected. This reason is easily associated with the stress and higher anxiety present during the pandemic COVID-19 period, and can also boost the pathogenic mechanism of central vestibular disorders *i.e.* autoimmune encephalitis [17–20].

5. Conclusion

Post-vaccination vertigo/dizziness can manifest as exacerbation of previous neurotological disorder. The median time to the onset of vertigo/dizziness following COVID-19 vaccination is 10d. Since the outcome is fair after supportive treatment, the immunomodulatory effect of the vaccines does not undermine the necessity of the COVID-19 vaccination.

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Declaration of competing interest

None.

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