



Incidence of headache after COVID-19 vaccination in patients with history of headache: A cross-sectional study

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Abstract

Background: Headache is an adverse event of coronavirus 2019 (COVID-19) vaccination. Whether patients with history of headache suffer more from vaccination-induced headaches is unknown. We aimed to uncover if headache patients develop more headaches after COVID-19 mRNA vaccination than healthy controls.

Methods: We performed a questionnaire survey for nursing staff in our hospital from April to May 2021. Based on baseline characteristics, we divided the participants into migraine, non-migrainous headache, and healthy control, and examined the occurrence and features of headache after COVID-19 vaccinations.

Results: We included 171 participants (15.2% migraine and 24.6% non-migrainous headache). Headache incidence after vaccinations was significantly higher in the migraine (69.2%) and non-migrainous headache (71.4%) groups than in the healthy control (37.9%) group. The incidence of headaches was significantly higher after the second dose compared to the first (45.6% vs. 20.5%).

Conclusion: Migraineurs and non-migrainous headache participants developed more headaches compared to the healthy controls after COVID-19 vaccination.

Keywords

COVID-19, vaccination, migraine

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Introduction

Coronavirus 2019 (COVID-19) (1) has become a global pandemic with 185 million cases and 4.0 million deaths (8 July 2021, Johns Hopkins COVID-19 Dashboard (2)). COVID-19 vaccines are the most promising approach to prevent infections, and the development of vaccines has progressed worldwide, with vaccination beginning in many parts of the world at the end of 2020.

BNT162b2 (Comirnaty[®]; BioNTech and Pfizer) is an mRNA vaccine against COVID-19, which has proven to be 85% effective and is expected to prevent the spread of COVID-19 infection (3–5). Vaccines are effective in preventing not only the infection but also for moderate to severe cases including death (4). BNT162b2 is given as two injections usually 3 weeks apart. In clinical trials of BNT162b2, mild to moderate

headaches have been reported in 25–52% of patients, with the second dose having higher incidents of headaches than the first dose (39–52% vs. 25–42%) (5).

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The prevalence of migraine is reported to be approximately 14% in the general population (6). Headache is a frequent symptom of COVID-19, and studies conducted in the emergency department have shown that up to 68.3–74.6% of COVID-19 patients reported headache (7,8). In COVID-19 patients, 6.1–7.8% of patients without headache had a history of migraine, as opposed to 14.1–25.3% of patients with headache having a history of migraine (7–9).

This suggests that a history of migraine is also associated with headache after COVID-19 infection. Since a history of headache affects headache symptoms during COVID-19 infection, we hypothesized that headache sufferers may be at higher risk after the vaccination.

We compared the incidence of headache after vaccination between migraineurs or non-migrainous headache patients, which do not meet diagnosis of migraine, and healthy controls. We also investigated the features such as onset and duration of headaches after vaccination. We conducted a cross-sectional questionnaire study of nursing staff in our hospital to survey their incidence of usual headaches and headaches after COVID-19 vaccination. This is the first study to focus on headache after COVID-19 vaccination by comparing the difference between migraineurs, non-migrainous headache patients, and healthy controls.

Methods

This was a single-centre, cross-sectional study of nursing staff at Keio University Hospital, Tokyo, Japan. Appropriate consent was obtained from the participants included in the study based on Ethical Guidelines for Medical and Health Research Involving Human Subject issued by the Japanese Ministry of Health, Labour and Welfare. This study was approved by the Ethics Committee of Keio University School of Medicine (20210032).

