ORIGINAL

Assessment of multiple domains of pain following BNT162b2 mRNA COVID-19 vaccination

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Abstract : Pain at the injection site is the most frequent reaction among COVID-19 vaccine recipients, but its characteristics were not fully described yet. The purpose of this study was to investigate multiple domains of pain following BNT162b2 mRNA vaccination. We included 107 subjects undergoing primary shot of the vaccination twice into deltoid muscle with a 3-week interval. They completed 6 sessions of pain assessments, one before the first and second dose (1-0, 2-0), and 1st/7th day after the first and second dose (1-1/1-7, 2-1/2-7). Pain visual analog scale (VAS), pain distribution, and pressure pain threshold (PPT) on deltoid muscle were evaluated in each session. The mean VAS (at rest/shoulder motion) was 6.0/27.6 mm at 1-1, and 12.8/34.0 mm at 2-1. Approximately, 90% of recipients showed localized pain within the upper arm. Percentage change of PPTs at 1-1 and 2-1 was bilaterally (ipsilateral/contralateral) decreased to 87.4/89.4% and 80.6/91.0%, which was recovered to the baseline level at 1-7 and 2-7. Temporary, mild-to-moderate intensity, localized distribution, concomitant with bilateral mechanical hyperalgesia on the deltoid muscle, were typical pain characteristics following this vaccination. These findings provide a rationale that will be informative for future recipients. J. Med. Invest. 70 : 355-360, August, 2023

Keywords **:** *COVID-19, Vaccine, Vaccination, Pain, Pressure pain threshold*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has posed as a serious threat to public health and economy worldwide. Since there is still a lack of specific treatment, vaccination would be a significant tool against the pandemic of this virus. BNT162b2 (Comirnaty : Pfizer/BioNTech) is the first mRNA-based vaccine in human history, which has proven to be 85% effective and is expected to prevent the spread of COVID-19 infection in early reports (1, 2).

In Japan, this vaccine was the first to be authorized for emergency use by the Ministry of Health, Labor, and Welfare of Japan in February 2021, however, there was much concern about reactogenicity following the vaccine. It is probably associated with an incident in 2013, where the Japanese government suspended proactive recommendation of the human papillomavirus vaccine because of safety concerns raised by the general public (3). According to a recent cross-sectional internet survey completed by 2956 Japanese people, the proportion of participants with a high likelihood of getting a COVID-19 vaccine was 62.1%, and multiple logistic regression analysis showed that vaccine acceptance was lower among several sociodemographic groups (4).

Musculoskeletal pain is often included among extrapulmonary expression of COVID-19, and they can occur during the acute phase but also as short or long-term complications (5). A recent literature review showed that the incidence rate range of myalgia/arthralgia was 1.5-61.0% (6). Another prospective follow-up study by phone interview revealed that 92.3%, 72.7%, and 56.3% of COVID-19 patients reported any musculoskeletal symptoms at hospitalization, 2-week, and 1-month, respectively (7). The most common symptom was fatigue, followed by back pain, arthralgia, myalgia, low back pain, and neck pain (7). Although molecular mechanisms underlying this 'COVID-pain' have not been elucidated yet, the issue of direct viral damage, the role of macrophage activation, and the features of cytokine-induced damage are addressed (5).

Pain at the injection site was the most frequent reaction among COVID-19 vaccine recipients. Regarding BNT162b2 recipients (n = 8183), mild-to-moderate pain at the injection site within 7 days after the first/second dose were reported as : 71%/66% among recipients older than 55 years of age, and 83%/78% among younger recipients, which were mostly resolved within 1 to 2 days (8). According to a Japanese online survey (n > 3000), approximately 90% of participants reported pain at the injection site, however, number of days absent from their work was less than 3 days in almost all cases (9). Thus, it is not a serious problem in general, however, detailed characteristics of pain after this vaccination were not fully described yet and misinformation may cause unnecessary fear and subsequent vaccine hesitancy for future recipients. The purpose of this study was to provide clear and unbiased information about multiple domains of pain following the BNT162b2 mRNA COVID-19 vaccination.

