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Adverse Drug Reaction due to Covisheild Vaccine for Covid-19: A Longitudinal Observational Study

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ABSTRACT

Background: *In order to acquire defense quickly and effectively to the COVID-19 pandemic, a broad range of candidate COVID-19 vaccines are being investigated globally using various technologies and platforms. This study aims in evaluating the safety of Covishield vaccine through assessment of adverse drug reactions development among the participants enrolled in our institution.*

Methodology: *Institution-based, longitudinal observational study in a survey design pattern among health care professional who took Covisheild vaccine. We chose subjects who were from medical background, healthy and young without any comorbidities or negative social habits. The data were collected after 4th day of vaccine using a Google forms.*

Results and Discussion: *124 participants with a mean age of 20.75 (±1.596) reported ADR that occurred within 2 hours, through Google form. Out of total 210 ADRs, the injection site pain (50%) was the highest, followed by headache (29.03%), tiredness (18.55%). Reactions occurred after 2hours were 532. Fever (70.97%) was the predominant one followed by headache (69.35%), injection site pain (58.87%).They reported 58.15% moderate and 4.85% severe in nature. 62.5% Fever was intermittent and remaining were continuous. The status of ADR showed 82.26% recovered and remaining were in the stage of recovery. Assessment by Naranjo's scale revealed that 97.14% of < 2hours and 97% of > 2 hours adverse drug reactions as probable. The assessment by WHO-UMC scale revealed that 87.6% of < 2hours and 88.53% of > 2 hours adverse drug reactions were categorized as Certain, 12.4% and 11.46 % were likely/probable.*

Conclusion: *Acceptance of a COVID-19 vaccine was highly influenced by the safety of the vaccine and its effect. The ADR like fever, chills etc are common in vaccination which is normal, harmless and possibly helpful in immunity boost ups.*

Keywords: Covisheild, ADR, Vaccine, COVID-19

INTRODUCTION

In order to acquire defense quickly and effectively to the COVID-19 pandemic, a broad range of candidate for COVID-19 vaccines are being investigated globally using various technologies and platforms. These include various types of vaccine like viral-vectored, protein subunit, nucleic acid (DNA, RNA), live attenuated and inactivated vaccines. Some of these developments have entered clinical trials [1].

Despite the global spread of the virus, a large proportion of population in several countries is thought to have thus far escaped infection and remains non-immune to SARS-CoV-2 [2].

Vaccines could play a crucial role in increasing population immunity, preventing severe disease, and reducing the ongoing health crisis. In response, rapid global efforts to discover develop and test vaccines against SARS-CoV-2

have led to an unprecedented number of candidate vaccines starting clinical trials during 2020. Currently, 48 vaccines are under clinical evaluation worldwide [3].

In India vaccines under trial are COVAXIN, Covishield, ZyCoV-D, Sputinik, Biological E's novel Covid-19 vaccine. Covishield, is a vaccine developed in the Serum Institute of India (SII) and ICMR are jointly conducting a Phase II/III, Observer-Blind, Randomized, Controlled Study to Determine the Safety and Immunogenicity of Covishield (COVID-19 Vaccine). DCGI regulatory authorities have approved status for vaccine. It is targeted for healthy human volunteers. Covishield (SII-ChAdOx1 nCoV-19) is administered as 2 dose schedules on days 1 and 29 as 0.5 ml dose intramuscularly.

This vaccine is to be administered for volunteers who meet all inclusion criteria including age 18 to 99 years, both genders, written informed consent by participants, participant is resident of the study area and is willing to comply with study protocol requirements, healthy as determined by medical history and physical examination, female participants of childbearing potential must have a negative urine pregnancy test within 24 hours prior to study vaccine administration [1].

The main challenge of immunization program in India is fear and concern among the population regarding the safety and efficacy of vaccines. It is curbed by the medical experts through rigorous monitoring of adverse event following Immunization (AEFI). Vaccine pharmacovigilance plays important role to assess the adverse drug reactions among immunized participants. This study aims in evaluating the safety of Covishield vaccine through assessment of adverse drug reactions development among the participants enrolled in our institution.

