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Physical Characteristics of Injection Site Pain After COVID-19 mRNA BNT162b2 Vaccination

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ABSTRACT

Background BNT162b2, an mRNA COVID-19 vaccine, was launched in many countries as an intramuscular vaccination for COVID-19 infection. Few studies have assessed the physical indications of pain at the immunization site. This study aimed to characterize pain at the injection site and investigate morphological attributes using ultrasound.

Methods Forty-three of 211 healthcare workers who received a second dose of BNT162b2 between February 2021 and March 2021 were enrolled in the study. The mean age of the subjects was 40 years. We evaluated patients' pain at the injection site using the Numerical Rating Pain Scale (NRPS). We also assessed the thickness of the deltoid muscle fascia at the injection site by ultrasound. Bayesian robust correlation was employed to explore the relationship between the pain intensity scores and ultrasound measurements.

Results All eligible subjects complained of pain at the injection site. A median pain onset of 8 hours post-vaccination and a median peak intensity score of 4 were reported. Onset of relief occurred after 2 days. Ultrasound images demonstrated a 2.5-fold increase in fascia thickness at the injection site without intramuscular echogenicity change in all subjects. A correlation was established between the NRPS score and the non-injection-to-injection-side ratio of fascia thickness at the injection site (rho = 0.66).

Conclusion A sore arm was the most prevalent side effect of BNT162b2 vaccination and could be attributed to temporal fasciitis.

Key words COVID-19: fasciitis; intramuscular injection; vaccination

Coronavirus disease-19 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a severe global pandemic.[1] The pandemic has resulted in unprecedented medical, social, and economic damage globally with more than 100 million people infected and over 2,750,000 deaths as of April 1, 2021.[2] Developing vaccines against SARS-CoV-2 is critical to eradicating the COVID-19 pandemic. As of February 18, 2021, at least seven different vaccines across three platforms have been rolled out in various countries.[2]

One of these vaccines is the lipid nanoparticle (LNP)-formulated, nucleoside-modified RNA vaccine BNT162b2 (Pfizer–BioNTech, NY, and Mainz, Germany), which encodes a membrane-anchored SARS-CoV-2 full-length spike protein stabilized in the perfusion conformation. Polack and colleagues reported an efficacy of 94.8% against COVID-19 after two doses of the messenger RNA (mRNA) vaccine BNT162b2.[3] The most common side effect of the BNT162b2 vaccine is pain, especially when touched, at the site of intramuscular injection. Of trial participants aged 16 to 55, 83% reported pain at the injection site after the first dose, whereas 78% reported pain after the second dose.[3]

Here, we investigate this seemingly characteristic pain at the injection site, including time before onset, duration, and pain intensity. Considering the increased use of ultrasonography in the evaluation of muscle conditions, including damage and inflammation, over the years, we also performed an ultrasonographic assessment of the injection site after vaccination.

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Abbreviations: COVID-19, Coronavirus disease-19; HMC, Hamiltonian Monte Carlo; IQR, interquartile range; MCMC, Markov Chain Monte Carlo; mRNA, messenger RNA; NRPS, Numerical Rating Pain Scale; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; US, ultrasound

MATERIALS AND METHODS

Study design

Out of 478 healthcare workers at the Yonago Medical Center, 377 had received the first of two doses of the BNT162b2 vaccine on February 19, 2021, and a questionnaire of adverse effects was obtained from 284 subjects. In our pilot study of the first vaccination, 92% of those vaccinated complained of pain at the injection site, with the peak of pain at 24 hours after the injection. The two shots were to be administered 3 weeks apart. The present study included the subjects who received the second vaccination dose.

The inclusion criteria were as follows: (1) aged 20 years or more; (2) his/her schedule matched up with our work shift for ultrasound assessment after 24 hours of the injection, and (2) his/her consent to participation was obtained. This study was approved by the Ethics Committee of Yonago Medical Center (Ethical Code No.: 0303-01). Written informed consent was obtained from all participants after they were briefed on the purpose and procedures of the study.