The study period was from 12 April to 1 May 2021. We conducted a questionnaire survey (89% response rate), and the inclusion criteria were nursing staff who received two doses of the BNT162b2 vaccine at our hospital. There are three COVID-19 vaccines (5,10,11) in Japan as for July 2021, but at the time of survey, only the BNT162b2 vaccine was available. Those with history of headaches were classified as the migraine or non-migrainous headache group. Participants were classified as migraine if meeting diagnosis of migraine with typical aura or migraine without aura using International Classification of Headache, 3rd edition (ICHD-3), and non-migrainous headache if not meeting the diagnosis of the above (12). Those without history of headache were classified as the healthy control group. Monthly headache days (MHD), duration, and the numerical rating scale

(NRS) scores as pre-existing headache characteristics were collected from those in the headache groups.

We compared the incidence of headaches after vaccinations among the three groups, and between the first and second vaccination doses. If headaches occurred, the presence of fever ($\geq 37.5^{\circ}\text{C}$) was surveyed. Additionally, the features of post-vaccine headaches were evaluated, including the NRS score, time from vaccination to the onset of headache, headache duration, and headache characteristics (laterality, pulsating quality, aggravation by routine physical activity, presence of nausea/vomiting, photophobia and phonophobia). These were compared among the three groups and between the first and second vaccinations in each group. Also, the information on the use of pain killers during post-vaccine headache was collected.

Statistical analysis

The chi-squared test was used to compare the categorical data. The McNemar test was used to compare the incidence of headaches after the first and second vaccinations. For quantitative data, a Kruskal–Wallis test was used for three-group comparisons and a Wilcoxon rank-sum test was used for two-group comparisons and for comparisons of the first and second vaccinations. When there was a significant difference in the three-group comparison, two-group comparisons were performed and then p -values were adjusted with Bonferroni correction. We did not impute missing data. All p -values are two-sided, and p -values of <0.05 were considered statistically significant. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

One participant whose baseline headache status was unknown was excluded, and 171 participants were included in the study. Of the 171 participants, 26 (15.2%) had a history of migraine, 42 (24.6%) had a history of non-migrainous headache, and 103 (60.2%) were healthy controls. Of the participants in the migraine group, 42.3% (95% CI; 23.4%, 63.1%) were migraineurs with typical aura. In the non-migrainous headache group, 24 (57.1%) met the diagnosis of tension-type headache, 13 (31.0%) met the diagnosis of probable migraine, and five (11.9%) were solely probable tension-type headache (12). The overall median age was 31.0 years, and 93.6% were female. There were no significant differences for age and sex between the three groups ($p=0.802$ and $p=0.236$, respectively). The duration of baseline headaches and

the NRS scores were significantly higher in the migraine group than in the non-migrainous headache group ($p=0.002$ and $p=0.008$, respectively) (Table 1 and Supplementary Table).

Incidence of headaches after the vaccinations

The incidence of participants with headaches after the vaccinations was 69.2% in the migraine group, 71.4% in the non-migrainous headache group, and 37.9% in the healthy control group ($p<0.001$). The migraine and non-migrainous headache groups had significantly higher rates of headaches after vaccination than healthy controls (adjusted $p=0.012$ and adjusted $p<0.001$, respectively). There was no difference between the migraine and non-migrainous headache

groups (adjusted $p=1.000$). The overall incidence of post-vaccination headaches was significantly higher after the second vaccination dose than the first dose (45.6% vs. 20.5%, $p<0.001$). In the migraine group, the frequency of headaches after the second vaccination dose tended to be higher than that after the first vaccination dose ($p=0.065$), and in the non-migrainous headache and healthy control groups, the frequency of headaches was significantly higher after the second vaccination dose compared to the first ($p<0.001$).

The incidence of headaches after the first vaccination dose was 34.6% in the migraine group, 28.6% in the non-migrainous headache group, and 13.6% in the healthy control group. There was significant difference between the migraine group and healthy control group

Table 1. Characteristics of participants and the post-vaccination headache in each group. Please refer to Supplementary Table for 95% CI, estimate, and information on missing data.

