Original article

Side Effects Profile among Healthcare Workers after the Administration of Activated mRNA-1273 as a Booster Following 2 Shots of Inactivated (CoronaVac) Vaccine

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Abstract:

Objective: This study focuses on investigating the profile of all side effects of the mRNA-1273 vaccine for healthcare workers. Material and method: A cross-sectional design were used to explore the side effects of the mRNA-1273 vaccine for healthcare workers in Yogyakarta and Central Java, Indonesia. The survey was conducted through Google form after 119 healthcare workers in Yogyakarta and Central Java receiving the mRNA-1273 vaccination as a booster in May-August 2021. Results and discussion: The major goal of this research is to investigate the side effects of using the mRNA-1273 vaccine as a booster among healthcare workers in Yogyakarta and Central Java, Indonesia. Most (99.2%) of respondents admitted to feeling pain at the injection site, 42% the respondents also admitted to feeling swelling at the injection site as a moderate side effect, and 3.4% respondents reported vomiting as a rare side effect. This study found the low negative correlation between headache with p value 0.004 (p<0.05, r= -314) and nauseous with p value 0.012 (p<0.05, r= -300) towards the gender. We also found the low negative correlation between muscle aches with p value 0.033 (p<0.05) towards the ages (r= -257). Conclusion: The most common side effect after receiving the mRNA-1273 vaccine as a booster is a pain in the injection area. Female most frequent felt the headache and nauseous than man after received booster vaccination.

Keyword: COVID-19; mRNA-1273 vaccine; side effects; healthcare workers

Introduction

The increased frequency of COVID-19 in Indonesia directly raises morbidity and mortality rates among healthcare workers. As of February 2021, there were 757 healthcare workers who died due to Covid19¹. Indonesia is one of the countries with the highest mortality rate among doctors, nurses, and other healthcare workers². Hence, more aggressive measures should be taken into account to mitigate this fact, including the massive and systematic delivery of vaccine across the country. Indeed, more consideration have to be taken to put this policy into the public sphere³.

Following the issuance of the Emergency Use Permit for the mass distribution of the Covid19 vaccine, the Indonesian government has also approved and

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imported several types of vaccines to be given to the entire community. Until mid-2021, Indonesia has imported around 143 million doses of vaccine, mostly from the Sinovac company. Indeed, Indonesia has been named the fifth country in the world with the highest level of Covid-19 vaccination program. In addition to the standard protocol of having a set of two doses for all Indonesians, healthcare workers plan to have a third dosage of the mRNA-1273 vaccine as a booster. mRNA-1273 is an mRNA-1273 vaccine with a claimed efficacy of 94.1%, much higher than Sinovac.

The mRNA vaccine is a biological preparation of several viral proteins designed to fight the attack of the COVID-19 virus. The mRNA-1273 vaccine is made up of a fragment of genetic code that directs the creation of the coronavirus spike protein and is given in the form of a tiny fat bubble known as a lipid nanoparticle. The side effects would most certainly affect a large number of people. The researchers who did the initial analysis of the massive mRNA-1273 experiment discovered that side effects included weariness, muscular ache, joint pain, and headache. The COVID-19 mRNA-1273 vaccine, mRNA-1273 (100 g), is given by intramuscular injection in two doses (0.5 ml each) for 28 days. Allergic reactions to vaccines occurred at a rate of 1.31 (CI 95%, 0.90-1.84) cases per million doses of vaccine, as shown in large demographic surveys, with no reported deaths. Treatment of two doses of mRNA-1273 at 100 g is expected to protect against all newly discovered strains. mRNA-1273 states that it will test additional booster doses of mRNA-1273 to see if they can increase neutralizing titers against emerging strains outside the current primary vaccination series.

CoronaVac is an inactivated viral vaccine that joined the COVID-19 vaccine trial pipeline in April 2021. Based on the results of vaccine efficacy and safety from phase I/II trials, Emergency Use Authorizations (EUAs) were granted in several countries which were considered economically valuable. The current consensus findings of CoronaVac confirm its short-term safety for human use as well as its efficacy.

A crucial part of enhancing a vaccine is ensuring that known and hypothetical possible risks are recognized, assessed, and approximately weighed against prospective benefits. One of the potential risks addressed in the context of developing a COVID-19 vaccine is if the vaccine’s immune response could increase SARS-CoV-2 acquisition or worsen the disease if infection occurs after immunization. Vaccine-associated Enhanced Disease (VAED) is defined as an immunological reaction to a vaccine that is linked directly to an elevated risk with an increased risk of an adverse infectious outcome as compared to infection without prior immunization.