Intramuscular injection protocol

The COVID-19 mRNA BNT162b2 vaccine was supplied after dilution with saline to a total volume of 0.3 mL. In the usual method, after selecting the injection site, three finger breadths (5 cm) below the mid-acromion skin is retracted with the thumb and index finger.[4] The 25-gauge needle is then inserted through the muscle using the dart technique for intramuscular injection at a 90° angle. The second dose of the vaccine was administrated at close 3-week interval after the first dose of the vaccine in the same arm.

Assessment of pain at the injection site

To characterize pain at the injection site, data were collected using a paper-based questionnaire. The first part of the questionnaire included demographic data (age and sex) and the second part requested information on onset, duration, and intensity. Evaluation was performed using the Numeric Pain Rating Scale (NPRS) to obtain a descriptive rating of the injection pain intensity. The NPRS is a unidimensional measure of pain intensity in adults.[5–7] The 11-point numeric scale ranges from "0," representing no pain, to "10," representing worst possible pain.[6, 7]

Ultrasound evaluation of the deltoid muscle

Images of the injection site were obtained by B-mode ultrasonography (Xario 100G ultrasound, Canon Medical Systems Corporation, Ohtawara city, Japan) using a high-resolution linear array 7.5 MHz probe (38 mm). A single high-resolution, short-axis ultrasound (US) image of the deltoid muscle at the injection site was taken for each patient. We further assessed the images by comparing the injection site to the contralateral side, which served as normal control. All images were de-identified by a radiologist not involved in the blinded review of the images, and the images were assigned random numbers. These individual de-identified and numbered images were then reviewed blindly by two other physicians.

Statistical analysis

Categorical variables were computed as sums and percentages, whereas continuous variables were expressed as means and SDs and/or range and median and interquartile range (IQR).

In a classical Pearson's correlation test in which the data followed a bivariate normal distribution, serious outliers can lower the estimated correlation coefficient. On the other hand, Bayesian robust correlation analysis can be made robust to outliers by replacing the bivariate normal distribution with a bivariate Student's t-distribution.[8] In this study, Bayesian robust correlation analysis was used to evaluate the association between the pain intensity scores and ultrasound measurements. All statistical analyses were performed using the probabilistic programming language Stan (version 2.26)[9] using the statistical package R (version 3.6.3. 2020, The R Foundation for Statistical Computing, Vienna, Austria). Stan is built upon the Hamiltonian Monte Carlo (HMC) algorithm, part of the Markov Chain Monte Carlo (MCMC) family of algorithms[10] that samples efficiently from the posterior distribution of the correlation coefficient (rho). The code for the analysis is publicly available on the website.[11]

RESULTS

Subject characteristics

Two hundred and eleven healthcare workers at the Yonago Medical Center received the second dose of BNT162b2 vaccine, and were registered as questionnaire participants. Injection site pain (91%), injection site erythema (18%), and fever (32%) were the most frequent adverse events reported. Due to contradiction between ultrasound assessment and our work-shift timing, a final total of 43 subjects were eligible for further analysis. The mean age was 40 years (range 21–77 years), and 70.6% of the study population were female.

Onset, duration, and intensity of injection site pain

Median onset was 8 hours (range 2–24 hours) after the vaccination, and onset of relief occurred after a median

of 56 hours (range 24–144 hours) post-vaccination. Median pain duration was 2 days (range 0.4–5.8 days) and the median peak intensity score was 4 (range 1.5–6) (Fig. 1B). In eleven participants (25%), non-steroidal anti-inflammatory drugs (NSAIDs) were used as pain and fever relievers.

When intramuscular injection of 1 mL saline into the deltoid muscle was performed in three volunteers of eligible participants two weeks after the second dose of the vaccine, the median onset was 10 min, and the median duration was 30 min. The peak intensity score was 2 (range 1.5–2) (Fig. 2B).

Musculoskeletal ultrasound imaging

Sonograms were retrospectively assessed with respect to echogenicity (hypoechoic, isoechoic, or hyperechoic relative to uninvolved muscle), distribution of muscle involvement, and intramuscular pattern (focal versus diffuse and well defined versus poorly defined). No differences were observed in echogenicity, muscle involvement, and intramuscular pattern between the injection site and the contralateral side.