	Healthy n = 103	Migraine n = 26	Non-migraine n = 42	p-value
Age, year, median (IQR)	30.0 (25.0, 41.0)	31.5 (25.0, 41.0)	34.5 (25.0, 43.0)	0.802
Female, n (%)	94 (91.3)	26 (100.0)	40 (95.2)	0.236
Ordinary headache				
MHD, median (IQR)	–	4.0 (2.0, 7.5)	3.5 (2.5, 6.0)	0.439
Duration, hours, median (IQR)	–	6.0 (4.0, 10.0)	3.5 (2.5, 6.0)	0.002
NRS, median (IQR)	–	6.3 (5.0, 7.5)	5.0 (4.0, 7.0)	0.008
Post-first vaccination headache, n (%)	14 (13.6)	9 (34.6)	12 (28.6)	0.019
Onset, hours, median(IQR)	8.0 (6.0, 20.0)	12.0 (8.0, 24.0)	11.0 (6.8, 13.5)	0.601
Duration, hours, median(IQR)	4.5 (2.0, 12.0)	4.5 (2.0, 6.0)	8.0 (2.8, 42.0)	0.604
Laterality				
Unilateral location, n (%)	4 (28.6)	3 (33.3)	4(33.3)	0.957
Bilateral location, n (%)	10 (71.4)	6 (66.7)	8(66.7)	
Quality				
Pulsating, n (%)	7 (50.0)	5 (55.6)	2(18.2)	0.164
Non-pulsating, n (%)	7 (50.0)	4 (44.4)	9(81.8)	
Aggravation by routine physical activity, n (%)	5 (35.7)	4 (44.4)	5(41.7)	0.907
Nausea/vomiting, n (%)	0 (0.0)	2 (22.2)	1(8.3)	0.178
Photophobia, n (%)	0 (0.0)	2 (22.2)	0(0.0)	0.047
Phonophobia, n (%)	0 (0.0)	1 (11.1)	2(16.7)	0.303
Headache with fever, n (%)	1 (7.1)	3 (33.3)	1(8.3)	0.166
Pain killer use, n (%)	10 (71.4)	9 (100.0)	7(58.3)	0.092
Post-second vaccination headache, n (%)	33 (32.0)	16 (61.5)	29(69.0)	<0.001
Onset, hours, median (IQR)	12.0 (6.0, 18.0)	12.0 (8.0, 12.0)	12.0(8.0, 20.0)	0.388
Duration, hours, median (IQR)	8.0 (3.0, 24.0)	12.0 (4.5, 24.0)	7.3(4.8, 27.0)	0.503
Laterality				
Unilateral location, n (%)	7 (21.2)	6 (37.5)	7(24.1)	0.460
Bilateral location, n (%)	26 (78.8)	10 (62.5)	22(75.9)	
Quality				
Pulsating, n (%)	14 (45.2)	9 (56.3)	16(64.0)	0.365
Non-pulsating, n (%)	17 (54.8)	7 (43.8)	9(36.0)	
Aggravation by routine physical activity, n (%)	15 (46.9)	12 (75.0)	22(75.9)	0.036
Nausea/vomiting, n (%)	3 (9.1)	6 (37.5)	5(17.2)	0.052
Photophobia, n (%)	1 (3.1)	2 (12.5)	3(10.3)	0.422
Phonophobia, n (%)	5 (15.6)	4 (25.0)	7(24.1)	0.641
Headache with fever, n (%)	12 (36.4)	8 (50.0)	12(41.4)	0.660
Pain killer use, n (%)	28 (84.8)	12 (75.0)	28(96.6)	0.102

Healthy: healthy control; non-migraine: non-migrainous headache.

in the incidence of post-vaccine headache (adjusted $p=0.037$). The incidence of headaches after the second vaccination was 61.5% in the migraine group, 69.0% in the non-migrainous headache group, and 32.0% in the healthy control group. The incidence of post-vaccine headache in the migraine group and the non-migrainous headache group were significantly higher than the healthy control group (adjusted $p=0.017$ and adjusted $p<0.001$, respectively) (Figure 1(a)). There was no significant difference among the three groups in the proportion of people who had headaches with fever after the first and second vaccination ($p=0.166$ and $p=0.660$, respectively) (Table 1). In the healthy control and non-migrainous headache groups, headache with fever was significantly more common after the second vaccination dose than after the first ($p=0.041$ and $p=0.039$, respectively).