METHODS

Subjects

This observational study was conducted with a prospective manner. We announced the outline of this project to 471 consecutive subjects undergoing primary shot of the BNT162b2 mRNA COVID-19 vaccination twice from April to May 2021 in our hospital. Based on inclusion and exclusion criteria, healthy subjects who were willing to participate in this study were

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included, and subjects who were diagnosed as having painful shoulder disorders, neurological disorders, psychiatric diseases, skin disorders at examination sites, and taking pain killers 24 hours before the experiment were excluded. At first, 138 recipients were enrolled. Among them, 107 recipients had completed 6 consecutive sessions of pain assessments, one before the first dose (1-0), 1-day after the first dose (1-1), 7-days after the first dose (1-7), before the second dose (2-0), 1-day after the second dose (2-1), 7-days after the second dose (2-7), and were finally included in the analysis (Figure 1). We did phone interviews later and confirmed that most dropouts happened due to their personal reasons which were not associated with adverse events of the vaccination except for 2 recipients who had a high fever 1-day after the injection. Background of the participants was summarized in Table 1. The study protocol was approved by the Institutional Review Board of Kochi Medical School (No : 2020-162). All participants received verbal explanation of the study and provided written informed consent prior to the investigation. This study was conducted in compliance with the Declaration of Helsinki.

Table 1. Background of the study participants. Height, Body weight, and BMI are presented as mean ± SD.

Variable	
N	107
Age (years)	44.1 ± 13.9
Sex, n (%)	
Male	51 (48)
Female	56 (52)
Right-handed, n (%)	102 (95)
Height cm	163.7 ± 13.9
Body weight kg	62.2 ± 11.9
BMI kg/m^2	23.1 ± 3.6
Injected side, n (%)	
Left	100 (93)
Right	7 (7)

Vaccination

Vaccination was injected into the lower deltoid muscle using a 25-gauge (25 mm length) needle at the level of axillary line, which was a completely standardized technique to prevent possible bursitis around the shoulder (10). Then, recipients were given 15-minute rest to confirm that there was no acute adverse event such as anaphylaxis. They were given 2 tablets of 300 mg acetaminophen (Tylenol A®, Johnson and Johnson) available to use depending on their pain, and were asked the number of tablets used between the sessions. Three-week interval was secured between the first and second dose. This vaccination protocol was standardized for all recipients throughout the study period.

Pain assessments

In each session, body temperatures were checked prior to the assessment. Recipients indicated pain intensity at rest and during active shoulder elevation on a 100 mm visual analogue scale (VAS). The VAS was anchored with "no pain" and "worst pain imaginable" at 0 mm and 100 mm, respectively. If the VAS was 0 mm after the injection, we additionally interviewed when their pain had disappeared. Recipients were also asked to mark the pain distribution by filling in a body chart. They confirmed their ongoing pain at each session and drew the distribution by themselves. The occurrence of pain in 5 different areas was registered as depicted in Figure 2. Additionally, the quality of pain was assessed using the Japanese version of the Short-Form McGill Pain Questionnaire (SF-MPQ) (11) at the session 2-1. They selected all words that would be suitable for describing their pain quality.

For assessment of mechanical hyperalgesia around the injection site and remote area, a handheld algometer (Somedic, Hörby, Sweden) with a 1-cm^2 probe was used to record the pressure pain threshold (PPT) on the bilateral deltoid muscle of recipients in a sitting position (Figure 3). Assessment site was determined as a midpoint between the lateral edge of acromion and the injection site. Pressure was increased gradually at a rate of 30 kPa/s until the pain threshold was reached and the subject pressed a button. The PPT was defined to the subject as "the time point at which the pressure sensation changed into pain." The recording was repeated 3 times with a minimum interval of 20s in each session. Trained physiotherapists assessed the PPTs and mean value of the recordings was obtained. Then percentage change of PPT (each PPT value was divided by baseline PPT at 1-0 × 100) was calculated and used for analyses. Distance from the lateral edge of acromion to the assessment site was measured to ensure that PPTs were recorded on a similar site as possible in each session.