In order to determine a timecourse of change on ultrasound, three volunteer subjects were scanned at 0, 1 day, 2 days, 3 days, 5 days, and 7 days after administration of the second vaccination dose. Fascia thickness was indicated on the injection site of the deltoid muscle, peaking at 1 day post-vaccination (Figs. 1A and B). After confirming a time schedule for ultrasound schedule, in all the other subjects (n = 40), ultrasound imaging was performed 1 day after the vaccination. As fascia thickness is independent of age,[12] we assessed fascia thickness bilaterally, and the difference between the fascia thicknesses of both sides was indicated as the non-injection-to-injection-side ratio. The non-injection-to-injection-side ratio of fascia thickness 24 hours after vaccination was 2.5 (range 1.4–5.7) in all eligible subjects (n = 43).

Conversely, when 1 mL saline was injected into the deltoid muscle, the non-injection-to-injection side ratio of fascia thickness was 1.0–1.1 in three healthy volunteers (Figs. 2A and B).

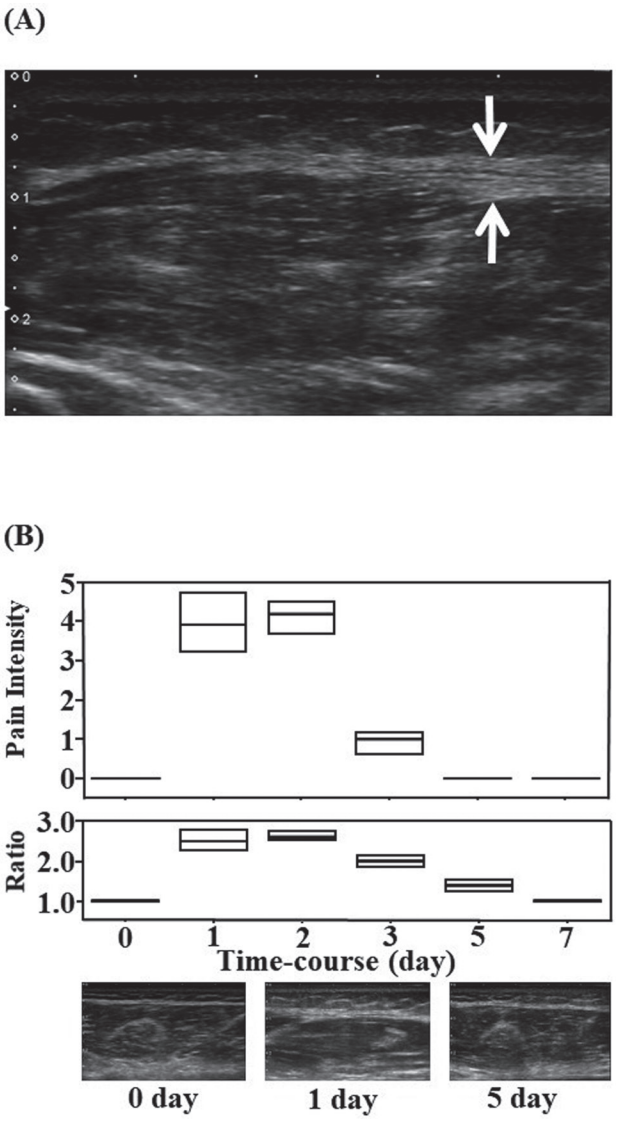

Fig. 1. A representative longitudinal ultrasound image of the deltoid muscle at the injection site at one day after intramuscular BNT162b2 vaccine (**A**). Two callipers have been placed to measure fascia thickness (arrows). Differences in the pain intensity, the non-injection-to-injection-side ratio of fascia thickness (rate) in the timecourse after the injection, and the ultrasound images of the injection site in three volunteer subjects who were administered intramuscular BNT162b2 vaccine (**B**).

Bayesian robust correlation analysis

The posterior density of the correlation coefficient (rho) was obtained to determine the association between the NRPS score and the non-injection-to-injection-side ratio of fascia thickness at the injection site. We used a burn-in of 500 steps, and then ran HMC for an additional 1,500 steps. The convergence of the HMC was confirmed based on all variables with Gelman–Rubin convergence statistic < 1.1. In addition, simulation values were found stable on a trace plot (Fig. 3A) and a marginal density plot (Fig. 3B). With MCMC convergence assured, point estimates and 95% confidence intervals of probability were retrieved for computing posterior quantiles and plotting the posterior density of rho. The Bayesian robust correlation obtained rho = 0.66 (range 0.45–0.81) with 99% probability (Fig. 3C).