Headache characteristics

The median NRS scores for headache after the first and second vaccination doses were 5.0 (IQR 4.0, 6.0) and 5.0 (IQR 4.0, 8.0), respectively. In the non-migrainous headache group, the NRS score of the second dose-induced post-vaccination headache was significantly higher than that of the migraine or healthy control groups (adjusted $p=0.018$ and adjusted $p=0.008$, respectively). In the non-migrainous headache group, the NRS of the second dose-induced post-vaccination headache was significantly higher than that of the headache induced by the first dose ($p=0.003$) (Figure 1(b)).

The median onset time of headaches after the first and the second vaccination doses was 10.0 h and 12.0 h, respectively, with no significant difference among the three groups ($p=0.601$ and $p=0.388$, respectively) (Table 1, Figure 2(a)). There was no significant difference in the onset time of headaches after the first and second vaccination doses in each group (migraine: $p=0.320$, non-migrainous headache: $p=0.259$, healthy control: $p=0.779$).

The median durations of headaches after the first and second vaccination doses were 4.5 h and 8.0 h in total, respectively, which were not significantly different among the three groups ($p=0.604$ and $p=0.503$, respectively) (Table 1, Figure 2(b)). There was no significant difference in the duration of post-vaccination headaches between the first and second vaccination doses in the non-migrainous headache and healthy control groups (non-migrainous headache: $p=0.416$, healthy control: $p=0.321$), but the duration in the migraine group tended to be longer after the second vaccination dose compared to the first ($p=0.078$). A graph plotting the onset and duration of headaches,

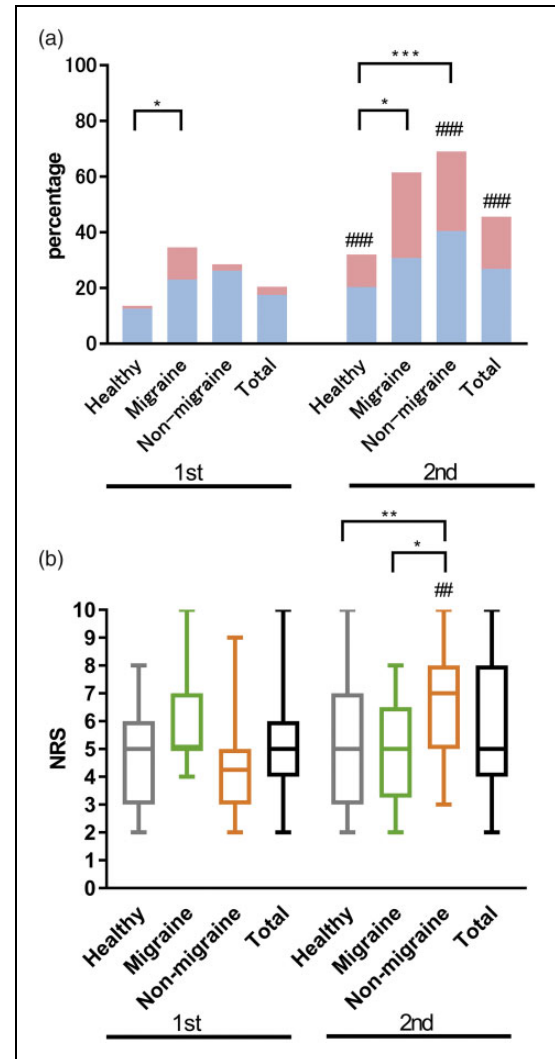


Figure 1. Incidence and numerical rating scale (NRS) scores of post-vaccination headaches.

(a) The incidence of post-vaccination headaches.

