Original Article

A cross-sectional survey of side effects after COVID-19 vaccination in Saudi Arabia: male versus female outcomes

Ahlam Alghamdi[1,2], Alnada Ibrahim[1,3]*, Rhagda Almutairi[4], Mercy Joseph[5], Ghaida Alghamdi[6], Aljohara Alhamza[7]

[1]Department of Pharmacy Practice, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia. [2]Department of Pharmacy, King Abdullah bin Abdulaziz University Hospital, Riyadh, Saudi Arabia. [3]Department of Pharmaceutics, Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan. [4]College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia. [5]Infection Control, King Abdullah bin Abdulaziz University Hospital, Riyadh, Saudi Arabia. [6]College of Medicine, Imam Mohammed Ibn Saud Islamic University, Riyadh, Saudi Arabia. [7]Department of Medical, King Abdullah bin Abdulaziz University Hospital, Riyadh, Saudi Arabia.

Correspondence: Alnada Ibrahim, Department of Pharmacy Practice, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia. Alaibrahim@pnu.edu.sa

ABSTRACT

COVID-19 pandemic is an ongoing public health crisis. Many COVID-19 vaccines have been developed with different efficacy and safety profiles. The current study aimed to investigate the short-term side effects associated with Oxford–AstraZeneca COVID-19 vaccine among males and females who received the first dose. A cross-sectional survey was conducted at KAAUH between February 28 and March 12, 2021. The main outcomes were the reported side effects at days 1, 2, and 3 post-vaccination.

The study included 528 participants, of whom 49.8% (n = 263) were males. The reported side effects among all participants during the first day included myalgia (49.8%), fever (42%), headache (40%), numbness (8.5%), eye muscle pain (6.3%), palpitations (4.7%), shortness of breath (4.4%), sore throat (4.2%), and gastrointestinal symptoms (4.2%). No anaphylaxis or thrombotic events were reported during the study period. There were statistically significant differences in the side effects reported (females vs males) during the first day, which included myalgia (63% vs 36.5%, p-value = 0.000), fever (51.7% vs 32.3%, p-value = 0.000), headache (55.5% vs 24.3%, p-value = 0.000), numbness (11.7% vs 5.3%, p-value = 0.009), sore throat (6.4% vs 1.9%, p-value = 0.009), eye muscle pain (9.4% vs 3%, p-value = 0.002), shortness of breath (7.5% vs 1.1%, p-value = 0.000), and palpitation (9.1% vs 0.4%, p-value = 0.000). The same side effects showed significant differences on day two. The reported side effects were common but not serious. Female respondents appeared to have more COVID-19 vaccine-associated symptoms.

Keywords: COVID-19, Vaccination, Safety, Tolerability

Introduction

The global burden associated with the SARS-CoV-2 virus remains an unmitigated public health crisis [1, 2]. The World Health Organization is frequently issuing recommendations to prevent and slow down the transmission of COVID-19. Public health agencies, for example, the Centers for Disease Control and Prevention (CDC), have endorsed different strategies to reduce the spread of the virus. Additionally, numerous governments have implemented travel restrictions, curfew, and physical distancing. Despite these efforts, the number of cases continues to increase [3]. Vaccines are now regarded as one of the effective preventive measures that can reduce the spread and the progression of such infectious diseases [4].

Many COVID-19 vaccines have been developed with different efficacy and safety profiles. There exist concerns regarding the

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Alghamdi A, Ibrahim A, Almutairi R, Joseph M, Alghamdi G, Alhamza A. A cross-sectional survey of side effects after COVID-19 vaccination in Saudi Arabia: male versus female outcomes. J Adv Pharm Educ Res. 2021;11(2):51-6. https://doi.org/10.51847/bCwca2qGfP

side effects of the newly developed vaccines. A dose-escalation phase 1 trial of a recombinant adenovirus type-5 vectored COVID-19 vaccine was conducted by Feng-Cai Zhu *et al.* [5] in China. The participants were grouped into three to receive a low dose, middle dose, or high dose of the vaccine. The findings of this study showed that the three doses were tolerable by healthy adults, nevertheless, fever, fatigue, headache, and muscle pain were encountered after receiving the vaccine among all age groups. The second phase of the randomized, double-blind, placebo-controlled study in Wuhan, China, found that the percentage of vaccine recipients who developed side effects such as fever, fatigue, and pain at the injection site was higher compared to placebo recipients. Both phases of this study concluded that the recombinant adenovirus type-5-vectored COVID-19 vaccine holds a good safety profile [6].