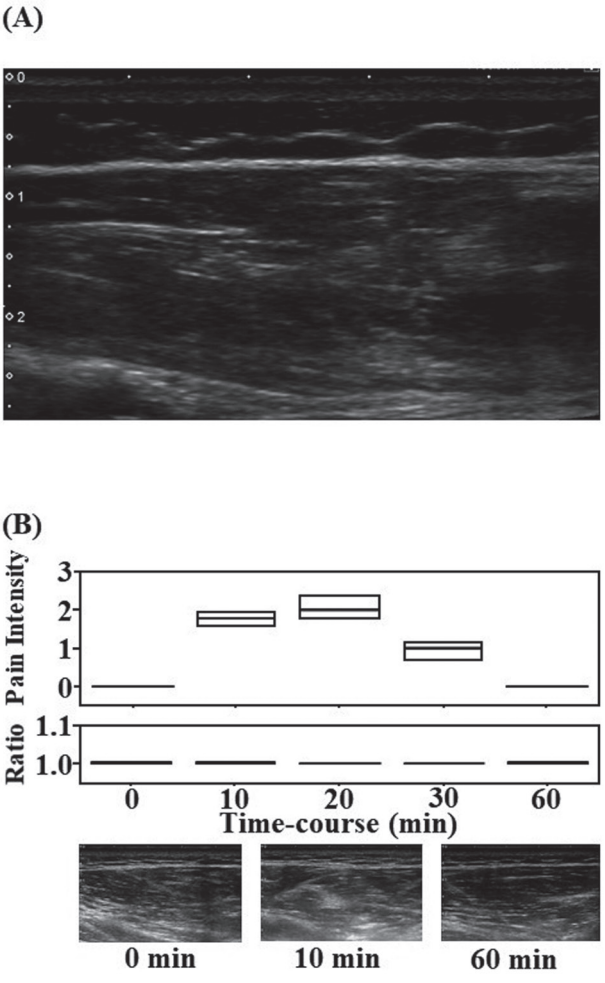

Fig. 2. A representative longitudinal ultrasound image of the deltoid muscle at the injection site at 20 minutes after 1.0 mL of saline (**A**), and differences in the pain intensity, the non-injection-to-injection-side ratio of fascia thickness (rate) in the timecourse after the injection, and the ultrasound images of the injection site in three healthy volunteers who were administered intramuscular saline injection (**B**).