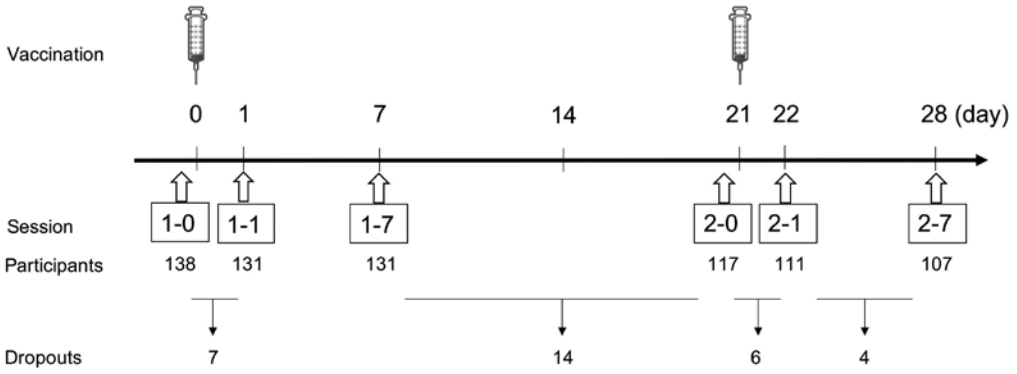

Figure 1. Schematic time course of vaccinations and pain assessment sessions. Number of recipients participated in each session and dropouts are also shown. 107 cases who completed 6 consecutive sessions were finally included in the study.

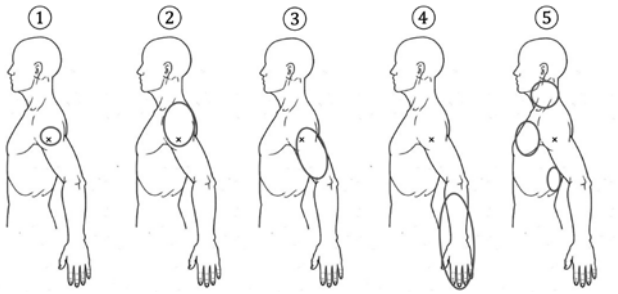

Figure 2. Patterns of pain distribution after the vaccination. ① Well-localized around the injection site, ② Proximally spread within upper arm, ③ Distally spread within upper arm, ④ Distally spread beyond the elbow, ⑤ Spread to neck and trunk. × : injection site

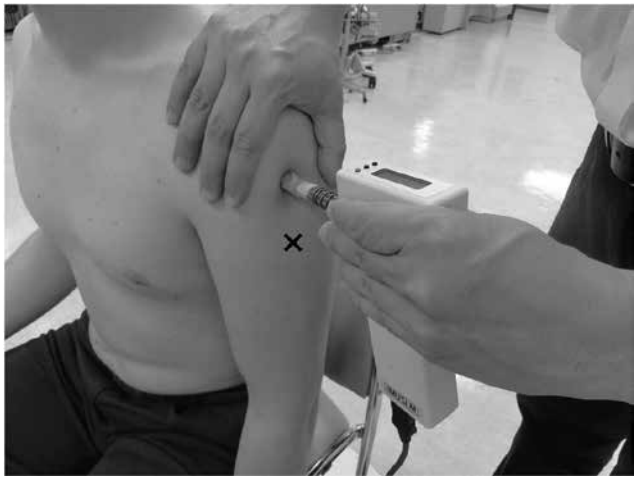

Figure 3. Recording of pressure pain threshold (PPT) on the deltoid muscle. Assessment site was determined as a midpoint between the lateral edge of acromion and the injection site (×).

Analysis

Body temperatures, pain VAS, and PPTs were not normally distributed and analyzed by the Friedman test followed by the Wilcoxon signed rank test with the Bonferroni collection. To address the effects of acetaminophen use on the time course of pain VAS and PPTs, additional Friedman tests were done after adjustment of subjects with or without taking acetaminophen.

Difference of pain VAS and distribution of pain was investigated between sessions after the first and second dose. According to previous reports, clinically significant difference of pain VAS was considered as >13 mm (12, 13). Frequency of pain distribution patterns was analyzed using Fishers' exact test. Also, frequency of male and female participants who showed higher pain VAS and wider pain distribution after the second dose than the first one was analyzed using the Fishers' exact test.

Effect of acetaminophen on pain VAS and PPTs at each session was analyzed using the Mann-Whitney U test. Correlations among age, height, weight, BMI, body temperatures, pain VAS, and PPTs were analyzed using the Spearman's correlation coefficients. All analyses were performed with SPSS version 26.0 software (IBM Corp. Armonk, NY, USA) and $P < 0.05$ indicated statistical significance.