*Significant difference between groups.

#Significant difference between first and second vaccination doses within the group. Blue bars represent headache without fever and red bars represent headache with fever.

(b) NRS scores of post-vaccination headaches. Whiskers, full range; box, interquartile range; horizontal line, median. Grey, green, orange, and black represent healthy control, migraine, non-migrainous headache, and total, respectively.

*Significant difference between groups.

#Significant difference between first and second vaccination doses within the group.

Healthy: healthy control; non-migraine: non-migrainous headache.

*adjusted $p < 0.05$; **adjusted $p < 0.01$; ***adjusted $p < 0.001$; ## $p < 0.01$; ### $p < 0.001$.

starting from the time of vaccination, is shown in the Supplementary Figure.

Characteristics of post-vaccine headache are shown in Table 1 and the Supplementary table. Seventy-four

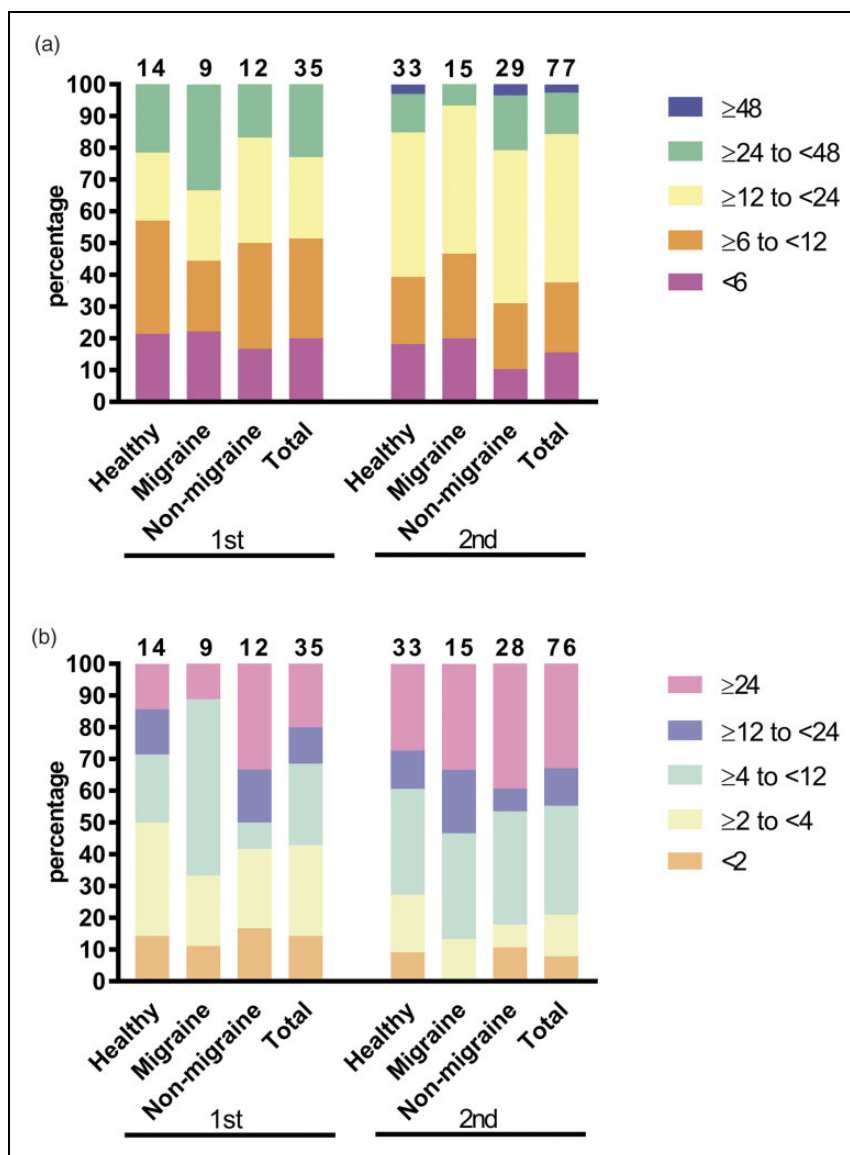


Figure 2. Proportion of time of onset and duration of post-vaccination headaches.

