Introduction

The coronavirus disease (COVID-19) vaccine is the most effective way to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and in Korea, three types (Oxford/AstraZeneca [AstraZeneca, Cambridge, UK], Pfizer/BioNTech [Pfizer, New York, NY, USA], and Johnson & Johnson [Johnson & Johnson, New Brunswick, NJ, USA]) of COVID-19 vaccines have been approved by the Korean Ministry of Food and Drug Safety. Beginning February 26, 2021, COVID-19 vaccination was started for healthcare workers and high-risk groups. As of May 18, 2021, 1,039,642 people (16.3% of the target population) had received two doses of the COVID-19 vaccine, and a total of 3,745,934 individuals (7.3% of the entire Korean population) had received at least one dose of the COVID-19 vaccine [1].

In the case of the Pfizer/BioNTech COVID-19 vaccine (Pfizer), local or systemic ad-
verse reactions were observed after the first dose, but most were reported to be alleviated within 1–2 days, becoming mild or moderate adverse events that did not interfere with the daily routine [2]. Because host immune responses to vaccines may vary, the efficacy and safety of the vaccine may differ based on the sex, race/ethnicity, and age [3-5]. As the domestic COVID-19 vaccinated population increases, reports of vaccine adverse events are also increasing. Despite the importance from a healthcare perspective, no research studies have compared the severity of adverse events associated with the vaccine type and the age and sex of recipients in Korea. Considering the need to vaccinate a huge population to obtain herd immunity, the safety of COVID-19 vaccine needs to be assessed regarding the wide range of clinical outcomes across diverse populations in a controlled setting.

Therefore, we initiated this study to clarify the adverse events associated with the vaccine to reduce vaccine hesitancy and facilitate vaccination campaigns to achieve herd immunity as well as to reduce the pressure on the healthcare system and overall severity and mortality associated with COVID-19. In this regard, we aimed to assess the differences in the frequency and severity of adverse events resulting from the BNT162b2 vaccine based on the age and sex of the recipients as well as the order of vaccination.

Materials and Methods

Participants and data collection

Online surveys based on the adverse effects of BNT162b2 vaccine for healthcare workers were conducted from March 12, 2021 to April 16, 2021 according to the monitoring policy for adverse events after vaccination. In total, 208 recipients who completed the first and second doses of the Pfizer’s vaccine with a 3-week interval (March 12 to April 2) were sent a link to the survey via a text message 2 weeks after vaccination, and 136 recipients agreed to participate in the online survey. Five recipients who either refused to participate or had missing clinical data were excluded. A total of 131 recipients were classified into subgroups by the sex and age (55 years old) based on the previous phase 2/3 clinical trial of the BNT162b2 vaccine, which helped in comparing the safety and efficacy of vaccine between a younger age group (20–54 years old) and an older age group (55 years old or older) [2].

The differences in the type, severity, time of occurrence, duration, and response method regarding the adverse events were analyzed by subgroup. The severity of adverse events were categorized as mild (not interfering with daily activities), moderate (some interference), and severe (interfering with daily activities) according to the US Food and Drug Administration’s toxicity grading scale for vaccine trials in healthy adults [6]. Local reactions included injection site pain and swelling, whereas systemic reactions included chills, headache, myalgia, arthralgia, nausea and fatigue, and allergic reactions (urticaria, facial edema, and lip edema). When dealing with the adverse events after vaccination, it was investigated whether the recipients took antipyretics or analgesics or visited the emergency room (ER) or outpatient department (OPD). The types of adverse events, including severity, onset time, and duration of symptoms, after the first and the second doses were compared between the subgroups by age and sex.

Statistical analysis

Statistical analysis was performed using the t-test for the means ± standard deviations for normally distributed continuous variables. The chi-square test was used to compare the categorical variables. All analyses were performed using RStudio ver. 1.4.1106 (RStudio, Boston, MA, USA), which runs R ver. 4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Results with p-values <0.001 were considered statistically significant.

Ethics statement

The study was approved by the Institutional Review Board of Myongji Hospital (IRB approval no., 2021-04-020). The requirement for written or verbal consent from the participants was waived based on the observational nature of the study and the fact that the data of the participants and identifiers were fully encrypted before analysis. The study was conducted in accordance with the Declaration of Helsinki.