RESULTS

There were no life-threatening adverse events such as anaphylaxis and no recipients showed hives, swelling of mouth, lips, tongue, or throat ; shortness of breath, wheezing, or chest tightness ; or low blood pressure or loss of consciousness(14) throughout the study period. Eight recipients took acetaminophen (6 persons : 1 tablet, 2 persons : 2 tablets) from the first dose to 1-1, while it was 57 recipients (19 persons : 1 tablet, 38 persons : 2 tablets) from the second dose to 2-1. The body temperature was significantly higher at 2-1 compared with the other sessions (Table 2). Nineteen recipients (17.8%) showed ≧37.5℃ at 2-1 while there were no recipients that presented such a fever increase at the other sessions.

Pain intensity

The pain VAS at rest and during active shoulder elevation was significantly higher at 1-1 and 2-1 compared with the other sessions (Table 2). This result was the same after adjustment of subjects with or without taking acetaminophen. (rest pain ; $P<0.0021$, motion pain ; $P<0.012$). The number (percentage) of recipients who had rest pain/motion pain/both rest and motion pain, was 40 (37.4%)/100 (93.5%)/40 (37.4%) at 1-1, and 44 (41.1%)/97 (90.7%)/43 (40.2%) at 2-1, respectively. No recipients complained pain in the other sessions except for one person at 2-7. The mean estimated duration for disappearance of pain after the vaccination was 2.7±1.3 days. Younger recipients showed higher pain intensity at 1-1 (motion pain : $r = -0.273$, $P = 0.005$), and at 2-1 (rest pain : $r = -0.255$, $P = 0.009$, motion pain : $r = -0.280$, $P = 0.004$). Rest pain VAS at 2-1 was negatively correlated with height ($r = -0.305$, $P = 0.001$), but not with weight and BMI. Body temperatures were positively correlated with pain VAS at 2-1 (rest pain : $r = 0.248$, $P = 0.012$, motion pain : $r = 0.285$, $P = 0.004$). There was no significant difference of pain VAS between 1-1 and 2-1, but 45 participants (42.1%) showed higher pain intensity (>13 mm) in 2-1 than 1-1, and this trend was more common in females compared with males ($P = 0.033$). Other background data were not associated with the worsening of pain between the sessions. The motion pain VAS at 2-1 was higher in recipients who received acetaminophen than those without (39.6 [32.8-46.4] vs 27.6 [22.2-33.1], $P = 0.024$).

Table 2. Median [interquartile range] of body temperature and shoulder pain VAS. * : $P<0.00003$ compared with the other sessions. † : $P<0.0003$ compared with 1-0, 1-7, 2-0, and 2-7

	1-0	1-1	1-7	2-0	2-1	2-7
Body temperature (℃)	36.3	36.3	36.4	36.4	36.6 *	36.4
	[36.2-36.5]	[36.2-36.5]	[36.2-36.5]	[36.2-36.5]	[36.4-37.3]	[36.2-36.5]
Shoulder Pain VAS (mm)						
Rest	0 [0-0]	0 [0-9]†	0 [0-0]	0 [0-0]	0 [0-26]†	0 [0-0]
Active motion	0 [0-0]	25 [15-40]†	0 [0-0]	0 [0-0]	35 [24-52]†	0 [0-0]

Pain distribution and quality

Patterns of pain distribution at 1-1 and 2-1 were summarized in Table 3. Approximately, 90% of recipients showed localized pain around the injection site or the spread pain within the upper arm, however, some cases demonstrated widespread pain to the neck and trunk (beyond the arm). This pattern was similar between 1-1 and 2-1, but 21 recipients (19.6%) revealed wider pain distribution in 2-1 than 1-1, and this trend was more common in females compared with males (P = 0.016). Other background data were not associated with the spread of pain between the sessions. The most 5 common words describing the quality of pain after vaccination were tender (36.1% of participants), aching (15.6%), heavy (6.7%), sharp (6.7%), and throbbing (5.6%).

Table 3. Patterns of pain distribution after the first and second vaccination. Number of participants (percentage) are displayed.