(a) Onset of post-vaccination headaches. Blue: ≥ 48 h, Green: ≥ 24 to < 48 h, Yellow: ≥ 12 to < 24 h, Orange: ≥ 6 to < 12 h, Magenta: < 6 h. Numbers on the top of the graph represent the number of participants in each group.

(b) Duration of post-vaccination headaches. Pink: ≥ 24 h, Blue: ≥ 12 to < 24 h, Green: ≥ 4 to < 12 h, Yellow: ≥ 2 to < 4 h, Orange: < 2 h. Numbers on the top of the graph represent the number of participants in each group.

Healthy: healthy control; non-migraine: non-migrainous headache.

(71.2%) out of 104 post-vaccine headache attacks (excluding nine attacks with missing data) exhibited clinical features of tension-type headache based on ICHD-3 except for the presence of fever (12). Among participants with post-vaccine headache, pain killers were used in 74.3% and 87.2% after the first and second vaccination doses, respectively with no significant difference between the three groups ($p = 0.092$ and $p = 0.102$, respectively). In the non-migrainous headache group, the pain killer use was significantly

higher after the second dose compared to the first ($p = 0.002$).

Discussion

This study is the first report to compare the incidence of headache after COVID-19 vaccination in participants with and without pre-existing headaches. The results showed that patients with pre-existing headache were more likely to suffer from headaches after

COVID-19 vaccination than those without pre-existing headache. There was no difference in the incidence of headaches after vaccination between the migraine and non-migrainous headache groups. There was no clear difference in the percentage of headaches with fever and the onset time or duration of headaches among the three groups, and the NRS score was higher after the second vaccination dose in the non-migrainous headache group. Of the 171 subjects, 39.8% had a history of headache and 15.2% had migraine. The prevalence of headache and migraine among nursing staff has been reported to be 42–45% and 15–17%, respectively, consistent with our results (13,14).

The strength of this study is that the questionnaire survey was conducted after vaccinations, avoiding the cognitive bias of triggering the anticipation of headaches. In addition, we were able to maintain a high response rate (89%), resulting in little selection bias. The limitation of this study is that, due to the study design, we cannot exclude potential recall bias about information including fever or headache pattern

changes after vaccination. The questionnaire survey was conducted only among nursing staff and the majority of the respondents were women (93.6%) and young with a median age of 31. Caution is required when directly applying the data to the general population. Since the number of cases is small, further verification is desirable. Although we found that those with pre-existing headaches were more likely to experience headaches after vaccination than healthy subjects, the mechanism and pathogenesis of the headaches are the subject of future research. Anxiety or stress generated by having to undergo vaccination could be a trigger for headache. Lastly, study participants were able to take a pain killer freely, so data on duration of headaches after vaccination may have been affected.

In conclusion, the incidence of headache after COVID-19 vaccination tended to be higher in those with pre-existing headaches, including migraineurs. It is important to note that headache patients may have higher incidence of headaches after COVID-19 vaccination.

Clinical implications

- Migraine and non-migrainous headache were associated with significantly higher incidences of headaches after BNT162b2 vaccination compared to healthy controls (69.2% vs. 71.4% vs. 37.9%).
- The incidence of headache after vaccination was significantly higher after the second shot compared to the first shot (45.6% vs. 20.5%).

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Declaration of conflicting interests


The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: HN received research funds and speaker's fees from Pfizer, but the company has no relation to the study. TT reports being an advisor for Otsuka and Amgen. TT received speaker's fees from Daiichi Sankyo, Eli Lilly Japan, Kowa, UCB Japan, and research fund from Tsumura outside the submitted work.

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