The safety of PfizerBioNTech and Moderna COVID-19 vaccines was assessed in United States population during the first month of the vaccination program. The reported side effects were evaluated based on approximately 14 million doses of PfizerBioNTech and Moderna COVID-19 vaccines. The majority of reports (90.9%) were for non-serious side effects. The commonly reported events involved headache, fatigue, dizziness, nausea, fever, chills, and pain at the injection site. Anaphylaxis was reported after administration of both vaccines with a rate of 4.5 cases per million doses administered [7]. A survey study of the side effects following Pfizer–BioNTech COVID-19 vaccine reported comparable side effects. The duration of the side effects lasted three days for one-third of the vaccine recipients [8]. Investigations from Saudi Arabia, on Pfizer-BioNTech COVID-19 vaccines, found similar side effects, with documented rare events that involved Bell's palsy and lymph nodes swelling [9]. Published research has also documented thrombotic adverse reactions as rare side effects due to Oxford–AstraZeneca vaccine [10-12].

Post-marketing studies on the severity and duration of side effects that are associated with COVID-19 vaccines are still needed. Reports from around the globe are highly recommended to better understand the associated side effects of COVID-19 vaccines. Upon this background, the current study aimed to investigate the short-term side effects associated with the Oxford–AstraZeneca COVID-19 vaccine among people who received the first dose at King Abdullah bin Abdulaziz University Hospital (KAAUH), Riyadh, Saudi Arabia. A special focus was on gender differences in the reported side effects after the first dose of the vaccine.

Materials and Methods

Study design

This cross-sectional study was performed using a telephone-based survey of individuals who received the first dose of the Oxford–AstraZeneca COVID-19 vaccine at KAAUH, Riyadh, Saudi Arabia.

Study participants

This study targeted all individuals who received Oxford–AstraZeneca COVID-19 vaccine at KAAUH from February 28 to March 12, 2021. Two of the authors contacted the vaccine recipients on day three post-vaccination and invited them to participate in the survey. Individuals were contacted using the hospital telephone number. The objectives of the study and the expected outcomes were explained to the target individuals.

Study tool

A survey was developed for the purpose of the study that consisted of two domains. The first domain involved demographic characteristics such as age, weight, height, gender, co-morbid conditions, and previous exposure to COVID-19 disease. The second domain included information about the symptoms experienced after getting the COVID-19 vaccine. The symptoms listed in the survey included fever, sore through, myalgia, eye muscle pain, loss of smell or taste, shortness of breath, headache, numbness, palpitation, gastrointestinal symptoms, anaphylaxis, and thrombotic events. Additionally, the participants could add any other symptoms, not mentioned above, in the provided space. The participants were also asked to describe the severity of each symptom in the first three days after receiving the vaccine. The severity of symptoms was rated as mild, moderate, or severe. The onset and duration of the side effects, and whether symptoms that can be monitored by painkillers were relieved, were also included in the second domain. A physician and a clinical pharmacist checked the content and the construct validity of the survey. The survey underwent face validity with five vaccine recipients.

Ethical considerations

This study received ethical approval from KAUUH Institutional Review Board (IRB Log #: H-01-R-059). The aim of the study and expected outcomes were communicated to the participants. Participants gave their consent in an electronic form before taking part in the study. Participants were informed that their involvement in the study is voluntary and they could withdraw from the study at any time, and this would not affect their relationship with KAAUH. Additionally, participants were also informed about the confidentially of the data collected, and anonymous presentation of the information gathered.

Statistical analysis

Data analysis was carried out using Statistical Package for Social Sciences (IBM SPSS – version 24). Categorical data were described using frequencies and percentages and compared using the chi-square test or Fisher's Exact test as appropriate. Continuous data were presented as mean with standard deviation and compared using t-test after checking the normal distribution behavior of the data. A significance level of 95% (P-value < 0.05) was assumed in this study.

Results and Discussion

Participants' characteristics

The study included 528 male and female participants. Their characteristics are presented in **(Table 1)**.