MATERIALS AND METHODS

Study Design and Study Settings

It is a Longitudinal observational institution-based study based on online survey among health care professionals who took Covisheild vaccine. Healthy and young population from medical background was selected for the study and the data were collected after 4th day of vaccine using a Google forms. The major objectives were to find out the occurrence of vaccine ADR, to assess the severity, preventability and causality with outcome.

Ethics, Privacy and Confidentiality

The exposure happened and the adverse effects were asked using an online questionnaire. There was no risk for participants who involved in the study and a prior inform consent form were obtained. The data collected were solely accessible to the investigators and assured that all provided information's would be used for research purpose with strict confidentiality.

Subject Recruitment and Study Participants

The study included all medical professionals who got 1st shot of Covisheild vaccine without any comorbidities and social habits like alcoholism and smoking. The study collected information about registered participants for vaccination, explained about the study and identified the potential candidates with proper inclusion criteria and e-mailed the Google form. A total of 720 participants were vaccinated in the 1st phase in the hospital under study and 124 subjects were selected based on consent, inclusion and exclusion criteria.

Survey Questionnaire and Data Collection

A predesigned, structured, pretested questionnaire containing specific questions regarding the ADR was prepared by reviewing the available information of vaccine. The questionnaire was divided

into two sections: inform consent section and question section which contains age, sex, weight, height, date of vaccination, ADR occurred <2 hours (hrs) and >2hrs, social habits, severity of fever and ADR, Type of fever and outcome. Also, the management and day of onset of reaction

Data Analysis

All statistical analysis was done using SPSS software. Frequency, percentage, means, Standard deviations were evaluated. Causality, severity, and preventability were analyzed using various scales like WHO-UMC, Naranjo, Schumock and Thronton scale *etc*.

RESULTS

A total of 124 participants were enrolled in the study with a mean age of 20.75(±1.596) in which 119 (95.98%) were females and rest of them were males. The mean BMI of participants was 19. With a standard deviation of ±2.81. Majority of participants resided in normal weight category (60.48%) followed by underweight (35.485) (Table 1).

Table 1: Distribution of BMI

Particulars I	Particulars II	Frequency (%)
Under weight (<18.5)	Very severely underweight (<16)	6 (4.84%)
	Severely underweight (16-16.9)	14 (11.29%)
	Under weight (17-18.4)	24 (19.35%)
Normal weight (18.5-24.9)		75 (60.48%)
Over weight (≥25)	Overweight (25-29.9)	5 (4.03%)
	Obese class I, II, III (≥30)	0

Majority of the participants were non vegetarians (79.8%) and rest 20.2% were vegetarians. 9.68% of the population were previously diagnosed with COVID-19 and every participant reported at least one ADR. Most of the ADR occurred on the 1st day (64.52%) and 2nd day (33.06%) (Table 2).

Table 2: Dietary habits, Previous diagnose to COVID-19 and Day of Onset of reaction

Dietary habit	
Vegetarians	25(20.2%)
Non vegetarians	99(79.8%)
Diagnosed with covid-19 previously	
Yes	12(9.68%)
No	112(90.32%)
Day of onset of ADR post vaccination	
1st day	80(64.52%)
2nd day	41(33.06%)
3rd day	3(2.42%)

The reactions reported by the participants were classified as occurred within 2 hours were 210 in number, out of which injection site pain (50%) was the highest, followed by headache (29.03%), tiredness (18.55%), fever (16.13%), body ache (16.13%) and chills (5.64%). The number of reactions that occurred after 2 hours were 532 in 124 patients. Which were observed as Fever (70.97%), the predominant one followed by headache (69.35%) and injection site pain (58.87%) (Table 3).

