Review article

Aspiration During Vaccination: Evidence for SARS-CoV-2 Vaccination

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Abstract

Aspiration has always been performed during intramuscular vaccine injections to ensure that the needle does not puncture one of the blood vessels. However, at the beginning of the twenty-first century, this procedure became debatable.

Using an advanced search builder and logical operators, we searched the PubMed database for all articles about aspiration guidelines. The deltoid blood vessels are large and diverse, with potentially dangerous changes occurring in certain groups such as athletes or people with connective tissue diseases. The pharmacokinetics and reported side effects of improperly applied vaccines differ. Some reported vaccine-related injuries, such as subacromial bursitis, can be avoided by using the aspiration technique. We discussed experiments that provide evidence that intravenous administration of mRNA vaccines can cause myopericarditis. Aspiration during vaccination is not technically demanding and does not require much time. Previous arguments against aspiration were based on efforts to make the procedure of vaccinating children less painful. In response to public concern about vaccine-induced thrombotic thrombocytopenia as a possible side effect, Denmark issued a guideline on mandatory aspiration during vaccination in March 2021.

Guidelines vary by country, and there is a need for an updated and globally applicable instruction manual. Countries should carefully document vaccine side effects so that they could be compared between countries that aspirate and those who do not. More focused research experiments are needed to determine the relationship between aspiration and side effects. We propose a randomized study to compare the effectiveness of aspiration.

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Introduction

The vaccination campaign against COVID-19 focused public attention on the safety of vaccines and vaccine side effects. Not only is the vaccine being called into question due to side effects, but so is the method of administering the vaccine. The aim of this article is to encourage reflection on vaccination techniques in the hope that a discussion on this issue will increase confidence in COVID-19 vaccination and increase vaccination uptake.

Twenty years ago, aspiration was a common procedure during vaccination

Aspiration used to be a common procedure during intramuscular vaccine injections to ensure that the needle did not puncture any blood vessels. However, the guideline recommending this procedure was not evidence-based, and the procedure was disputed at the beginning of the twenty-first century (1). Because of its unproven value, the WHO removed aspiration from intramuscular vaccine administration procedures in 2004 (2). According to Plotkin and Orenstein, aspiration was unnecessary because there were no large blood vessels at the site intended for intramuscular injections. In a more recent edition of their book, they cited the 2007 Ipp study, which found the procedure to be painful, especially for infants (3,4). Based on the WHO guidelines and the 5th edition of Plotkin's book (5,6), the official 2013 UK immunization guidelines, the Green Book, stated that aspiration was unnecessary. The Centers for Disease Control and Prevention guidelines confirmed this, citing an article that makes no mention of aspiration or the distance of large blood vessels from the injection site (7,8). Similarly, the Canadian Government's Canadian Immunization Guide does not recommend aspiration (9).

Search strategy related to aspiration procedure

Using the AND and OR logical operators, we searched the PubMed database using the advanced search builder. The following search strategy was used: ((("intramuscular administration" [All Fields]) OR ("intramuscular injection" [All Fields])) AND (("aspiration" [All Fields]) OR ("technique" [All Fields]))) AND (("vaccine" [All Fields]) OR ("medication" [All Fields])).

Table 1. Search results with mentioning of aspiration

S.no	Author	Publication year	Type of article	Sample size
1.	Nicoll and Hesby(12)	2002	Review	-
2.	Wynaden et al.(50)	2006	Review and questionnaire	-
3.	Hunter(51)	2008	Review	-
4.	Taddio et al.(52)	2009	Review	-
5.	McDonnell et al.(53)	2010	Research	-
6.	Ogston-Tuck(54)	2014	Review	-
7.	Taddio et al.(55)	2015	Review	-
8.	Silva et al.(56)	2021	Research	148*

*Randomized clinical trial that compared adverse events with or without aspiration

There were 77 results in total, with 8 articles mentioning aspiration and 17 articles discussing medication and vaccine administration but not mentioning aspiration (see Table 1). We also searched the reference and citation lists of the studies that were included. Aspiration as part of intramuscular injection was first mentioned in John H. Stokes' 1945 book Modern Clinical Syphilology: Diagnosis, Treatment, Case Studies (10). Although the book was not available to us, we found a figure from it in a 1961 article by Zelman, which simply stated the importance of aspiration (11). The most detailed instructions for needle aspiration were provided by Nicoll and Hesby in 2002: after inserting the needle into the muscle, the first step is to pull back the plunger for 5-10 seconds; if blood is aspirated into the syringe, the administration should be stopped and the needle withdrawn from the muscle; the syringe with blood should be discarded; new syringe should be prepared and administered at a new administration site (12).

