



# Could inadvertent intravenous injection of COVID-19 vaccines cause severe adverse events?

Zohreh Tajabadi<sup>1</sup>, Seyed Amir Ahmad Safavi-Naini<sup>1</sup>, Bharat Kwatra<sup>2</sup>, Ali Safavi-Naini<sup>1</sup>

<sup>1</sup>National Research Institute of Tuberculosis and Lung Diseases, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Applied Sciences, Sabarmati University, Gujrat, India

## \*Correspondence to

Ali Safavi Naini,

Email:

alisafavi2000@gmail.com

# These authors contributed equally

Received 26 February 2022

Accepted 6 April 2022

Published online 17 Apr. 2022

## Abstract

The emergence and rapid spread of COVID-19 led to the development of novel vaccines to fight against the disease. Although COVID-19 vaccines are the major key to controlling the disease and have a good safety profile, they may be associated with some adverse events. Recently, a few studies noted that inadvertent incorrect injection of COVID-19 vaccines may lead to the development of serious adverse events. Herein, we report a case of inadvertent intravenous COVID-19 vaccine injection who developed severe anaphylactic shock following receiving the COVID-19 vaccine. Proper vaccine injection technique training may help to reduce the risk of developing adverse events and improve vaccine safety and efficacy.

**Keywords:** COVID-19 vaccines, Adverse events, Anaphylaxis, Intravenous injection, Vaccination, Sputnik V vaccine

**Citation:** Tajabadi Z, Safavi-Naini SAA, Kwatra B, Safavi-Naini A. Could inadvertent intravenous injection of COVID-19 vaccines cause severe adverse events? *Immunopathol Persa*. 2022;x(x):e31392. DOI:10.34172/ipp.2022.31392.



Since the emergence of COVID-19 in late December 2019, more than 437 million people have been affected and more than 5.9 million have died (1). The emergence and spread of this novel disease led to the development of several COVID-19 vaccines to fight against COVID-19 spread, morbidity, and mortality. Like many other vaccines, COVID-19 vaccines may be associated with side effects. Since vaccination is a vital step in controlling COVID-19, it is necessary to evaluate associated side effects and the potential underlying mechanism to lower the risk of adverse events and increase the safety and acceptance rate of vaccination by individuals. Studies showed that COVID-19 vaccines have a good safety profile and post-vaccination adverse outcomes are mainly local and self-limited. However, serious side effects such as anaphylactic reactions may also occur although their prevalence is low.

Similar to many other vaccines, COVID-19 vaccines are designed to be administered through the intramuscular route and COVID-19 vaccine developers advise preventing intravascular, subcutaneous, or intradermal vaccination (2). Intramuscular vaccination initiates the immune response in nearby lymph nodes and provides higher immune protection against the desirable microbial agent in comparison with other

## Key point

Although COVID-19 vaccines have a relatively good safety profile, they may be associated with adverse events. Recently, the development of adverse events following inadvertent incorrect injection of COVID-19 vaccines has been noted. We report a case of severe anaphylactic shock following inadvertent intravenous injection of the COVID-19 vaccine. Training proper vaccine injection techniques may help to reduce the risk of adverse events and improve vaccine safety and efficacy.

routes of administration (3, 4). Since the majority of vaccines are not developed for the purpose of systemic distribution along the body (2), the entrance of vaccine components into the systemic circulation through muscle vasculature may cause severe side effects, likely due to raising an immunological reaction against vaccine antigens. Recently, several adverse events have been reported following intravascular injection of COVID-19 vaccines in human and animal models, including platelet aggregation and activation, thrombocytopenia, myocarditis, and pericarditis (3, 5). Merchant proposed that vaccine distribution to distant organs can result in developing an immune-mediated reaction in tissues beyond the vaccination site (2). Herein, we report a case of immediate anaphylactic shock following inadvertent intravascular administration of

the second dose of the Sputnik V vaccine.