Table 3: Distribution of ADR

ADR	Frequency (Percentage)	Frequency (Percentage)
	< 2hrs	< 2hrs
Fever	20(16.13%)	88(70.97%)
Chills	7(5.64%)	30(24.19%)
Tiredness	23(18.55%)	64(51.61%)
Headache	36(29.03%)	86(69.35%)
Injection site swelling	2(1.61%)	9(7.25%)
Injection site Pain	62(50%)	73(58.87%)
Redness	1(0.806%)	1(0.806%)
Rashes	1(0.806%)	1(0.806%)
Injection site Itching	1(0.806%)	2(1.61%)
Stiffness of upper arm	9(7.25%)	15(12.09%)
Weakness in injected arm	13(10.48%)	16(12.90%)
Body ache	20(16.13%)	70(56.45%)
Nausea	5(4.03%)	21(16.93%)
Vomiting	0	12(9.68%)
Urticaria	1(0.806%)	1(0.806%)
Myalgia	3(2.42%)	9(7.26%)
Diarrhea	2(1.61%)	3(2.42%)
Difficulty in breathing	0	3(2.42%)
Increase heart rate and BP	1(0.806%)	4(3.2%)
Dizziness	0	11(8.87%)
Fatigue	1(0.806%)	6(4.84%)
Giddiness	1(0.806%)	2(1.61%)
Cold peripherals	1(0.806%)	0
Sweating and shivering	0	1(0.806%)
Back Pain	0	3(2.42%)
Loss of appetite	0	1(0.80650
Total ADR	210	532

All ADR were managed symptomatically with drugs and 13 participants presented to same institution due severe nature of ADR. A total of 96 (77.42%) participants had fever which were reported either in < 2hrs or > 2hrs. In the view of participants, most of the ADR that occurred were of moderate (58.15) type. Only about 4.85% of ADR were found to be of severe in nature. In case of fever 62.5% reported that the nature of fever was intermittent and remaining were continuous. Most of the fever were classified under mild/ low grade fever (34.7%) followed by moderate category (33.1%). The status of ADR showed 82.26% were recovered and remaining was in the stage of recovering (Table 4).

Table 4: Characteristics of ADR, Fever and Outcome

Severity of ADR reported by the participant (n=124)	
Mild	46(37.1%)
Moderate	72(58.1%)
Severe	6(4.8%)
Severity of Fever (n=124)	
No fever	28(22.6%)

Mild/low grade fever- 38.1-39 degree	43(34.7%)
Moderate grade fever- 39.1-40 degree	41(33.1%)
High grade fever- 40.1-41 degree	12(9.75)
Type of fever (n=96)	
Intermittent	60(62.5%)
Continuous	36(37.5%)
Status/Outcome of ADR (n=124)	
Recovered (Hospitalized - 7)	102(82.26%)
Recovering (Hospitalized - 6)	22(17.74%)

Causality assessment of ADRs for both less than and greater than 2hours were done by using both Naranjo's causality assessment and WHO-UMC scale. Assessment by Naranjo's scale revealed that 97.14% and 97% adverse drug reactions as probable, remaining were found to be possible. The assessment by WHO-UMC scale revealed that 87.6% and 88.53% adverse drug reactions can be categorized as certain, 12.4% and 11.46 % were likely/probable. Severity assessment by using Modified Hartwig and Seigel scale stated that 50.47% and 35.15% were Mild level 1 reaction. 37.17% and 56.06% were under moderate level 3. Preventability assessment was based on Schumock and Thronton scale and showed that majority were definitely preventable (95.24% & 92.3%) (Table 5).

Table 5: Causality, Severity, preventability of ADR <2hours and > 2hours

Particulars		**<2hours (n=210)**	**>2hours (n=532)**
Causality Assessment using WHO-UMC			
Certain		184(87.6%)	471(88.53%)
Likely/probable		26(12.4%)	61(11.46%)
Causality assessment using Naranjo scale			
Probable		204(97.14%)	516(97%)
Possible		6(2.86%)	16(3%)
Severity assessment Modified Hartwig and Seigel			
Mild	Level 1	106(50.47%)	187(35.15%)
	Level 2	0	0
Moderate	Level 3	78(37.14%)	298(56.01%)
	Level 4a	14(6.67%)	27(5.07%)
	Level 4b	5(2.38%)	7(1.31%)
Severe	Level 5	7(3.34%)	13(2.44%)
	Level 6	0	0
	Level 7	0	0
Preventability assessment by Schumock and Thronton scale			
Not preventable		1(0.48%)	5(0.94%)
Probably preventable		9(4.28%)	36(6.8%)
Definitely preventable		200(95.24%)	491(92.3%)

DISCUSSION

A total of 124 participants were enrolled in the study, all were young adults of mean age 20.75 years and were healthy participants without any co morbidities. Assessing the body mass index indicated that majority were in the normal weight category. Most of the participants were female due to higher involvements of females in medical field who were

allocated in first phase of vaccination program.

