SHORT COMMUNICATION

Heterologous COVID-19 vaccines intervention effect on reactogenicity

Wajeha Najeeb[1], Palvasha Waheed[2], Rehana Khadim[3]

Abstract

To determine the change in the occurrence of short-term vaccine reactions on the use of heterologous Covid-19 booster, a single centre short-term study of two months duration was conducted. It was designed as an interventional study with registered clinical trial number # SLCTR/2022/008. It was conducted on medical students and faculty of a National university of medical sciences, Rawalpindi affiliated public sector medical college. A total of 348 individuals were administered with Ad5-nCoV vaccine and 101 with mRNA-1273 vaccine. They all had been previously vaccinated with two doses of BBIBP-CorV. BBIBP-CorV reactogenicity was considered a control group. Vaccine reactions, including pain and redness at the injection site, fever, no observed reactions at all, myalgia, feeling cold, dizziness, paraesthesia in the arm, light-headedness, had a significant change in their frequencies in comparison to homologous vaccine (BBIBP-CorV) reactogenicity. It was concluded that mixing and matching of COVID-19 vaccines result in an increase in frequency of post-vaccine short-term reactions.

Keywords: COVID-19 vaccines, Booster immunisation, Adverse effects.

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Introduction

SARS-CoV-2 infection causes a respiratory disease called Corona-virus disease (COVID-19). World confronted the most noteworthy test of the century when, at the end of 2019, this illness emerged as a pandemic. It caused significant mortality and morbidity alongside socioeconomic disturbance apparent in the form of the most noticeable and awful lock down of history. Active immunisation has become the cornerstone of global healthcare policies against COVID-19.[1] The first vaccine against SARS-CoV-2 virus was administered in December 2020.[2] Various problems have occurred amid inoculation and preparation of vaccines, including insufficient supply of vaccines in low income countries, atypical adverse reactions on massive administration of some vaccines, and the emergence of new variants which specifically resulted in decreased effectiveness of the available vaccines against COVID-19.[2,3] This led to the idea of mixing-and-matching of vaccines to confront this deadly pandemic vigilantly, i.e., use of heterologous vaccines as booster dose. Literature published in mid-2021, reveals that mixing and matching of vaccines produce robust immune responses, hence exhibiting effectiveness of this strategy. However, this has raised an important question about the reactogenicity due to heterologous vaccine use.

This study was designed to assess the reactogenicity of heterologous COVID-19 vaccines booster dose intervention among participants compared to COVID-19 vaccine reactions of homologous vaccine booster. It also intended to analyse frequencies of any change in most common vaccination reactions among participants due to mixing and matching of COVID-19 vaccines.

Patients/Methods and Results

This study was designed as interventional study conducted on medical students and faculty of National university of medical sciences, Rawalpindi affiliated public sector medical college. It was registered in ICTRP clinical trial registry with trial number of SLCTR/2022/008. The duration of the study was two months, from March 2022 to April 2022.

Participants were randomly allotted into two groups. Group-I consisted of participants with BBIBP-CorV as initial vaccination dose and first booster dose, and Ad5-nCoV as second booster dose. Group-II consisted of participants with BBIBP-CorV as initial vaccination dose and first booster dose, and mRNA-1273 as second booster dose.

Inclusion criteria was: participants above 18 years, healthy or having stable chronic medical conditions like asthma, stable HIV, hepatitis B or C virus infection.

Exclusion criteria consisted of participants with vaccination other than BBIBP-CorV as initial and first booster dose, who had not received the first two doses from the same vaccination centre, i.e. from the public sector medical college, or whose record of last two doses was missing. Those with duration of less than six months between two

[1]Pakistan Institute of Medical Sciences, Islamabad, Pakistan; [2]Army Medical College, National University of Medical Sciences, Rawalpindi, Pakistan; [3]Army Medical College, Rawalpindi, Pakistan.

Correspondence: Rehana Khadim. e-mail: dr.rehana.butt@gmail.com

ORCID ID. 0000-0002-9089-9691

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boosters, history of pregnancy, flu or cough at the time of trial, COVID-19 active infection, on immuno-suppressive therapy were also not included.