Using an online survey questionnaire among many healthcare workers in the Yogyakarta and Central Java area, this study offers to investigate a more detailed side effect profile of the mRNA-1273 vaccination as a booster after the administration of two doses of the Inactivated Coronavirus vaccine.

Materials and Method

Study design

A descriptive cross-sectional design was used to investigate the side effects of the mRNA-1273 vaccination as a booster after two doses of CoronaVac for healthcare workers.

Study sample

A total of 119 healthcare workers in Yogyakarta and Central Java became respondents who voluntarily filled the survey. The online survey was distributed to several groups of social media. The study was conducted in August 2021 recently after the respondents received the mRNA-1273 vaccine. The inclusion criteria include the respondents were healthcare workers, and the respondents received the mRNA-1273 vaccine as a booster within an interval of 1 month or more. Sixty-nine respondents identified the female and male, then 50 respondents were not identifying themselves.

Data Collection and Analysis

The data was collected on August 2021 through a web-based questionnaire via Google form. The Google Forms were sent by the WhatsApp platform. The data was obtained through an online survey and analysed using the Statistical Package for Social Sciences (SPSS) program in program 25 versions. Descriptive analysis was used to analyse the side effect profile of mRNA-1273 for healthcare workers.

Ethical Clearance

The UMY Research Ethics Committee No.182/EC-KEPK FKIK UMY/VI/2021 granted ethical approval for this study. The online survey form included information sheets and informed consent forms from respondents. Respondents were given the option of opting out of the study at any time. The participation was completely voluntary.
Results and Discussion

Demography characteristic

In the table 1 reported that the average age of the respondents is 29 years old, 39.5% female, 18.49% male, and gender unknown 42.02%. Eleven (9.24%) of the total respondents were diagnosed as COVID-19 patients. There are 23.53% of respondents with blood type A, 10.92% blood type AB, 32.77% blood type B, 32.77% blood type O.

Table 1. The characteristic of respondents

| Characteristic            | Number | Percentage (%) |
|---------------------------|--------|----------------|
| **Gender**                |        |                |
| Male                      | 22     | 18.49%         |
| Female                    | 47     | 39.5%          |
| Unidentified              | 50     | 42.02%         |
| **Age**                   |        |                |
| 20-29                     | 21     | 17.65%         |
| 30-39                     | 79     | 66.39%         |
| 40-49                     | 11     | 9.24%          |
| Above 50                  | 8      | 6.72%          |
| **Blood type**            |        |                |
| A                         | 28     | 23.53%         |
| AB                        | 13     | 10.92%         |
| B                         | 39     | 32.77%         |
| O                         | 39     | 32.77%         |
| **History of COVID-19**   |        |                |
| Yes                       | 11     | 9.24%          |
| No                        | 108    | 90.76%         |

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Figure 1. The side effect of mRNA-1273 vaccination

In figure 1, most respondents reported that they obtained pain in the injection area 99.2%, muscle aches 59.7%, headache 56.3%, fever 52.9%, joint pain 52.9%, and tired quickly 42.9% the most common frequency effects. Then, this result showed several moderate frequency effects such as 42% swelling at the injection area, 39.5% shivering, 29.4% nauseous, and 20.2% red rash on the injection area. On the other side, the researcher also classified the rare frequency side effects of mRNA-1273 side effects such as 3.4% vomiting, 3.4% diarrhea, 0.8% red rash on the body, and some respondents did not get the side effects (0.8%).

*Spearman’s rho

In the table 2, the data reported that there was a low negative correlation between headache with p value 0.004 (p< 0.05, r = -3.41) and nauseous with p value 0.012 (p<0.05, -300) towards the gender. The data showed that female (63.85%) mostly felt this symptom. Meanwhile, there was also low negative correlation between muscle aches with p value 0.033 (p<0.05) towards the age (r=0.257). Mostly, respondents with age range 30-39 (68.6%) got this symptom.

On the question of “What would you do if you had side effects after vaccination such as headaches, muscle aches, fever, nausea, vomiting, diarrhea, joint pain, shivering and get tired quickly?” the respondents answered that they only drink enough water (77.3%), 57.1% of respondents consume antipyretic, 37% of the respondents consume painkiller (Analgesic), 5% of the respondents consume anti-nausea drugs, 5% of the respondents take a rest after they got the side effects, 1.7% of the respondents’ consultation to the healthcare facilities and 0.8% of the respondents consume vitamin.

On the question of “What can you do if you get post-vaccination side effects such as pain, red rash on the skin, swelling in the injection site, and red rash on the body?”, most of the respondents answered they ignored (54.6%) the side effects, several of them moving their arms (32.8%), 16% of respondents take a wet towel in the area that got vaccination side effects, some of them consumed the medicine (10.1%), 5% of the respondents did cold compress and then 10.1% of respondents go to the doctor.

