Syringe aspiration when vaccinating intramuscularly was not recommended before the pandemic due to the lack of conclusive evidence that it provides any benefit. However, in vivo evidence suggests that intravenous injection of mRNA vaccine can potentially lead to myocarditis, while introducing adenoviral vector to bloodstream can possibly result in thrombocytopenia and coagulopathy. These rare reactions were recorded in humans following the administration of the COVID-19 vaccines. Although the syringe aspiration may increase the level of pain at the injection site, it represents a simple technique to decrease the risk of vaccine introduction into the vascular system and potentially decrease the risk of severe reactions to mRNA and adenoviral vaccines. We are of the opinion that this cannot be disregarded if one considers that the COVID-19 vaccines will continue to be administrated globally in the form of initial and booster doses. Therefore, the aspiration when giving mRNA and adenoviral vaccines appears to be fully in line with the precautionary principle.

Keywords  Pandemic · Massive vaccination · SARS-CoV-2 · Myocarditis · Thrombosis · Acute side effects

Introduction

The first coronavirus disease 2019 (COVID-19) vaccines received emergency authorizations within a year of the first documented COVID-19 outbreak was reported in Wuhan, China. The landscape of COVID-19 vaccine candidates was highly diverse in 2020 [1], with eventually over 20 approved in different parts of the world [2]. Although some of these vaccines are based on a more classical approach, i.e., inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or recombination proteins, the major role in global vaccination campaigns is played by vaccines based on innovative solutions employing adenoviral vectors and messenger RNA (mRNA) enveloped by lipid nanoparticle carriers [3]. As yet, all these vaccines are given as an intramuscular injection, although intranasal versions are under development in clinical trials [4].

Post-authorization monitoring has proven that adenoviral vector and mRNA-based vaccines are generally safe. However, various rare side effects were reported, including myocarditis, pericarditis [5, 6], appendicitis [7], liver [8], pancreatic [9] and kidney injuries [10], and thrombotic thrombocytopenia [11, 12]. The exact mechanisms behind these events require further investigations, although several potential explanations were offered [5, 13–15]. Notably, some of these events were documented in animals after an intravenous vaccine administration, i.e., heart inflammation in case of mRNA vaccine [16] and acute thrombocytopenia and coagulopathy in the case of the adenoviral vector vaccine [13].

These observations fuel the discussion of whether the administration of the COVID-19 vaccines should be preceded with the syringe aspiration for 5–10 s after the needle is introduced intramuscularly [17, 18]. This technique was specifically developed in the past to ensure the medication is not inadvertently delivered into a blood vessel. Before the pandemic, the aspiration has generated numerous
pericarditis. Two days after treatment, the animals revealed calcific deposits on the visceral pericardium, interstitial edema, pericardial and myocardial infiltration of white blood cells, and transiently upregulated inflammatory cytokines and chemokines cardiomyocytes degeneration, apoptosis, and necrosis. The serum troponin levels were also markedly elevated. Moreover, the amount of mRNA encoding SARS-CoV-2 spike protein and its subsequent myocardial expression was significantly higher in heart tissue when compared to the animals receiving the intramuscular injection. Notably, the histological changes of myopericarditis persisted for 14 days and were aggravated considerably by intravenous injection of the second dose of the BNT162b2 vaccine.

These findings indicate that introducing the mRNA vaccine into the circulatory system can lead to acute cardiac inflammation. The mechanism behind this requires further elucidation. However, it is speculated that this may be due to the pro-inflammatory properties of lipid nanoparticles (LNPs) used as carriers for mRNA, as some of LNPs were shown to induce lung inflammation when introduced intranasally [16]. The other possible mechanism behind the observed myopericarditis (as observed in treated animals) is related to the expression of spike protein in transfected cardiomyocytes leading to excessively activated cytokine production and inflammatory cell infiltration [16]. Notably, the study did not find any differences in reaction to vaccines between female and male mice, while the effect of age was not studied. Therefore, the results are insufficient to explain the association between myocarditis following mRNA vaccination and male gender and younger age [5, 25, 26]. Nevertheless, they clearly show that invalid administration of mRNA vaccines into circulation can increase the risk of acute cardiomyopathies and should be avoided at all costs. This is essential if one considers that although post-vaccination acute inflammatory heart disease events are rare, their risk is increased for the first 30 days compared to unvaccinated individuals [27].