Results

Demographic and clinical characteristics

The demographic profiles of the 131 participants are summarized in Table 1. The mean age of the participants was 39.9±14.7 years, and 56 participants (42.7%) were male out of the total 131 participants (Supplement 1). The time between the vaccination and the first symptom onset was 8.43±5.59 hours and the duration of symptoms was 2.18±2.0 days (Supplement 2).
Local and systemic adverse reactions after vaccination

After the first dose of the vaccine, the overall rate of adverse events was 32.8% (n=42). The most frequent adverse events were local injection site pain (n=43, 32.8%), myalgia (n=28, 21.4%), and fatigue (n=23, 17.6%). There were more people who experienced adverse events after the second dose than the people who experienced adverse events after the first dose. Among all participants, 80 (61.1%) experienced adverse events after the second dose: local injection site pain in 71 recipients (54.2%), fatigue in 57 recipients (43.5%), and myalgia in 57 recipients (43.5%) were observed. Fever occurrence was observed in 13 recipients (9.9%) after the first dose and in 47 recipients (35.9%) after the second dose. No recipient was found to have body temperature above 40°C after the first dose; however, three recipients (2.3%) showed above 40°C temperature after the second dose (Fig. 1).

Table 1. Demographics of participants

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Male (n=56)</th>
<th>Female (n=75)</th>
<th>Overall (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29</td>
<td>14 (25.0)</td>
<td>31 (41.3)</td>
<td>45 (34.4)</td>
</tr>
<tr>
<td>30–39</td>
<td>10 (17.9)</td>
<td>19 (25.3)</td>
<td>29 (22.1)</td>
</tr>
<tr>
<td>40–49</td>
<td>9 (16.1)</td>
<td>16 (21.3)</td>
<td>25 (19.1)</td>
</tr>
<tr>
<td>≥50</td>
<td>23 (41.1)</td>
<td>9 (12.0)</td>
<td>32 (24.4)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Subgroup analysis according to age and sex

There was no difference in the frequency and severity of adverse events according to sex after both first and second doses (Table 1). In order to assess the age-related differences in adverse events, we compared the mean ages between those who experienced adverse events and those who did not (Table 2). After the first dose, the mean age did not differ between the event and non-event groups. However, after the second dose, the age of the event group was significantly lower than that of the non-event group (36.2±11.9 years versus 45.6±16.9 years).

Table 2. Age difference after 1st and 2nd dose of BNT162b2 vaccine recipients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age (yr)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recipients with AEs</td>
<td>Recipients without AEs</td>
</tr>
<tr>
<td>1st dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>43</td>
<td>88</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>40.2±12.6</td>
<td>39.7±15.7</td>
</tr>
<tr>
<td>Median (min–max)</td>
<td>40.0 (24.0–71.0)</td>
<td>33.0 (23.0–77.0)</td>
</tr>
<tr>
<td>2nd dose</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>80</td>
<td>51</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>36.2±11.9</td>
<td>45.6±16.9</td>
</tr>
<tr>
<td>Median (min–max)</td>
<td>33.0 (23.0–71.0)</td>
<td>42.0 (24.0–77.0)</td>
</tr>
</tbody>
</table>

AEs, adverse events; SD, standard deviation.

Fig. 1. Proportions of reported adverse events (AEs) after 1st dose vs. 2nd dose of BNT162b2 vaccine. ER, emergency room; OPD, outpatient department.
The incidence of injection site pain (local reaction) and that of muscle pain (systemic reaction) after the first dose was significantly higher in the younger age group than that in the older age group (34.3% versus 26.1%, p<0.001 for injection site pain and 23.1% versus 13.0%, p<0.001 for muscle pain). Other types of adverse events tended to be more frequent in the younger age group after the first dose (Supplement 3). Notably, the incidence of adverse events after the second dose was significantly higher in the younger age group regardless of the type of adverse event, as shown in Fig. 2 (Supplements 3, 4). However, there was no significant age-related difference in the occurrence of allergic reactions, such as urticaria, facial edema, and lip edema.

In the case of ER or OPD visits due to adverse events, there was no difference between the two groups after both first and second vaccine doses. However, the frequency of self-medication (antipyretics and analgesics) was significantly higher in the younger age group after the second dose (Supplement 4, Fig. 2).

The severity of each adverse event after the first and second doses is summarized in Fig. 3 (Supplement 5). It was found that the frequency and severity of adverse events after the second vaccination dose (indicated in red at the bottom of the graph in Fig. 3) were significantly greater than those after the first vaccination dose (indicated in blue at the top of the graph in Fig. 3).

**Discussion**

In the present study, we assessed the profiles of adverse events after the first and second doses of BNT162b2 vaccine using an online survey in which 131 healthcare workers participated. The frequency and severity of adverse events to the vaccine were greater after the second dose than those after the first dose. There were no sex-related differences in the profiles of adverse events. Of note, we observed that the frequency of adverse events, including both local and systemic reactions, except for allergic reactions, was significantly more frequent in the younger age group than in the older age group. Although there were no clinically significant adverse events, the younger age group took more pain relievers, such as acetaminophen (Tylenol) or ibuprofen, and more frequently visited the ER or OPD due to symptomatic adverse events. To
the best of our knowledge, this is the first study in Korea to analyze the profiles of adverse events after BNT162b2 vaccination by the sex and age.