This study examines mRNA-1273 as a booster. The findings provide information on the side effects of mRNA-1273 after the respondent had received the second dosage of CoronaVac. According to the findings, people who received the vaccine were more vulnerable to the adverse effects associated with the third vaccination or after getting the two doses of CoronaVac, such as pain at the injection site, muscle aches, headache, fever, and fatigue as the most common frequency, followed by fatigue, swelling at the injection site, joint pain, nauseous, and red rash at the injection site as the moderate frequency.

Furthermore, the results of the study revealed effects with less frequency such as diarrhea and red rashes on the body, but some respondents did not experience side effects. The origin of adverse effects or responses
Table 2. Correlation of side effects of mRNA-1273 towards gender and ages

| Symptom                  | Headache | Nauseous | Muscle aches |
|--------------------------|----------|----------|--------------|
| Gender                   | Yes      | No       | Yes          | No          | Yes        | No          |
| Male                     | 6 (8.7%) | 16 (23.2%) | 2 (9.1%)    | 20 (29%)   | 15 (21.7%) | 7 (10.1%)   |
| Female                   | 30 (43.5%) | 17 (24.6%) | 18 (26.1%)  | 29 (42%)   | 29 (42%)   | 18 (26.1%)  |
| Mean                     | 1.48±0.53 | 1.71±0.457 | 1.36±0.484  |
| p                        | 0.004*   | 0.012*   | 0.608        |
| Age                      |          |          |              |
| 20-29                    | 9 (13%)  | 5 (7.2%) | 5 (7.2%)     | 9 (13%)    | 6 (42.9%)  | 8 (57.1%)   |
| 30-39                    | 24 (34.8%) | 23 (33.3%) | 12 (17.4%)  | 35 (50.7%) | 31 (66%)   | 16 (34%)    |
| 40-49                    | 3 (4.3%)  | 1 (1.4%) | 3 (4.3%)     | 1 (1.4%)   | 4 (5.8%)   | 0 (0%)      |
| Above 50                 | 0 (0%)   | 4 (5.8%) | 0 (0%)       | 4 (5.8%)   | 3 (4.3%)   | 1 (1.4%)    |
| Mean±(SD)                | 1.48±0.503 | 1.71±0.457 | 1.36±0.484  |
| p                        | 0.190    | 0.799    | 0.033*       |

* Spearman’s rho
* SD - Standard Deviation

Figure 2. The respondent’s early treatment after getting the side effect of mRNA-1273 vaccine such as headaches, muscle aches, fever, nausea, vomiting, diarrhea, joint pain, shivering, and getting tired quickly.

Figure 3. The respondent’s early treatment after affected the side effect of mRNA-1273 vaccine such as pain, red rash on the skin, swelling in the injection site, and red rash on the body.
to the mRNA-1273 vaccination is currently uncertain. According to the CDC, 2.5 occurrences of anaphylaxis, which includes symptoms such as trouble breathing, swelling of the face and throat, rash, and low blood pressure, occurred shortly after receiving the mRNA-1273 vaccine\textsuperscript{15}. Several mRNA-1273 side effects, including fever, nausea, and diarrhea, may cause to the death of some elderly people (8). Additionally, because the respondents were first-timers, no mortality data were collected in our study (directly from vaccine recipients). As a result, we recommend that somebody who has been immunized be monitored for at least 15 minutes after getting the vaccination, as advised by the CDC.

In an in vitro study, mRNA-1273, which investigated the efficacy of the mRNA-1273 vaccine in the case of the British and African variants, reported the presence of high neutralizing antibody titers in the British variant and generally consistent with the neutralizing titers established in the previous variant. However, mRNA-1273 in the African variant was six times lower in antibody neutralizing titers in non-human primates to wild-type virus challenge, resulting in a higher risk of COVID-19 exposure\textsuperscript{16}.

At a dose of 50 micrograms, the mRNA-1273 vaccine is recommended for people 18 and older (0.5 mL). It is 94.5% effective against COVID-19. It also offers an antibody response for at least 119 days after vaccination. However, some allergic reactions to the mRNA-1273 vaccine have been reported. The COVID-19 vaccine can cause infrequent side effects such as pain, redness, or inflammation at the injection area, fever, headache, muscle aches, nausea, vomiting, itching, joint pain, etc. after the first or second dose\textsuperscript{17}.