Table 1. Baseline characteristics of the participants (N = 528)

Characteristics	Male (N=263)	Female (N=265)	P-Value
Age in years, mean (SD)	43 (11.9)	37 (13.5)	0.00
BMI, n (%)			
Under weight	10 (4.3)	19 (7.5)	0.73
Normal weight	78 (33.3)	104 (41.3)	
Over weight	75 (32.1)	68 (27)	
Obese	71 (30.3)	61 (24.2)	
Previous COVID-19 infection, n (%)	21 (8)	15 (5.7)	0.28
Comorbidities, n (%)			
Heart disease	7 (2.7)	6 (2.3)	0.768
Immune disease	0 (0)	4 (1.5)	0.045
Lung Disease	9 (3.4)	21 (7.9)	0.025
Hypertension	22 (8.4)	24 (9.1)	0.77
Diabetes mellitus	22 (8.4)	15 (5.7)	0.22
No comorbidities, n (%)	218 (82.9)	212 (80)	0.39

Abbreviations: SD: Standard Deviation; BMI: Body Mass Index

Reported side effects during the three days post-vaccination

Participants were asked about the side effects they experienced during days 1, 2, and 3 after the vaccination. Responses to this section are presented in **(Table 2)**. No anaphylaxis or thrombotic events were reported during the study period.

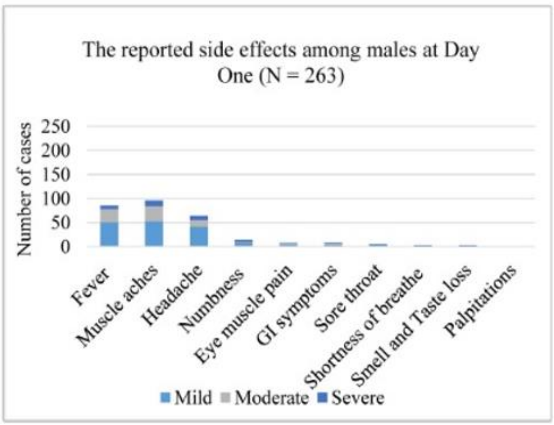
Table 2. Side effects of COVID-19 vaccine reported within three days after receiving the first dose (N = 528)

Side Effects after vaccination	Male (N = 263)	Female (N = 265)	P-value
Day One, n (%)			
Myalgia	96 (36.5)	167 (63)	0.000
Fever	85 (32.3)	137 (51.7)	0.00
Headache	64 (24.3)	147 (55.5)	0.00
Numbness	14 (5.3)	31 (11.7)	0.009
Gastrointestinal	8 (3)	14 (5.3)	0.19
Sore throat	5 (1.9)	17 (6.4)	0.009
Eye muscle pain	8 (3)	25 (9.4)	0.002
Smell and taste loss	1 (0.4)	3 (1.1)	0.57
Shortness of breath	3 (1.1)	20 (7.5)	0.00
Palpitation	1 (0.4)	24 (9.1)	0.00
Day Two, n (%)			
Myalgia	74 (28.1)	142 (53.6)	0.000
Fever	58 (22.1)	107 (40.4)	0.00
Headache	39 (14.8)	115 (43.4)	0.00
Numbness	8 (3)	19 (7.2)	0.03
Gastrointestinal	8 (3)	13 (4.9)	0.27
Sore throat	5 (1.9)	13 (4.9)	0.057
Eye muscle pain	6 (2.3)	26 (9.8)	0.00
Smell and Taste Loss	4 (1.5)	3 (1.1)	0.69
Shortness of breath	4 (1.5)	11 (4.2)	0.069
Palpitation	16 (6)	20 (3.8)	0.007
Day Three, n (%)			
Myalgia	30 (11.4)	66 (24.9)	0.00
Fever	11 (4.2)	38 (14.3)	0.00
Headache	19 (7.2)	54 (20)	0.00
Numbness	5 (1.9)	4 (1.5)	0.25
Gastrointestinal	6 (2.3)	10 (3.8)	0.3
Sore throat	5 (1.9)	6 (2.3)	0.7
Eye muscle pain	3 (1.1)	9 (3.4)	0.082
Smell and taste loss	2 (0.8)	0(0)	NA*
Shortness of breath	4 (1.5)	7 (2.6)	0.36
Palpitation	2 (0.8)	12 (4.5)	0.007

Comparison between the two groups is based on the Chi-square or Fisher's Exact test as appropriate

*NA: the test is not applicable

The severity of the side effects (mild, moderate, or severe) was also investigated. Differences between males and females in the severity of the reported side effects are presented in **(Figure 1)**.