**Reactogenicity and safety of vaccination**

Reactogenicity is the physical manifestation of the inflammatory response to vaccination, whereas the safety of vaccination is a broader term, triggered or worsened by vaccination, and includes all adverse events that may occur at any point in time [7]. In this study, we conducted an online survey 2 weeks after each of the two-dose regimens of the BNT162b2 vaccine. Therefore, the adverse events collected from our study participants mainly focused on the reactogenicity following vaccination. Indeed, the reactogenicity of vaccines is related to the vaccination rate; vaccines associated with high reactogenicity can negatively affect the willingness of a person to be vaccinated [7].

Because there were only a few recipients who had completed the second dose of the ChAdOx1 nCoV-19 vaccine in Korea until April 2021, a complete comparison of the reactogenicity and adverse events between the various available COVID-19 vaccines is not available. According to a domestic study comparing the adverse effects that occurred after the first dose of the ChAdOx1 nCoV-19 vaccine and the BNT162b2 vaccine, the recipients of the ChAdOx1 nCoV-19 vaccine had more adverse events than those administered the BNT162b2 vaccine (90.9% versus 52.5%, p<0.001) [8]. Another study comparing the adverse events of these two vaccines after the first dose also reported that adverse events were more frequent among the ChAdOx1 nCoV-19 vaccine recipients [9]. However, because these studies only reported adverse events after the first dose of vaccination, it is not sufficient to compare the overall incidence of adverse events according to the vaccine type after completion of the two-dose vaccination regimen.

In the present study, the BNT162b2 vaccine recipients showed more frequent and severe adverse events after the second dose than after the first dose of vaccine; however, these symptoms appeared on the day of vaccination or 1 day after vaccination and resolved quickly. These findings are in concordance with a previous study on the two mRNA vaccines (Pfizer-BioNTech [Pfizer] and Moderna [Cambridge, MA, USA]) [10,11]. In our study, the administration procedure was the same, since the same vaccinators performed an intramuscular injection into the deltoid muscle of the participants with the same type of low dead space syringes in a series of two doses (0.3 mL each) 3 weeks apart.

Because most of the available COVID-19 vaccines require a two-dose regimen, the differences in the adverse event profiles after each dose are important not only from a clinical point of view but also from a public healthcare point of view. Previous studies have shown that the reactogenicity and safety of the BNT162b2 vaccine are similar to those of the Pfizer-BioNTech vaccine [12]. However, there are differences in reactogenicity between the BNT162b2 and Moderna vaccines [13]. Future studies are needed to compare the reactogenicity and safety of these vaccines in Korea to ensure that the public can make informed decisions about vaccination.

**Fig. 3.** The severity of adverse events after 1st and 2nd dose of BNT162b2 vaccine. COVID-19, coronavirus disease 2019.
ous immunology studies have shown that the first dose of vaccination provokes an innate immune response induced by the vaccine antigens or vaccine components, which is an inflammatory response that occurs when the virus enters the body and induces an adaptive immune response. After the formation of virus-specific antibodies from the first dose, a more robust immune response induced by memory T cells and B cells occurs immediately after the second dose [7]. However, it is interesting that not all vaccines have an increased reactogenicity with each additional vaccine dose. Indeed, the adverse events observed after the second dose of the ChAdOx1 nCoV-19 vaccine were less common than those observed after the first dose [12].

The occurrence of more intense local and systemic reactions after the second dose seems to be a specific response to the mRNA vaccine compared with other platforms. This may be due to differences in the innate immune response related to the mRNA structure design or purification, or may be related to lipid nanoparticle (LNP) delivery agents, such as LNPs and polyethylene glycol, which are used to stabilize mRNA. In particular, allergic reactions caused by polyethylene glycol, which is an anaphylaxis-causing agent in mRNA vaccines have been attracting attention. mRNA vaccines mediate type I interferon responses, and this can elicit cytotoxic T cell responses and the production of other inflammatory cytokines, which may play an important role in reactogenicity [13]. In our study, adverse events after the second dose were mostly mild to moderate, with no major adverse events, and all adverse events resolved within 2 days after dosing. However, if the vaccine composition factor is a relevant contributor, unexpected and severe adverse events may occur. This concern can be realized in specific situations, such as when an adapted booster vaccine is needed for new SARS-CoV-2 variants, annual vaccinations are needed for endemic infection, or newly developed mRNA vaccines are required for other diseases. Therefore, further research is required to investigate why mRNA vaccines exhibit more severe immune reactions after the second dose than after the first dose, compared to the adenovirus vectored vaccine, and which components of the mRNA vaccine contribute to more severe adverse events and to further reduce the innate immune activity/reactogenicity if the mRNA vaccine does not affect the immunogenicity.