In this study, it was found that the majority of respondents experienced pain in the injection area. This is because the skin reacts to the vaccination. Previous studies also supported these findings, which suggested that skin biopsy specimens revealed a rare-frequency mixed perivascular infiltrate dominated by lymphocytes and eosinophils, consistent with a dermal hypersensitivity reaction\textsuperscript{18}. After both doses, participants also reported systemic and local side effects such as myalgia, headache, fatigue, and abdominal pain\textsuperscript{19}. According to the findings of another study, respondents reported the most pain at the injection site after getting one or two doses of the mRNA-1273 vaccine\textsuperscript{19}. They reported that respondents experienced local symptoms such as pain (94.21%) and swelling (15.05 percent)\textsuperscript{16}.

According to the CDC, vaccine responders experienced higher local response rates after dose two or after dose one. Local reactions were more common in the younger population (90.5%), ages 18 to 64 years) then in the older population (83.9%, ages 65 years and over) after receiving dose 2. Pain at the injection site is the most common and frequently reported local reaction among vaccine recipients. The younger population reported more pain than the older population after dose 1 (86.9% vs. 74.0)\textsuperscript{15}.

The second most commonly reported local response is axillary swelling or tenderness. Axillary swelling or tenderness was reported more frequently in the younger population (16.0%) than in the older population (8.4%) after dose 2. Redness and swelling at the injection site have been reported infrequently after both doses. Redness and swelling may be more common after receiving 2 doses\textsuperscript{15}. The second most common local response is axillary swelling or tenderness. The younger population reported more axillary swelling or tenderness than the older population (16.0% and 8.4%) after dose 2. Redness and swelling at the injection site have been reported infrequently after both doses\textsuperscript{15}. In this study, we compared the side effects of the mRNA-1273 vaccine as a booster and the side effects that occurred in people receiving mRNA-1273 at both doses 1 and 2. Both as a booster and mRNA-1273 as doses 1 and 2. The most common symptom is pain at the site of the vaccine injection.

There are various limitations to this study. Because this was an independent study, anonymous responses to a web-based survey were used to investigate detailed self-reported symptoms. The study investigator did not investigate or confirm the study participants’ receipt of vaccine or self-reported symptoms, and they were not clinically or officially recorded or documented. This study found the low negative correlation between headache and nauseous towards the gender. We also found the low negative correlation between pain in the injection area towards the ages. The majority of study participants were female (63.85%). This suggests and reflects the fact that women outnumber men in our study subjects. The preponderance of the symptoms reported above happened during the vaccine’s booster vaccination period. We did not look into the vaccinations’ long-term effects. There was no accurate data on the time of onset of symptoms following vaccine delivery or
the duration of symptoms reported in this research. This study also explains why women feel sick more easily. In a previous study said that women were 50% more likely than males to experience chronic pain in all parts of the body\textsuperscript{19,20}. Migraines that affect only one side of the head affect women 2.5 times more frequently than males\textsuperscript{21}. Aside from the observable difference when approaching puberty, some types of pain are indeed tied to hormones, such as estrogenic, which can worsen migraines. Hormonal variations between men and women are thought to influence pain response as well. While men respond to pain more physically, discomfort can alter emotions and moods in women (mood).\textsuperscript{20} According to previous studies, women who focus on the emotional element of pain experience more intense pain because the emotions linked with pain are always negative.

**Conclusion**

In summary, researchers classified side effects according to frequency, such as the most common, moderate, and rare side effects. The most common frequency effects include pain at the injection site, muscle aches, headache, fever, joint pain, and fatigue. Some moderate frequency effects include swelling at the injection site, shivering, nausea, and a red rash on the injection area. The rare side effects of mRNA-1273 were vomiting, diarrhea, red rash on the body, and some respondents did not get any side effects. There was low negative correlation between headache and nauseous towards the gender and also muscle aches towards the ages. Most of the female respondents reported have headaches and nauseous. Respondent around 30-39 reported that they felt muscle aches after booster vaccination m-RNA1273. Pain in the injection area is currently one of the effects felt by respondents after receiving the mRNA-1273 vaccine. In comparison, a red rash on the body is a less common effect after receiving the mRNA-1273 vaccine. Most of the respondents did not treat the side effect of pain at the injection site from the results. Other respondents move their hands to reduce pain at the injection site.

**Disclosure of conflict of interest**

The researchers did not find a conflict of interest in this study.

**Acknowledgment**

We would like to thank Universitas Muhammadiyah Yogyakarta for providing financial support and guidance in conducting this research.

**Authors’ Contribution**

- dr. Nova Maryani, MMR., Sp.An: Conceptualization, writing-original draft, methodology, data analysis, project administration, and writing-review & editing
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