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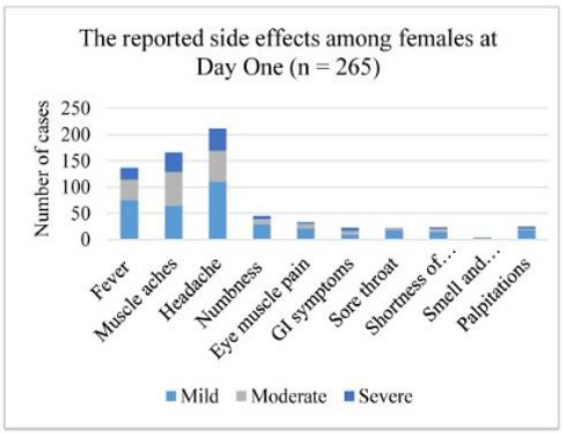

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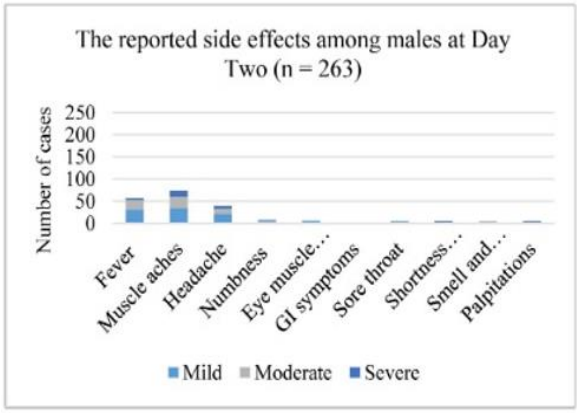

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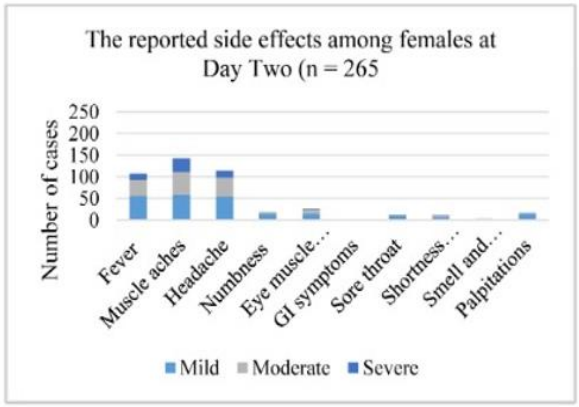

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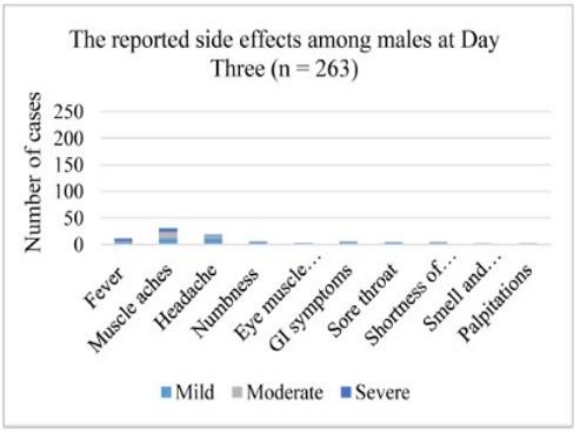

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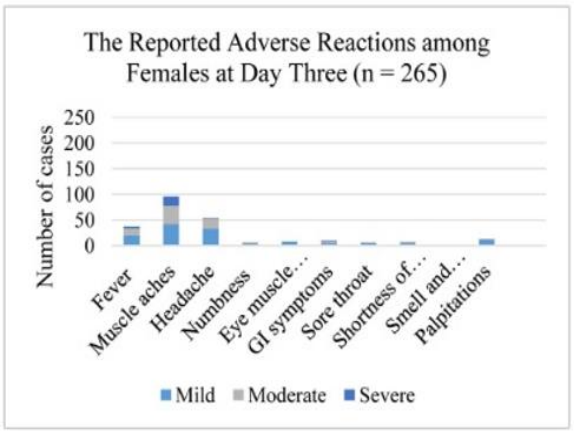

f)

Figure 1. Differences between males and females in the severity of the reported side effects.

Onset and duration of the reported side effects

Participants were asked about the average time their symptoms started and the duration the symptoms persisted. Additionally, participants were asked whether using a pain killer resolved the symptoms that can be managed by the pain killers. The results of this section are illustrated in **(Table 3)**.