A 54-year-old woman was referred to our hospital to receive the second dose of the Sputnik V vaccine. The patient had a history of hypertension and hyperlipidemia and was under atorvastatin, amlodipine, and valsartan treatment. She denied any family history of allergy, angioedema, or anaphylactic reactions. The patient reported no history of severe adverse reactions to previously received vaccines. Injection of the Sputnik V vaccine was performed in the right arm. Immediately after vaccination, significant inject-site bleeding was started, which did not stop despite manual compressing with gauze, raising the suspicion of accidental intravenous injection. A few minutes after injection, the patient suddenly developed dizziness, facial edema, flushing, dyspnea, and severe compressive chest pain. Vital sign evaluation revealed a heart rate of 140 bpm, blood pressure of 85/60 mm Hg, respiratory rate of 30/minute, the oral temperature of 36.9°C, and O<sub>2</sub> saturation of 91% on room air.

Regarding these symptoms, an anaphylactic shock was considered. The patient was admitted and prompt oxygen therapy, intravenous fluid therapy with 500 cc normal saline, 100 mg intravenous hydrocortisone, and 500 cc 5% dextrose water was initiated. At the admission, a blood test was performed which revealed a red blood cell count of 5.04 cell/ $\mu$ L, hemoglobin of 14.0 g/dL, white blood cell count of 7.61 cell/ $\mu$ L, and a platelet count of 258 000/ $\mu$ L. Biochemical parameters were within normal ranges. After receiving therapy, the patient's clinical situation improved and the majority of symptoms were relieved gradually. After two days, she was discharged from the hospital in good general condition.

COVID-19 vaccines have high efficacy and safety when injected intramuscularly. Inadvertent subcutaneous, intradermal, or intravenous injections of these vaccines may affect the efficacy rate and increase the risk of side effects (6). Recent human and animal studies have raised a major concern about the incorrect COVID-19 vaccine administration. Recently, Ng reported a case of accidental subcutaneous injection of COVID-19 vaccine who developed a large localized injection site skin reaction (6). Another case of accidental subcutaneous injection of BNT162b2 was reported by Gyldenløve et al, who developed recurrent skin rash and exanthema following vaccination (7). Nicolai et al, showed that incorrect intravenous injection of ChAdOx1 nCov-19, an adenoviral COVID-19 vaccine, resulted in platelet aggregation and thrombocytopenia both in humans and mice (3). In our case, the remarkable injection site bleeding following vaccination with Sputnik V, an adenoviral vaccine against COVID-19, raised the concern about an inadvertent intravenous injection which led to the development of an anaphylactic shock. Similarly, it has been previously reported that intravenous adenoviral vaccine injection can induce shock through upregulation of platelet-activating factors via the reticuloendothelial system in mice (8).

The anaphylactic shock might be a severe consequence of the intravascular injection of COVID-19 vaccines. Studies have shown that vaccines against COVID-19 have good safety and the prevalence of anaphylactic shock following vaccination has been reported to be very rare (9). It is worth noting that our case might show that anaphylactic reactions among COVID-19 vaccine recipients might be in part due to accidental intravenous vaccine injection. Thus, it seems that syringe aspiration prior to intending intramuscular injection of COVID-19 vaccines can help to reduce the risk of accidental incorrect vaccine injection and related adverse events.

The role of aspiration a few seconds before intended intramuscular injection has been studied extensively. Although aspiration prior to intramuscular injection was recommended by many guidelines for long years to minimize the risk of developing adverse events resulting from incorrect vaccine injection (10), some organizations such as the Centers for Disease Control and Prevention and the World Health Organization no longer suggest aspirating during intramuscular injection, in part due to increased injection pain (11). However, it seems that, in the case of adenovirus-based COVID-19 vaccines, aspiration before intramuscular injection might help to reduce the risk of severe adverse events and improve vaccine safety. Though infrequent, the inadvertent incorrect vaccine injection may occur. Thus, reconsideration of intramuscular vaccination guidelines might be useful in reducing the risk of accidental incorrect injection. Moreover, vaccinators should be trained and assessed for vaccination procedures and injection skills to maintain the vaccine optimal efficacy and minimize the risk of developing adverse events. Further investigations are needed to characterize the adverse events and associated mechanisms following inadvertent incorrect injection of COVID-19 vaccines in both humans and animals.