The blood vessels in the muscle are large and diverse

The deltoid muscle is a common vaccination site. It is well supplied with blood from several sources: the deltoid and acromial branches of the thoracoacromial artery, anterior and posterior branches of the humeral circumflex artery and deltoid branches of the deep brachial artery. These arteries are accompanied by large veins that drain into the axillary and cephalic veins (13,14). The intersection of the anteroposterior axillary line and the perpendicular line from the mid-acromion is the safest area for intramuscular injections. The lower half of the muscle is avoided due to the significant risk of injury to the arteries and the axillary nerve (15), whereas the upper third is avoided due to the risk of hitting the subacromial bursa. Complications involving the subacromial bursa have been reported after unintentional injection of COVID-19 vaccines into the bursa (16). The deltoid's excellent blood perfusion alters the pharmacokinetics of the injected medication and causes absorption at this site to be faster than at other intramuscular injection sites (17). Furthermore, athletes have a thinner arterial wall and a larger vessel diameter, which might make them more susceptible to aneurysms and ruptures (18,19). The importance of blood supply to muscles is also demonstrated by the avoidance of intramuscular administration in people with hemophilia due to frequent formation of intramuscular hematomas (20).

Renewed interest in vaccine administration during COVID-19 pandemic

The ongoing worldwide vaccination campaign against COVID-19 has reignited the interest in vaccine administration (21). Newspaper articles, letters to the editor, and scientific discussions on YouTube channels have all addressed the topic of aspiration (22–26). We searched the PubMed database for articles published between 2019 and the end of 2021 that contained one of the following terms: vaccine administration method, vaccine administration methods, vaccine administration practices, vaccine administration recommendations, vaccine administration technique, vaccine administration techniques. There were fifteen studies found, four of which discussed vaccine administration and one of which discussed COVID-19 vaccine administration (27–30).

Pharmacokinetics of mRNA vaccine during intravenous and intramuscular administration

During intramuscular administration, the peak concentration of any drug is lower and delayed, and it is higher and instantaneous during intravenous administration (31). To induce immunity, mRNA vaccines must be translated into spike protein (32). There have been no studies that compare the pharmacokinetics of mRNA vaccines administered intramuscularly versus intravenously, but an in vivo study examined the pharmacokinetic translation of mRNA luciferase delivered by lipid nanoparticles (33). Intravenous administration led to a shorter translation half-life and higher total protein formation (33). Because solid lipid nanoparticles, carriers for the mRNA of the spike protein, have different affinities for various tissues due to their charge (34), they should be carefully monitored in trials. For BNT162b2 vaccine, the distribution of lipid nanoparticles has been reported only for the liver, spleen, adrenal glands and ovaries, while the rest of the data is not publicly available (35). All of these differences raise the question of whether they are significant enough to affect immunogenicity and thus create more potent side effects.

Intravenous injection of mRNA vaccine may induce myopericarditis in a mouse model

An increased incidence of myocarditis and pericarditis was observed following mRNA-based COVID-19 vaccination (36). The link between myopericarditis and vaccination has yet to be established. Li et al. compared intramuscular and intravenous vaccine administration in a mouse model with saline as a control. Despite the fact that the intramuscular group exhibited significant weight loss and higher serum cytokine concentrations after the first dose, only the intravenous group developed a histopathological picture of myopericarditis. Histological changes in the intravenous group lasted for two weeks and worsened significantly after the second dose, regardless of whether the injection was intramuscular or intravenous. According to the authors, these in vivo findings show that intravenous administration of mRNA vaccines can cause myopericarditis (37). There is also evidence that Spike protein can cause pericarditis on its own via CD147 receptor signaling (38).