Table 3. Reports on the onset and duration of the side effects, and whether symptoms were resolved by pain killers

Variable	Male (N=263)	Female (N=265)	P-value
Onset of the Side Effects in hours, mean (±SD)	15 (14)	12.4 (10.5)	0.037
Duration of the Side Effects in hours, mean (±SD)	31.5 (16.7)	35.8 (18)	0.35
Reported symptoms relieve upon the use of painkillers, n (%)	5 (1.9)	8 (3)	0.5
Possible symptoms relieve upon the use of painkillers, n (%)	9 (3.4)	17 (6.5)	0.1581
Did not use painkillers, n (%)	95 (36.1)	43 (16.3)	0.0001
Did not report symptoms relieve upon the use of painkillers, n (%)	154 (58.6)	197 (74.1)	0.0003

Abbreviations: SD, Standard Deviation

The current study aimed at investigating the short-term side effects associated with Oxford–AstraZeneca COVID-19 vaccine among individuals who received the first dose at KAAUH in Saudi Arabia. A special focus was on the gender-related differences in the reported side effects.

The study included 528 participants, of whom 49.8% (n = 263) were males. At baseline, findings show no statistically significant differences between males and females in the majority of characteristics. However, statistically significant difference was observed for age (p-value = 0.000), immune diseases (p-value = 0.045), and lung diseases (p-value = 0.025).

The reported side effects included fever, sore throat, myalgia, eye muscle pain, smell or taste loss, shortness of breath, headache, numbness, palpitation, and gastrointestinal symptoms. Females reported more side effects compared to males. The types of side effects after receiving the vaccine were common and consistent with other studies that found myalgia, headache, gastrointestinal symptoms, and fever among the commonly reported side effects [5-7]. Approximately half of the females experienced the side effects within the first two days, compared to approximately one-fifth of males. The study included 528 participants, of whom 49.8% (n = 263) were males. The reported side effects among all participants during the first day included myalgia (49.8%), fever (42%), headache (40%), numbness (8.5%), eye muscle pain (6.3%), palpitations (4.7%), shortness of breath (4.4%), sore throat (4.2%), gastrointestinal symptoms (4.2%), and smell or taste loss (1%). No anaphylaxis or thrombotic events were reported during the study period. Females reported more side effects compared to

males. There were statistically significant differences between the two genders in side effects reported during the first day, which included myalgia (63% vs 36.5%, p-value = 0.000), fever (51.7% vs 32.3%, p-value = 0.000), headache (55.5% vs 24.3%, p-value = 0.000), numbness (11.7% vs 5.3%, p-value = 0.009), sore throat (6.4% vs 1.9%, p-value = 0.009), eye muscle pain (9.4% vs 3%, p-value = 0.002), shortness of breath (7.5% vs 1.1%, p-value = 0.000), and palpitation (9.1% vs 0.4%, p-value = 0.000). The same side effects showed significant differences on day two. Gastrointestinal symptoms and smell and taste loss were not significantly different according to gender. Overall, the occurrence of the side effects showed a decrease between both groups on the second and the third day as presented in **(Figure 1)**.

A significant difference was noted in using analgesia to relieve symptoms after vaccination; the majority of female respondents appeared to have more symptoms and more use of painkillers, contrasting male respondents. This is in line with the observations of Raftery *et al.* [13] on gender disparities and pain treatment, in which women were more likely than men to use analgesia. Concerning the onset of the side effects, females developed symptoms more rapidly than males with a P-value of 0.037.

Mild to moderate severities were also noted with the above-mentioned side effects [14]. The severity of myalgia and headache was reported more with females than males. Palpitation severity remained high with females until the third day, yet other symptoms' severities were converging. The difference in severity might be associated with gender-related factors observed with others. Studies propose that females' perception of pain is mostly higher than males due to psychosocial factors e.g. gender roles beliefs, coping strategies, or biological factors such as sex hormones. Further, the prevalence of chronic pain conditions among females is higher than males [15, 16]. This is also in line with our findings, in which males exhibited less severe symptoms and had less use of painkillers. Nevertheless, further research is needed to support observations of gender-related factors and symptoms reporting.

Conclusion

The reported side effects were common but not serious. Female respondents appeared to have more COVID-19 vaccine-associated symptoms.

Limitations

The study had some limitations. Participants were liable for recall bias when responding to the survey on the third day after receiving the vaccine, which influences the accurate retrieving of events. Using the subjective scale to determine the severity of symptoms e.g. *mild, moderate, or severe* rather than using an objective criterion may have created variation in participants' responses. Additionally, the sample of this study was collected from one site KAAUH. Hence, the findings might not be generalized to other contexts. Additionally, the presence of some confounders might affect the interpretation of the results.

Acknowledgments: This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fast-track Research Funding Program.

Conflict of interest: None

Financial support: This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fast-track Research Funding Program.

Ethics statement: The study involved an informed consent from where participants received information about the study. Participants gave their consent in an electronic form before taking part in the study.

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