Pain distribution	1st vaccination	2nd vaccination	P-value
None	6 (5.6)	6 (5.6)	1.00
①	66 (61.7)	63 (58.9)	0.78
②	15 (14)	8 (7.5)	0.19
③	14 (13.1)	15 (14)	1.00
② + ③	0 (0)	4 (3.7)	0.12
(① or ② or ③) + ④	1 (1)	0 (0)	1.00
(① or ② or ③) + ⑤	5 (4.6)	9 (8.4)	0.41
(① or ② or ③) + ④ + ⑤	0 (0)	2 (1.9)	0.50

Pressure pain sensitivity

PPTs were recorded on the deltoid muscle where 3.2±0.5 cm distal from the lateral edge of acromion. The baseline value of PPT at 1-0 [mean (95%CI)] was 293 (268-319) kPa on ipsilateral side and 316 (285-346) kPa on contralateral side. Percentage change of PPTs at 1-1 and 2-1 was bilaterally (ipsilateral/contralateral) decreased to 87.4/89.4% and 80.6/91.0%, respectively, however, this change was recovered to the baseline level at 1-7 and 2-7 (P<0.05, Figure 4). There were no significant differences between the PPTs at 1-1 and 2-1. This result was the same after adjustment of subjects with or without taking acetaminophen. (ipsilateral side ; P<0.016, contralateral side ; P<0.023). Age was positively correlated with PPT on the ipsilateral deltoid at 2-1 (r = 0.200, P = 0.043). There were no significant correlations between the percentage change of PPTs and pain VAS at 1-1 and 2-1, however, a weak negative correlation was found between the baseline value of PPT at 1-0 on the ipsilateral side and motion pain VAS at 1-1 (r = -0.293, P = 0.002) and 2-1 (r = -0.223, P = 0.021). PPT on ipsilateral deltoid was lower (i.e. more painful) in recipients who received acetaminophen than those without (68.1 [46.1-90.0] % vs 88.9 [83.2-94.6] %, P = 0.029) at 1-1.

DISCUSSION

This report mainly focuses on multiple domains of pain following primary shot of the BNT162b2 mRNA COVID-19 vaccination including pain intensity, distribution, quality, and pressure pain sensitivity over time. All recipients were Japanese and most of them were non-obese subjects. Since this is a novel mRNA-based vaccine than ever before, there is much concern about misinformation focused on its adverse effects in social media (15), and that's why we aimed to provide a rationale for possible pain reaction based on a scientific approach.

In this series, most recipients showed mild-to-moderate pain at rest and during shoulder motion, which was localized around the injection site and disappeared within a few days. Younger and shorter recipients tended to show higher pain intensity. These findings were roughly consistent with published investigations with larger cohorts (8, 9). The age-related differences in local reactions can be explained by the varying levels of binding antibodies, which were reportedly lower among seniors and older adults (16). Similarly, non-obese status was significantly associated with a greater frequency of post-vaccine side effects and higher levels of antibody titers were detected in non-obese participants compared with obese ones (17). Since most of the participant were non-obese Japanese in our study, shorter height, but not weight and BMI, might be associated with worse pain. Additionally, it became clear that the pain manifestation was similar between the two injections overall, however, 40% of recipients reported higher pain intensity and 20% showed wider pain distribution after the second dose compared with the first one, and this trend was more common in females compared with males.

Mechanisms underlying pain following COVID-19 vaccination is quite unclear, however, a plausible explanation is immune-mediated inflammation due to a higher humoral response after exposure to the spike protein of SARS-CoV-2. In fact, a recent observational study of over 600 healthy Japanese cohorts demonstrated that participants who experienced adverse reactions (i.e., fever and general fatigue) demonstrated a higher antibody titer after BNT162b2 vaccination than those without adverse reactions (18). It could be speculated that subsequent

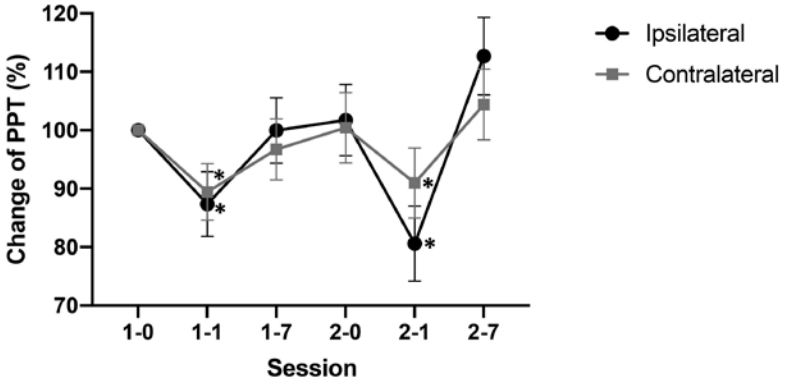

Figure 4. Mean (± 95% CI) of PPT recorded on ipsilateral (black circle) and contralateral (gray square) deltoid.
* : P<0.05 compared with session 1-0, 1-7, 2-0, and 2-7

macrophage activation and cytokine-induced damage, which were considered as essential molecular mechanisms of pain due to COVID-19 infection itself (5), would also contribute to the pain after the vaccination. However, further research is required to discuss the difference between the 'infection-associated' and 'vaccine-associated' COVID-pain.