Although the mechanism behind rare events of thrombotic thrombocytopenia following the administration of the adenoviral vector vaccines also requires further elucidation, and it is not a specific subject to this article, certain observations are needed to be considered in relation to the potential benefit of aspiration practice. There is compelling evidence that selected adenoviruses, used as vectors, can directly interact with platelets. Some of them can bind using the coxsackie and adenovirus receptor (CAR), which represents an initial step for virus entry into thrombocytes [28]. This has also been shown for replication-deficient recombinant chimpanzee ChAdOx1 vector, which is the main component of the AZD1222 vaccine (Oxford/AstraZeneca, UK/Sweden) [14, 29]. In the case of human adenovirus type 26, the replication-deficient recombinant version is the main component of the Ad26.COV2.S vaccine (Janssen/Johnson&Johnson, Leiden, Netherlands/New Brunswick,
adenoviral vaccines contains approximately $5 \times 10^{10}$ viral particles. This is relatively low but not zero [49]. One should also consider that such a low risk corresponds to a rare incidence of thrombotic thrombocytopenia after COVID-19 adenoviral vaccines’ administration, does not have the proximity of major blood vessels [20] except the posterior circumflex humeral artery. However, it must be kept in mind that several branches of the posterior circumflex humeral artery supply the middle and posterior portions of the deltoïd. Together with the thoracoacromial artery (bifurcating into the deltoïd artery and the acromial artery) and their smaller branches, they form a blood vessel network of this muscle. Hence, the introduction of the vaccine into the blood is relatively low but not zero [49]. One should also consider that such a low risk corresponds to a rare incidence of thrombotic thrombocytopenia after COVID-19 adenoviral vaccines or myocarditis after mRNA vaccinations. It can be argued, though, that lack of aspiration and subsequent accidental introduction of the vaccine into the bloodstream cannot be responsible for all acute cases of myocarditis/pericarditis after mRNA vaccines or thrombotic thrombocytopenia after vaccination with adenoviral vaccines. This is due to demographical differences in incidences of these events, e.g., heart inflammation significantly more frequently reported after vaccination in younger, male adults [6]. Young males have substantially higher muscle mass, greater muscle thickness with more blood vessels. The injection technique and sometimes needle size must be individually adjusted. Basic needle size for intramuscular injection (deltoid muscle) in children (5 years and more), adolescents and adults are usually 0.5–0.6 mm and 25–30 mm (22–25 gauge, 1–11/2”) [50, 51]. One should also note that skin bunching, often performed during vaccination, can create a skin-to-muscle distance of 20 mm or greater, leading to insufficient muscle penetration, particularly in case of individuals with higher body mass index and arm circumference [52].
vaccine doses [23]. On the other hand, more than 20 different COVID-19 vaccines were already available by the end of 2021 in different part of the world [2], while a major concern was not the production capacity, but the inequality of vaccine distribution and accessibility due to insufficient involvement of developed regions in supporting the vaccination campaigns in the low-income countries [2, 43].

Conclusions

There is no definitive evidence that improper intramuscular administration of COVID-19 vaccines, leading to the introduction of components into the bloodstream, is behind the reported rare cases of myocarditis and pericarditis (in case of mRNA vaccines) and thrombotic thrombocytopenia (in case of adenoviral vector vaccines). On the other hand, experimental in vivo data suggests that such events can be induced after the intravenous administration of these vaccines. Although COVID-19 vaccines are intended for intramuscular injection, the deltoid muscle, a preferred site, has enough vascularity to accidentally and rarely lead to the vaccine’s introduction into the bloodstream and its translocation to distant tissues. Although the aspiration may increase the level of pain at the injection site, it represents a simple technique to decrease the risk of vaccine introduction into the vascular system. It can potentially reduce the risk of acute severe reactions to mRNA and adenoviral vaccines. We are of the opinion that this cannot be disregarded if one considers that the COVID-19 vaccines will continue to be administered globally in the form of initial and booster doses. Therefore, the aspiration when giving mRNA and adenoviral vaccines appears to be fully in line with the precautionary principle, particularly given that many countries are already vaccinating children against COVID-19.

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Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

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To aspirate or not to aspirate? Considerations for the COVID-19 vaccines

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