The alterations in effect of vaccine depending on the previous COVID19 disease exposure resulted in 9.62% registered cases. The adverse events reported were assessed for its onset and most of the participants reported onset within the day on within first day of vaccine administration. When the vaccine is injected into a patient, it prompts the immune system to generate antibodies for protection against corona virus. The distribution of ADR was commonly seen among the enrolled participants with the highest as fever followed by chills, tiredness, headache, fatigue, vomiting etc which is the same as the ADR reported in various other articles so far. The rare ADR reported were urticaria, increased blood pressure and cold peripheries.

The time of ADR onset was categorized as within 2hours and after 2 hours. Some participants report their ADR onset within 2 hours and also after 2 hours therefore the duplication is considered while calculating the results. Since fever was the most frequent ADR reported there were participants reporting it within 2 hours and continuing to after 2 hours. Severities of ADR reported by the participants were categorized as mild, moderate, and severe. Most of the participants showed moderate level of the ADR.

This classification was made as per the adverse events classification of immunization program. Among the fever reported it was observed that the mild to low grade fever was very common. While further assessing the type of fever it was intermittent fever common than continuous fever. Intermittent fever was the temperature which was elevated but falls to normal (37.2°C or below) each day. Continuous or sustained fever is usually not associated with true chills or rigors [4].

While looking into the outcome of the ADR in population it was observed that most of the subjects recovered from casualty on their own and few are at recovering stage. All the ADR reported in the participants were manageable symptomatically with drugs like antipyretics, analgesics, anti-emetics and anti-histamines.

The causality assessed has reported to be mostly probable by Naranjo scale and certain by WHO-UMC scale. This emphasis the occurrence of these reported ADR to be common and predictable. Naranjo's causality assessment scale consists of 10 questions addressing different issues related to alleged adverse drug reactions, which can be answered with 'yes,' 'no' or 'do not know.

Scores are attached to the answers, and these scores result in a cumulative value, which can be translated into a causality category. Questions are weighed, with the total at the end of the question categorizing the adverse event as a definite ($\geq$9), probable (5-8), possible (1-4) or doubtful (0) related to the suspected medication. Whereas, causality assessment by WHO-UMC identifies adverse events with the high causal association (probable and certain) with the drug are likely to recur. Thus, providing information on this causal link may be useful in preventing future recurrences [4,5,6].

Modified Hartwig and Siegel Severity Scale is used for severity assessment. Depending upon the severity of the suspected reaction, this scale was divided into 3 categories: mild, moderate, and severe. They also have 7 levels; the 'mild' type reaction level 1 requires no change in treatment with the suspected drug. In level 2 the ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No treatment is required, and there is no increase in the length of stay.

For moderate reactions, level 3; suspected drug should be withheld, discontinued or otherwise changed, and treatment is required, but no increase in the length of hospital stay for these patients. In level 4(a) are level 3 reactions that increase the length of stay by at least one day, and in level 4(b) the ADR is the reason for the hospital admission. In the severe type of ADR, level 5 are reactions which require intensive care unit attention. Level 6; reactions cause permanent harm to the patient, whereas in level 7, ADR leads to the death of the patient either directly or indirectly. The participants in our study are at level 1 and level 3 [4,5,6].

The Schumock and Thornton Preventability scale was used to categorize the ADR into Definitely, Probably and Not preventable. Section 'A' an ADR is definitely preventable if there was a history of allergy or a previous adverse reaction to that drug, or if the drug involved was inappropriate for the patient's clinical condition, or if the drug dose, route, and frequency of administration are inappropriate for the patient's age, weight or disease state. Section B, ADR is considered to be probably preventable if required therapeutic drug monitoring or other necessary tests not performed or if there was a drug interaction or compliance problem, or appropriate preventable measure was not taken, or if the preventative measure is inadequate. Finally, if ADR occurs, even after all necessary prevention, it is considered as 'not preventable.' In this study all the ADRs were definitely preventable [5, 6, 7].

CONCLUSION

Acceptance of a COVID-19 vaccine was highly influenced by the safety of the vaccine and its effect. Preparing the public to accept the vaccine without knowledge of safety and effectiveness may be difficult. The ADR like fever, chills *etc.* are common in vaccination and are to be considered as normal, harmless and possibly helpful to fight the pandemic by boosting the immunity.

Supplementary Materials: Nil

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