Intravenous injection of adenovirus causes thrombocytopenia in a mouse model

Adenovirus vectors are another type of COVID-19 vaccine vectors. Adenovirus-induced thrombocytopenia was first observed some twenty years ago, with the introduction of gene therapy (39,40). Vaccine-induced thrombotic thrombocytopenia has also been observed as a side effect of adenovirus-based COVID-19 vaccines (41). These vectors were first effective in in vivo gene delivery transduction, and their advantage is that most cells have adenovirus receptor on their membrane, making adenovirus vectors easily infectable (42). Gene therapy requires high adenovirus concentration via intravenous injection because of the quantitative transduction of the entire organ (40). This high viral particle concentration in the blood may cause adenovirus-induced thrombocytopenia via the following mechanism: The virus attaches to and activates platelets via the Coxsackie adenovirus receptor. After activation, platelets expose P-selectins on their membranes and aggregate with leukocytes. Platelet and leukocyte aggregates then activate other leukocytes and endothelial cells. This type of abnormal platelets is phagocytosed by macrophages. Macrophages and activated endothelial cells release large amounts of high-molecular-weight forms of von Willebrand factor and microparticles. As a result, Von Willebrand factor and microparticles cause a strong pro-coagulant stimulus (39). There is also a more recently proposed mechanism of action that is similar to heparin-induced thrombocytopenia and is caused by the presence of anti-platelet factor 4 (43). The mechanism of vaccine-induced immune thrombotic thrombocytopenia is initiated by the complex of adenovirus vector and platelet factor 4. This complex induces lymphocytes B cells, which produce anti-platelet factor 4. This type of antibody stimulates platelets, monocytes and neutrophils. Activated platelets and monocytes release pro-coagulant microparticles, while activated neutrophils exert a pro-inflammatory effect (44). This complex interaction between adenovirus vector ChAdOx1 and platelet factor 4 was confirmed by Baker et al in 2021 (45).

At the end of March 2021, Denmark issued a guideline for mandatory

aspiration during intramuscular vaccine administration

Following the increased public concern about vaccine-induced thrombotic thrombocytopenia, Denmark issued a guideline on mandatory aspiration during vaccination. The English version of the guideline can only be found in the Janssen vaccination procedure instructions on the Statens Serum Institute website (46). A population-based cohort study from Denmark that followed participants from 1 October 2020 to 5 October 2021 found 69 cases of myocarditis or myopericarditis within 28 days of vaccination. Data from this study does not correspond to the data from United States and Israel indicating an increased rate of myocarditis and myopericarditis in men aged 12-39 (47). On 17 February 2022, the Robert Koch Institute published an update for COVID-19 vaccination, stating that vaccines should only be administered intramuscularly and that aspiration during vaccination makes sense for increased safety to avoid intravascular injection (48).

Conclusion

Aspiration during vaccination is neither technically demanding nor time-consuming. Arguments against it were based on efforts to alleviate a painful procedure when vaccinating children, thereby reducing stress and achieving better child cooperation. Although one study examined the safety of the injection site on the deltoid muscle, its sample size was insufficient and unrepresentative (49). Larger sample size studies are required to support or refute the safety of aspiration omission during vaccination.

There are two study types that could be used. The first type should be designed to determine the prevalence of positive blood aspirations during intramuscular injections. The second type should compare the number of side effects associated with intramuscular injections with and without aspiration. The previous study, which found that intravenous injection of mRNA vaccine caused myocarditis in mice, failed to establish a cause-and-effect relationship, but did indicate the potential presence of a preventable factor. Furthermore, the results of that experiment cannot be translated to humans. All countries should document vaccine side effects much more thoroughly, allowing comparisons to be made between countries where aspiration is performed and those where it is not. Although findings obtained in this manner would not be sufficient to demonstrate a causal relationship between side effects and aspiration, they would provide sufficient evidence to begin a more direct research experiment.

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