Cases of shoulder injury related to vaccine administration (SIRVA), defined as atypical shoulder pain and limited range of motion after vaccination, have been reported particularly in the influenza vaccine (19, 20). SIRVA usually occurs due to an inappropriate injection technique such as "too high" or "too deep" needle insertion, which typically causes subacromial-subdeltoid bursitis (21). Recently, there has been some case reports presenting similar condition following the COVID-19 vaccination (22-25). In addition, another very rare conditions with painful shoulder such as the Personage-Turner syndrome (26) and polymyalgia rheumatica (27) have also been reported after the BNT162b2 mRNA vaccination. In this regard, our study demonstrated a typical time course and characteristics of pain after the novel vaccination in detail, which will help differentiate diagnosing atypical pain conditions as above.

PPT has been widely used for assessing altered mechanistic pain profile in musculoskeletal pain disorders (28). Interestingly, PPTs were significantly decreased from the baseline value and not only on the injected side but also on contralateral side at 1-1 and 2-1. In general, localized hyperalgesia may indicate tissue damage and subsequent sensory dysfunction at peripheral level, whereas widespread hyperalgesia to remote non-painful area seems to be a proxy for abnormalities in central nervous system processing (28). As far as we had investigated, there were no reports including quantitative assessment of mechanical hyperalgesia following COVID-19 and any other vaccines. Although exact mechanisms of altered nervous system are unknown, Widyadharma *et al*. (29) reported that COVID-19 virus enters the brain circulation which facilitates the interaction of the virus spike protein with angiotensin-converting enzyme 2 (ACE-2). Then the virus come to the neuron, they will interact with the ACE-2 receptor expressed in the neurons and lead to nervous system damage. Fortunately, our experience was a temporary phenomenon and recovered to the baseline value within a week, however, bilateral mechanical hyperalgesia was quite unique characteristics and it may partly explain underlying mechanisms of systemic myalgia that has been reported commonly after the BNT162b2 mRNA vaccination (8, 30-32). In addition, monitoring of PPT may help predicting motion pain intensity after vaccination from the aspect of inherent mechanical pain hypersensitivity. Furthermore, it may detect precursory symptoms of above-mentioned, abnormal shoulder pain condition though further studies are warranted.

Higher pain VAS and lower PPTs were observed during the next day for recipients who received acetaminophen than those who did not, suggesting that more painful recipients would likely receive the drug after the vaccination, but it was not so effective for relieving the pain. Although the pain would be mild-to-moderate and disappear naturally within a few days in normal course, it concerns some people who have excruciating pain after the vaccination and an alternative drug should be discussed for them.

Several limitations should be noted in this study such as a small sample size with relatively young recipients, lack of standardization for acetaminophen use, lack of multivariate regression analysis for considering possible confounders, and a lack of comparison with another vaccines. There was a possibility that participants received other analgesic medications by themselves without reporting. However, this is a preliminary report with the exploratory nature of the design focused on a timely topic, which will provide directions for further investigations.

In conclusion, temporary pain with mild-to-moderate intensity and localized distribution, concomitant with bilateral mechanical hyperalgesia on the deltoid muscle, were typical characteristics of pain after the vaccination. This manifestation was similar between the two injections overall, however, 40% of recipients reported higher pain intensity and 20% showed wider pain distribution after the second dose compared with the first one. Inherent mechanical pain hypersensitivity may predict motion pain intensity after the vaccination. These findings provide a rationale for possible pain reaction after this novel vaccination, which will be informative for future recipients.

DISCLOSURES

The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTION

Study design : M Izumi, TM, SO, NK, HS. Data collection : M Izumi, TM, SO, DO, YH, TS, KO, AN, RS, YF. Data analysis : M Izumi, TM, SO, M Ikeuchi. Drafting or revising manuscript : M Izumi, TM, SO, NK, HS, M Ikeuchi. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data ; took part in drafting the article or revising it critically for important intellectual content ; agreed to submit to the current journal ; gave final approval of the version to be published ; and agree to be accountable for all aspects of the work.

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