**Age and sex differences regarding the adverse events to BNT162b2 vaccine**

According to a landmark trial on the safety of BNT162b2 vac-
cine, the incidence of adverse events was relatively low in older participants [2]. The V-safe Active Surveillance System, which is a vaccine adverse event reporting system operated by the US Centers for Disease Control and Prevention, also reported less reactogenicity in recipients aged 65 years or older, compared to younger recipients after the administration of both Pfizer-BioNTech and Moderna vaccines [11]. In line with previous studies, we observed that the frequency and severity of adverse events after the second dose of the BNT162b2 vaccine were greater in the younger age group. However, there were no sex differences in the frequency and severity of adverse events, being in contrast with the two domestic studies that reported more frequent adverse events in women than in men after the first dose of the ChAdOx1 vaccine [8,14].

The differences observed in adverse events based on age and sex are not only due to vaccine factors, but also to intrinsic host factors (such as age, sex, race/ethnicity, body mass index, circadian cycle, and psychological stress) and administration factors (such as needle length, rapidity of injection, and injection route), which can contribute to reactogenicity [7]. Therefore, the differences in the true adverse events caused by the vaccine from the influences of intrinsic host factors and administration factors is often difficult, as seen in a Finnish twin study. They compared the adverse events observed after the measles, mumps, and rubella (MMR) vaccination between the vaccinees and their placebo-injected twins in different sequences at 3-week intervals. In this double-blind, placebo-controlled, crossover study, the true frequency of adverse events caused by the MMR vaccine was estimated from the discordance rates of individual signs and symptoms in both groups [15].

**Reactogenicity and immunogenicity of BNT162b2 vaccine**

There is a concern that fewer adverse events may result in reduced antibody production. Indeed, several previous studies have suggested this “no pain, no gain” hypothesis after vaccination [16]. However, there is no scientific proof that someone with more obvious adverse events from the vaccine can have better immunity against COVID-19 [17]. After vaccination, two reactions occur as immunologic responses. The first reaction is the innate immune response, which includes the mobilization of neutrophils and macrophages and the removal of chip particles by the activated immune cells within a few hours or days. The second reaction is the long-lasting adaptive immune response, which is the reaction in which T cells and B cells learn to recognize and remember chip particles to
form antibodies. This adaptive immune response is completed approximately 2 weeks after vaccination and provides long-lasting protection against the virus. The recipients usually undergo local or systemic reactions immediately after the vaccination. These reactions result from an early adaptive response with an innate response that occurs immediately to remove the foreign molecules (vaccine components). Since this is not a complete adaptive immune response induced by the vaccine, there is no significant correlation between the severity of adverse events and the acquisition of immunity [7]. The reactogenicity and immunogenicity of the BNT162b2 vaccine are also expected to follow the same immunologic mechanism. However, further research is warranted to investigate the relationship between adverse events and the immunogenicity of COVID-19 vaccines.

At this point, the fear of adverse events and vaccine hesitancy may lower the vaccination rate and cause vaccine avoidance among at-risk populations that need to be protected, delaying the achievement of herd immunity. This can be more threatening for herd immunity when the risk of adverse events is higher after the second dose than after the first dose, when the second dose is necessary to obtain appropriate immunity. In this study, the frequency of adverse events was higher after the second dose than after the first dose of the BNT162b2 vaccine. However, it should be noted that severe adverse events requiring hospitalization did not occur, and most of the mild to moderate adverse events were self-limited and could be managed with self-medication within 1–2 days of vaccination. We believe that these findings are worthy of attention, considering that our study showed real-world data obtained from healthcare workers at a tertiary hospital that is currently dedicated to the management of severe COVID-19 patients. We also believe that our results will facilitate the vaccination process, providing accurate information on the adverse events of the BNT162b2 vaccine.

Our study has several limitations. First, the number of study participants was small, and the period that falls within the scope of investigation was short. Second, since this was a self-reporting survey through anonymous responses using a web-based survey, although our data were obtained from healthcare workers, their symptoms and severity were not verified or confirmed clinically by the study investigators. Given the nature of self-reported questionnaire and the concerns on the vaccine's safety, over-reporting of adverse events might have biased the results.

**Conclusions**

The frequency of adverse events after the second dose of the BNT162b2 vaccine was higher than that after the first dose, and there were more local and systemic adverse events in the younger age group (age <55 years). However, there were no serious adverse events after vaccination. The BNT162b2 vaccine appears to be better tolerated in older adults than in younger adults, as observed with regard to the frequency and severity of adverse events after vaccination.

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**Supplementary Materials**

Supplementary materials are available at Clinical and Experimental Vaccine Research website (http://www.ecevr.org).

**References**


