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Link between COVID-19 vaccines and myocardial infarction

Zafar U *et al.* COVID-19 vaccines and myocardial infarction

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Abstract**BACKGROUND**

Vaccines for coronavirus disease 2019 (COVID-19) include ChAdOx1-SARS-COV-2 (AstraZeneca), Ad26.COV2.S (Janssen), mRNA-1273 (Moderna), BNT162b2 (Pfizer), BBIBP-CorV (Sinopharm), CoronaVac (Sinovac), and Bharat Biotech BBV152 (Covaxin).

AIM

This article focuses on finding the association between COVID-19 vaccines and myocardial infarction (MI).

METHODS

This is a systematic review, which involves searching databases such as MEDLINE, EMBASE, and PakMediNet after making a search strategy using MeSH and Emtree terms. Eligibility criteria were set, and studies having no mention of MI as a complication of COVID-19 vaccination, protocols, genetic studies, and animal studies were excluded. Data was extracted using a predesigned extraction table, and 29 studies were selected after screening and applying the eligibility criteria.

RESULTS

The majority of studies mentioned AstraZeneca (18 studies) followed by Pfizer (14 studies) and Moderna (9 studies) in subjects reporting MI after vaccination. Out of all the studies, 69% reported MI cases after the first COVID-19 vaccination dose and 14% after the second, 44% reported ST-segment elevation MI, and 26% reported non-ST-segment elevation MI. The mortality rate was 29% after MI.

CONCLUSION

In conclusion, many studies linked MI to COVID-19 vaccinations, but no definitive association could be found.

Key Words: Severe acute respiratory syndrome coronavirus 2 infection; Vaccination; Myocardial infarction; Association; Pfizer; AstraZeneca; Moderna; Sinovac; Janssen; Covaxin

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Core Tip: Although there are reports of myocardial infarction after Covid 19 vaccination yet no definitive link was found in previous literature linking the two.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus). The first case of COVID-19 was reported in Wuhan, China, and rapidly spread to the rest of the world^[1]. The COVID-19 outbreak was declared a pandemic on March 11, 2020^[2]. Although SARS-CoV-2 mainly affects the respiratory tract, it frequently causes cardiac, gastrointestinal, hepatic, nephrological, and central nervous system distress^[3]. It mainly causes nonspecific symptoms like fever, cough, and myalgia; however, in severe cases, it can lead to respiratory failure, septic shock, multi-organ dysfunction, and even death^[4].

COVID-19 treatment is most often general supportive care and nutritional support in addition to respiratory care. However, due to the lack of clinically approved interventions for COVID-19 treatment, attempts have been made for vaccine development to prevent the disease^[3]. As a result, the safety and efficacy of several vaccines have been approved by the World Health Organization. Among these are AstraZeneca/Oxford, Johnson and Johnson/Janssen (JnJ), Moderna, Pfizer/BioNTech, Sinopharm, Sinovac, and the Bharat Biotech BBV152 COVAXIN vaccine^[5]. Vaccines for SARS-CoV-2 have several different mechanisms of action, including: (1) RNA and DNA vaccines that are genetically engineered to produce a protein that warrants an immune response; (2) vector vaccines that introduce a type of virus that cannot produce disease but can effectively generate an immune response; (3) vaccines that use genetically modified viruses to become weaker or inactivated in order not to cause virulence but retain their antigenicity; and (4) harmless fragments of proteins or protein shells with similar antigenicity to the COVID-19 virus that are used in protein-based vaccines to produce immunity^[5].

It is not uncommon to experience side effects following a COVID-19 vaccine. Fatigue, headache, muscle pain, joint pain, chills, fever, generalized body pain and local reaction at the injection site are some of the side effects that have been reported after COVID-19 vaccination^[6]. Several cardiovascular adverse effects have also been reported after COVID-19 vaccination, including myocarditis, pericarditis, and thrombotic events. Additionally, rare cardiovascular events such as hypertension, acute coronary syndrome, stress cardiomyopathy, arrhythmias, and cardiac arrest have also been reported. Although the relationship between these rare events and the vaccination is doubtful, the incidence of these rare side effects post vaccination in the absence of any other obvious cause in otherwise healthy individuals may suggest a causal relationship between the two^[7].

When only focusing on myocardial infarction (MI), it is observed that after a person experiences an MI, there is a 20% chance of mortality in the first year and 10% thereafter^[8]. According to Johansson *et al*^[9] the relative risk of cardiovascular morbidity

and mortality was 30% higher in those who suffered from MI compared to the general population. The aims of this review are to identify the pathophysiological links between MI and COVID-19 vaccination and investigate the doses and frequencies of COVID-19 vaccines, the types of MI, and mortality statistics linked with the vaccine administration in the available literature.