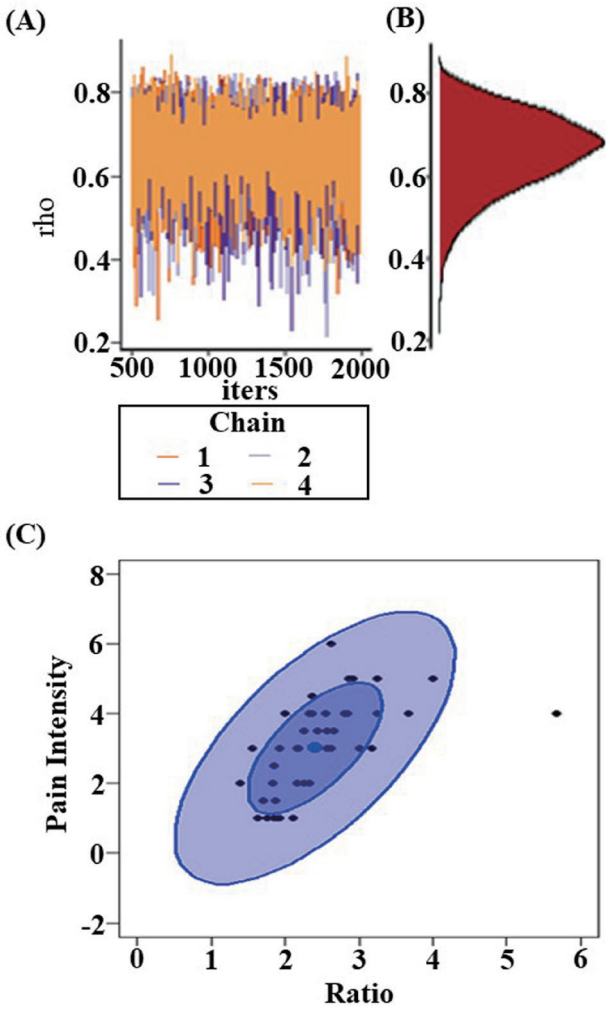

Fig. 3. (**A**) Trace plot, (**B**) marginal density plot of rho, and (**C**) correlation between pain intensity and measurement of fascial thickness, which is representative as the non-injection-to-injection side ratio. Trace plots of Markov chain Monte Carlo (MCMC) using Hamiltonian dynamics showed the history of a parameter value across 2,000 (iterations) simulations of the procedure. Marginal density plot of Bayesian posterior probability is the smoothened histogram of the values of rho and shows the posterior distribution of the correlation coefficient (rho) as the parameter.

DISCUSSION

In this study, transient immunization site pain was assessed using validated pain intensity, measured on NPRS. Arm pain at the intramuscular injection site occurred 8 hours after administration of the second dose of the BNT162b2 mRNA COVID-19 vaccine and lasted for 2 days with the pain intensity of 4 as NPRS. Ultrasound images suggest that pain at the injection site might be due to transient fasciitis.

Intramuscular injection is a common technique of delivering medication,[13, 14] and side effects of pain and discomfort in patients are often described. The results of one study showed that 40% of patients who received intramuscular injections described their experience as very painful.[15] Regarding vaccinations by intramuscular delivery, 13-valent pneumococcal conjugate vaccine (PCV13)[16] and Shingrix, a recombinant zoster vaccine (RZV),[17] had injection site pain incidence rates of 24% and 79.1%, respectively. In the present study, 96% of the subjects who received a second BNT162b2 intramuscular injection complained of pain at the injection site. The onset of pain began 8 hours after the vaccination, and continued for 2 days.

In our study, intramuscular injection of saline contributed to an immediate hyperechoic lesion at the

injection site in the deltoid muscle, which spontaneously regressed within one hour after the vaccination, without fascia thickness. The acute muscle edema may be related to the extravasation of protein-rich fluid to the damage/injury site, which occurs due to an increased membrane permeability of small blood vessels.[18] On the other hand, we found a significant 2.5-fold increase in thickness of the deltoid muscle fascia in the subjects who received BNT162b2 vaccine. Based on previous measurement errors of 3%–5% determined in fascial tissues,[19] this ratio was significant. This finding was similar to those observed in patients with dermatomyositis (DM) and polymyositis (PM).[20] Some reports provide evidence that fasciitis in the deltoid muscle is involved in the pathogenesis of DM/PM and is associated with patient symptoms of myalgia.[21, 22]

In this study, we showed positive relationship between pain intensity and measurement of fascial thickness. A statistical correlation was reported between pain and fascial thickness in patients with upper trapezius myofascial pain syndrome.[23, 24] Patients who received the BNT162b2 vaccine have also reported increased rates of palpable unilateral lymphadenopathy at axillary lymph node, which was usually resolved within 10 days post-injection.[25] The local response with pain might be demonstrated as temporal fasciitis at the injection site of the deltoid muscle due to drain the produced antigens from the injection site to the axillary lymph node.[26]

The limitations of this study included a small sample size and variation. Further studies are required and must involve a larger number of samples and different age groups, ensuring ample representation of the elderly. Another potential limitation is self-selection bias by the use of data collected only from subjects who decided to enroll in the study. However, this bias was limited in this study, because the statistics from the registered participants (n = 211) equaled the eligible subjects (n = 43) parameter as mean age, sex, and adverse effects including fever and headache. Furthermore, our study had no pathological findings of temporal fasciitis. Future investigations should also explore for evidence of local reactions in the muscle fascia.

Based on the results of the present study, transient pain at the site of intramuscular BNT162b2 vaccine was predominantly reported, with pain lasting for 2 days. This side effect could be attributed as temporal fasciitis. Future studies clarifying the possible pathological impact of fasciitis at the injection site are recommended.

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The authors declare no conflicts of interest.

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