#### Authors' contribution

ZT and SAASN were the principal investigators of the study. ZT and ASN were included in preparing the concept and design. ASN and BK revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

#### Ethical issues

This paper as an "epidemiology and prevention" manuscript was conducted in accord with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this report. Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or redundancy) have been also observed by the authors.

#### Conflicts of interest

The authors declare that they have no competing interests.

#### Funding/Support

There was no financial support.

**References**

1. WHO Coronavirus (COVID-19) Dashboard. World Health Organization; 2022. <https://covid19.who.int/>.
2. Merchant H. Inadvertent injection of COVID-19 vaccine into deltoid muscle vasculature may result in vaccine distribution to distance tissues and consequent adverse reactions. *Postgrad Med J.* 2021;postgradmedj-2021-141119. doi: 10.1136/postgradmedj-2021-141119.
3. Nicolai L, Leunig A, Pekayvaz K, Anjum A, Riedlinger E, Eivers L, et al. Thrombocytopenia and splenic platelet directed immune responses after intravenous ChAdOx1 nCov-19 administration. *Biorxiv.* 2021. doi: 10.1101/2021.06.29.450356.
4. Rahamimov N, Baturov V, Shani A, Ben Zoor I, Fischer D, Chernihovsky A. Inadequate deltoid muscle penetration and concerns of improper COVID mRNA vaccine administration can be avoided by injection technique modification. *Vaccine.* 2021;39:5326-5330. doi: 10.1016/j.vaccine.2021.06.081.
5. Li C, Chen Y, Zhao Y, Lung DC, Ye Z, Song W, et al. Intravenous injection of COVID-19 mRNA vaccine can induce acute myopericarditis in mouse model. *Clin Infect Dis.* 2021:ciab707. doi: 10.1093/cid/ciab707.
6. Ng JY. Inadvertent subcutaneous injection of COVID-19 vaccine. *Postgrad Med J.* 2021;97:400. doi: 10.1136/postgradmedj-2021-139870.
7. Gyldenløve M, Skov L, Hansen CB, Garred P. Recurrent injection-site reactions after incorrect subcutaneous administration of a COVID-19 vaccine. *J Eur Acad Dermatol Venereol.* 2021;35:e545-e546. doi: 10.1111/jdv.17341.
8. Xu Z, Smith JS, Tian J, Byrnes AP. Induction of shock after intravenous injection of adenovirus vectors: a critical role for platelet-activating factor. *Mol Ther.* 2010;18:609-16. doi: 10.1038/mt.2009.279.
9. Greenhawt M, Abrams EM, Shaker M, Chu DK, Khan D, Akin C, et al. The Risk of Allergic Reaction to SARS-CoV-2 Vaccines and Recommended Evaluation and Management: A Systematic Review, Meta-Analysis, GRADE Assessment, and International Consensus Approach. *J Allergy Clin Immunol Pract.* 2021;9:3546-3567. doi: 10.1016/j.jaip.2021.06.006.
10. Sepah Y, Samad L, Altaf A, Halim MS, Rajagopalan N, Javed Khan A. Aspiration in injections: should we continue or abandon the practice? *F1000Res.* 2014;3:157. doi: 10.12688/f1000research.1113.3.
11. Knowlton KU. Insights from a murine model of COVID-19 mRNA vaccination-induced myopericarditis: Could accidental intravenous vaccine injection induce myopericarditis? *Clin Infect Dis.* 2021:ciab741. doi: 10.1093/cid/ciab741.