Primary outcomes included fever, myalgia, pain and redness at the injection site, feeling cold, dizziness, paraesthesia in the arm, light-headedness, anaphylactic reaction, dyspnoea, tachycardia, and no reaction at all. No secondary outcome was monitored.

After enrollment, detailed demographic evaluation along with general physical examination of all participants was done. As the study cohort was related to medical profession they all knew their symptoms very well and a detailed history of their previous vaccine reactions was noted down. These histories and records were used as an indicator of the inherent ability of vaccine reactions. It was later on used for comparative analysis with heterologous reactions as a control-group in both the groups. Participants were not aware of which COVID-19 vaccine was administered as second booster dose, also whether it was homologous (similar to their previously received vaccine) or heterologous. Vaccines were given intramuscularly in deltoids with 0.5 ml Ad5-nCoV and 0.25 ml mRNA-1273 vaccine. Site staffs who were injecting the vaccines and the medical officer on duty were also blinded. Vaccination centre was a well-equipped facility. A medical specialist was also present at the time of intervention, to deal with any immediate severe reaction and to entertain mild complaints in the post vaccination period. A well-equipped ambulance facility and 24-hour tertiary care hospital facility were also made available. The participants were kept under observation after vaccination. Participants' reactogenicity data form was filled seven days after the vaccination.

Statistical Package for Social Sciences (SPSS) version 25.0 was used for data analysis. The qualitative variables were summarised as frequency and percentages. Chi-square test and Fisher exact test was applied. The p-value ≤ to 0.05 was considered significant.

Our study participants were divided into two groups. Group-I consisted of 348 subjects—182 (52.3%) males and 166 (47.7%) females with mean age of 20.45±1.116 years. Group-II had a total of 101 participants—22 (21.8%) males and 79 (78.2%) females with mean age of 21.88± 4.070 years.

The reactogenicity observed in Group-I is mentioned in Table-1. The most frequent vaccine reaction in Group-I was "Pain at injection site". Higher frequencies were observed in Ad5-nCoV vaccine reactions in comparison to BBIBP-CorV, for pain at injection site, fever, myalgia, feeling cold, dizziness, paraesthesia, light headedness, dyspnoea, and tachycardia. It was seen that vaccine reactions like "No reactions" and anaphylactic reaction manifested lower frequency for Ad5-nCoV vaccine. These observed changes in reactogenicity among both vaccines of Group-I, was statistically significant, as described in Table-1. No unexpected complication was seen during the study in this group.

In Group-II, mRNA-127 was administered in participants with previous homologous BBIBP-CorV booster vaccine intervention. It was seen that the most common reaction in this group was also "Pain at injection site". Frequencies of reactions in mRNA-127 were seen to be increased in the following categories: pain at injection site, fever, myalgia, feeling cold, dizziness, paraesthesia, light headedness and tachycardia. In Group-II there was no reported anaphylactic reaction and complaint of dyspnoea for both vaccines. Fewer participants reported "No reaction" with mRNA-1273 vaccine. These changes in reactogenicity among vaccines in Group-II were observed to be statistically significant in the aforementioned categories. They were pain at injection site, fever, myalgia, feeling cold, dizziness and paraesthesia.

Table-1: BBIBP-CorV and Ad5-nCoV Reactogenicity in Group-I (n=348).

Post Vaccine Short Term Reactions	BBIBP-CorV Vaccine Reactions n (%)	Ad5-nCoV Vaccine Reactions n (%)	*p*-value
Pain at injection site	142 (40.8)	159 (45.7)	<0.001
Fever	127(36.5)	151 (43.4)	<0.001
No reaction	117 (33.6)	111(31.9)	<0.001
Myalgia	39 (11.2)	60 (17.2)	<0.001
Feeling cold	35 (10.1)	92 (26.4)	0.001
Dizziness	34 (9.8)	62 (17.8)	<0.001
Paraesthesia in arm	15 (4.3)	32 (9.2)	0.007
Light-headedness	14 (4)	39 (11.2)	<0.001
Anaphylactic Reaction	11 (3.2)	9 (2.6)	0.002
Dyspnoea	7(2%)	13(3.7)	0.001
Tachycardia	2 (0.6%)	19 (5.5)	1.000

Table-2: BBIBP-CorV AND mRNA-1273 Reactogenicity in Group-II (n=101).