MATERIALS AND METHODS

Databases and search strategy

This systematic review was conducted over a period of six months. The databases searched were MEDLINE, EMBASE, and PakMediNet. MeSH and Emtree terms were used as well as free text words (Table 1) to develop a search strategy. Various concepts were identified and then searched using Boolean operators. "AND" was used to separate various concepts, and synonyms for a single concept were separated by "OR". The data was searched, and studies from the first delivery of COVID-19 vaccines in December 2020 until May 1, 2022, were included.

Eligibility criteria

Articles that mentioned COVID-19 vaccination along with MI as a vaccine complication were included. Case reports, case series, original research, and systematic reviews were also included.

Exclusion criteria

All studies that included COVID-19 cases but had no mention of vaccinations were excluded. Studies with no mention of MI as a complication of a COVID-19 vaccination were also excluded. Protocols and research based on animals and studies mentioning vaccinations for similar diseases, like influenza, were also excluded. Genetic studies involving COVID-19 without mention of vaccination and narrative reviews not identifying a link between MI and COVID-19 vaccination were further excluded (Figure 1).

Data extraction

The data was then extracted from the eligible studies by a structured data extraction form. Two independent researchers were engaged in both screening and data extraction, and data was analyzed for frequencies and percentages.

RESULTS

A total of 56 studies were identified but only 29 were selected after applying the eligibility criteria (Table 2)^[5-7,10-35]. The majority of these were case reports that reported the incidence of MI after COVID-19 vaccination but could not prove any causative relation between the two. They also could not prove whether MI was due to vaccination-related changes in the body.

The majority of side effects reported were from AstraZeneca followed by Pfizer and Moderna vaccines (Figure 2).

Based on the studies included in this report, patients usually suffered from MI after the first dose of the vaccine (69%). Of these studies, 53.3% case reports reported MI within a few hours of vaccine administration, and the rest within 10 d. Out of these patients, 44% of cases reported were of ST-segment elevation MI (STEMI) and 26% were non-ST-segment elevation MI (NSTEMI). The mortality rate was 29% (Figure 3).

Possible mechanisms behind MI that have been identified after the literature review are as follows: (1) Kounis syndrome, which can cause MI through different mechanisms like allergic vasospasm and stent occlusion with a thrombus infiltrated by eosinophils or mast cells; (2) Vaccine-induced thrombotic thrombocytopenia (VITT); (3) Acute coronary syndrome after influenza vaccine administration as both influenza and COVID-19 vaccines share a common excipient (polysorbate 80); (4) Demand-supply mismatch ischemia, which can be caused by the stress of getting the vaccine in elder people with other associated comorbidities; and (5) Myocarditis.

DISCUSSION

Globally, 65.8% of people⁶ have received at least one dose of a COVID-19 vaccine, and 11.79 billion doses have been administered globally^[36]. The doses of various vaccines administered up until May 25, 2022, are as follows: Pfizer, 613 million; Moderna, 147 million; AstraZeneca, 67 million; Janssen, 19 million; Sputnik V, 1.85 million; Sinopharm, 2.31 million; Sinovac, 3737; and Covaxin, 44.² Pakistan has administered at least 248672457 doses of COVID-19 vaccines so far. Assuming that every person needs two doses, that is enough to have vaccinated about 57.4% of the country's population^[37].

MI remains one of the rare complications of a COVID-19 vaccination^[7]. In this review, nearly 69% of the studies reported MI occurrence after the first dose, and 14% reported it after the second. It is a known fact that a subsequent or a booster dose of a vaccine is given to increase the antibody titer. This is especially crucial in those with a weakened immune response due to comorbidities^[38]. A theory based on this finding is that since MI occurrence is higher after the first vaccine dose, immune response probably plays no role or only a minimal role in MI pathophysiology. If MI was due to overstimulation of the immune system, then the frequency of MI after the second dose would be higher.

A study showed that COVID-19 vaccination produces an optimum immune response in chronic inflammatory disease patients on immunosuppressive therapy, and the risk of adverse consequences is not higher than in the normal population^[39].⁵ No single inflammatory biomarker of systemic manifestations of vaccines has been identified but rather a battery of biomarkers, specifically, interleukin-6, C-reactive protein, and the interferon-signaling pathway. A vaccine starts its action within minutes, starting from the injection site and spreading throughout the body. The factors known to affect the reactogenicity of various COVID-19 vaccines are age, gender, psychological/physical stressors, obesity, pre-existing immunity, vaccine characteristics (route, site, and method of vaccine administration), vaccine composition, antigen type, combination, and dose^[40].