Post Vaccine Short Term Reactions	BBIBP-CorV Vaccine Reactions n (%)	mRNA-1273 Vaccine Reactions n (%)	*p*-value
Pain at injection site	44 (43.6)	55 (55.4)	<0.001
Fever	31 (30.7)	40 (39.6)	<0.001
No reaction	39 (38.6)	26 (25.7)	<0.001
Myalgia	7 (6.9)	13 (12.9)	0.005
Feeling cold	5 (5)	10 (9.9)	0.075
Dizziness	6 (5.9)	19 (18.8)	0.011
Paraesthesia in arm	3 (3)	18 (17.8)	0.081
Light-headedness	1 (1)	3 (2.9)	0.030
Anaphylactic reaction	-	-	-
Dyspnoea	-	-	-
Tachycardia	1 (1)	2 (2)	-

The change was not statistically significant in categories like light-headedness, anaphylactic reaction, dyspnoea, and tachycardia, i.e. $p>0.05$ (Table-2).

Discussion

Short-term reactions related to the administration of heterologous COVID-19 vaccines was the main query of the study as safety of heterologous vaccine use was declared.[4] Findings indicate, that on the use of heterologous vaccine a notable increase in reactogenicity was observed.

A study similar to the present study, also reported reactogenicity of AstraZeneca (ChAdOx1 nCoV19) as prime and booster vaccine in one group and ChAdOx1 nCoV19 as prime and BNT162b2 booster vaccine in second group.[5] Common vaccine reactions in both the studies were pain at injection site, myalgia, and fever. In homologous vaccine use, the percentage of pain at injection site, fever, and myalgia were 51%, 25%, and 15%, respectively and on heterologous vaccine use it was 80%, 23%, and 25%, respectively. In the present study, in Group-I, on homologous vaccine use, pain at injection site, fever, myalgia with proportion of 40.8%, 36.5%, and 11.2%, respectively was noted. In contrast, on heterologous vaccine use similar reactions reported percentages of 45.7%, 43.4%, and 17.2%, respectively. The reactions they reported, which were not in our study, were headache, arthralgias, nausea, and vomiting. The findings in this study are similar to ours as they also reported a marked increase in reactogenicity on heterologous vaccine use.[5]

Findings of the study met our expectation and our hypothesis that if robust cellular and humoral response[3] and high antibody titres[6] are measured due to heterologous COVID-19 vaccines, there would be a noticeable increase in short- term vaccine reactions. Greater duration of interval between two booster doses also caused higher peaks of antibody titers.[3] Studies also report that longer duration of effective antibody titre occurs in response to heterologous vaccine use.[7] The literature is divided in two groups regarding reactogenicity due to mixing and matching of COVID-19 vaccines. One that declared that there was no significant difference in frequency and severity vaccine reactions in their study in comparison to homologous vaccine intervention.[3] The second group claimed that there was a marked difference of reactogenicity between heterologous vaccine intervention and homologous vaccines.[8] Our trial results supported the second group. In addition, many recent studies reported findings similar to the current study.[9,10]

The present study had a few limitations, as it had a small sample size. The duration of interval was longer between homologous and heterologous booster dose intervention which might have been the cause of noticeable reactogenicity. Most of the study participants were of young age group, i.e. between 18 to 35 years. No human variations were present but there was absence of an active control group. The post vaccination observation period was also short.

It is recommended that studies should be carried out to evaluate reactogenicity in age groups younger than 18 years and over 55 years and to see the effects of heterologous vaccine intervention on long-term vaccine reactions. Use of other vaccines, specifically of different vaccine groups must be considered for heterologous intervention trial for both long-term and short-term vaccine reactions.

Conclusion

The frequencies of short-term vaccine reactions were noted to be increasing. A decreasing trend was noted in the percentage and frequency of participants with no reaction on heterologous intervention to homologous intervention. This indicates a significant evidence of change in reactogencity on heterologous vaccines use.

Patients Consent: Informed consent was taken from all patients to publish this study.

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Author Contribution:

WN: Design the study, acquiring data, analysis, drafting work, final approval, accountable for all the work.
PW: Design the study, acquiring data, analysis, drafting work, final approval, accountable for all the work.
RK: Design the study, acquiring data, analysis, drafting work, final approval, accountable for all the work.