According to McManus *et al*^[41] the incidence of STEMI compared to NSTEMI has reduced over the past few years. In the present research, patients with STEMI were

present in 44% of the studies compared to 26% with NSTEMI after COVID-19 vaccination^[41]. A recent case reported STEMI in a post-COVID-19-vaccinated patient in April 2022, and the patient also had a history of myocarditis. A possible explanation was the transient atrial fibrillation or plaque rupture after the myocarditis^[42]. So, myocarditis, on the one hand, is a primary complication of COVID-19 vaccination, and on the other hand, it is a secondary cause of MI development after COVID-19 vaccination.

In his blog, Labos wrote a critique in which he pointed out that in order to state the link between inflammation and MI after COVID-19 vaccination, the inflammatory biomarkers need to be measured before, soon after, and a month after vaccination^[43]. Jabagi *et al*^[10] proved that there was no association between increased risk of MI post Pfizer vaccination for COVID-19. He did a serial analysis one day, one week, and two weeks post vaccination^[10].

Kounis syndrome is one of the mechanisms identified for the occurrence of MI post COVID-19 vaccination as it has been observed in various patients who received a COVID-19 vaccination (Pfizer, AstraZeneca, and Sinovac vaccines)^[5,15]. It manifests as an acute coronary syndrome accompanied by mast cell activation due to hypersensitivity or an allergic or anaphylactic reaction^[44]. It is more commonly linked with STEMI, which probably explains the higher percentage of STEMI cases after COVID-19 vaccination compared to NSTEMI in the present research.

VITT is another mechanism linking MI with COVID-19 vaccines. In VITT, tetramers of platelet factor 4 crosslink with vaccine proteins to form multimolecular aggregates. The ethylenediamine tetraacetic acid ¹ in the vaccine possibly causes capillary leakage and dissemination of components in the blood. The multimolecular aggregates are recognized by immunoglobulin G antibodies, which activate platelets, neutrophils, and the complement system, resulting in massive coagulation system activation^[45]. This can lead to MI and eventually mortality or long-term morbidity.

Polysorbate 80 (PS80), an excipient in AstraZeneca, is seen to trigger allergic reactions in those allergic to the compound. Similarly, polyethylene glycol (PEG) is the excipient

found in Pfizer and is a cause of severe anaphylaxis in those allergic to PEG. However, PEG allergy is very rare compared to PS80^[46], which probably explains the increased number of MI cases reported in patients vaccinated with AstraZeneca compared to other vaccines.

The literature searched and analyzed in this research was quite diverse, so one of the challenges faced while compiling this review was to bring the results under one umbrella. It was observed that robust original research needs to be conducted to probe the mechanisms of and the association between MI and COVID-19 vaccination. Considering the amount of clinical evidence available linking MI with COVID-19 vaccination, it is a bit early to make definitive deductions regarding their link.

CONCLUSION

It can be concluded that there is a link between COVID-19 vaccinations and MI in temporal terms of occurrence. However, there is also a possibility that the link was found purely by chance as a majority of cases were reported within one day, which is too short a time for a build-up of definitive causative mechanisms for MI. This is due to the diversity of risk factors for MI, such as age, gender, body mass index, ethnicity, and physical/mental stressors. This link can be definitively proven by conducting research while taking into account the confounders. AstraZeneca is seen to induce the greatest amount of coronary artery disease, with STEMI as the leading type, and this has mostly followed the first vaccination dose.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) hit the world population hard, in November 2019. The situation was pretty much out of hand, until the development of vaccines against it. From then on, a global campaign commenced to vaccinate majority of the world's population. The implications of these vaccines have been researched abundantly.

Research motivation

The side effects of covid vaccines and in particular serious cardiovascular side effects mention Myocarditis, as well documented. However, myocardial infarction (MI) and its link with COVID-19 vaccines remain unclear.

Research objectives

To investigate and pinpoint if any link exists between COVID-19 vaccination and MI reports amongst the vaccinated individuals.

Research methods

We devised a search strategy to search MEDLINE, EMBASE, and PakMediNet. All studies which reported MI after COVID-19 vaccine delivery were included in this research. A structured ⁹ data extraction form was developed to extract the data from the eligible studies.

Research results

The majority of MI cases reported were after Astrazeneca. Out of all the studies, 69% reported MI cases after the first COVID-19 vaccination dose and 14% after the second. Majority (44%) of MI reported was STEMI.

Research conclusions

Many studies linked MI to COVID-19 vaccinations, but no definitive association could be found.

Research perspectives

Perhaps more robust clinical trials in this regard could clarify the link between COVID-19 vaccinations and MI.

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