Etiology Model for Clinical Studies’ Intramuscular Injection of Saline Solution Control Driving Innate Immune Response Associated Adverse Events in Volunteers

Darrell O. Ricke, Ph.D. (✉ doricke@gmail.com)
https://orcid.org/0000-0002-2842-2809

Research Article

Keywords: Histamine, vaccines, adverse events, histamine intolerance, saline solution, placebo effects

Posted Date: May 31st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1702797/v1

License: ☑️ ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Clinical studies include placebo controls to enable differentiation between treatment efficacy and adverse events from placebo effects. Intramuscular injection of saline solution was used in COVID-19 vaccine clinical trials as the placebo control. The underlying hypothesis is that intramuscular injection of saline solution does not cause adverse events. Herein, an alternative hypothesis is advanced that intramuscular injection of saline solution can stimulate innate immune responses in volunteers and that these adverse events are not placebo effects. This implies that clinical studies including intramuscular injection of saline solution controls are comparing vaccine associated adverse events with saline solution innate immune response adverse events. This article proposes that innate immune responses to intramuscular injection of saline solution triggers a temporary surge in histamine levels. Further, this temporary surge of histamine levels is causative for the local and systemic adverse events experienced by the control volunteers.

Introduction

The expectations of individuals about efficacy can influence the results of clinical studies; this is referred to as placebo effects. To control for placebo effects, clinical studies include a placebo that resembles the medication, therapy, or vaccine. COVID-19 clinical trials selected intramuscular injection of saline solution as the placebo control [1–3]. The underlying hypothesis is that intramuscular injection of saline solution is innocuous with no associated adverse events. These clinical studies compared treatment adverse events against placebo control adverse events; comparable adverse events in the treatment group that mirror those in the control group are discounted and are not likely to be associated with the vaccine that was administered. However, if both the vaccine and the saline solution intramuscular injection are both causing different levels of innate immune responses, then innate immune response associated adverse events associated with the vaccine are being discounted.

Inflammatory molecules including histamine are released as part of innate immune responses to pathogens and foreign substances. Multiple symptoms are associated with elevated histamine levels. Histamine intolerance results from an imbalance between accumulated histamine and the capacity for histamine degradation. The level of histamine released from innate immune response and histamine tolerance level can both vary by the individual. Multiple factors can influence an individual's histamine tolerance threshold, including drugs [4], foods (cocoa, spinach, tomatoes, beer, wine, cheeses, meat, soy, yogurt, fermented foods, etc. [4, 5]), gastrointestinal microbiome [4], and stage of menstrual cycle [5]. Histamine is metabolized intracellularly by histamine N-methyltransferase (HMNT) and aldehyde oxidase (AOX1), and extracellularly by the enzyme diamine oxidase (DAO). For some volunteers, their histamine tolerance level may be temporarily exceeded for a few days in response to intramuscular saline solution injection.

Hypothesis
Intramuscular injection of saline solution can stimulate innate immune responses in some control volunteers; elevated innate immune responses include release of inflammatory molecules including histamine. Based on the observed adverse events reported by some volunteers, the hypothesis is proposed that elevated histamine levels are causative for the majority of the adverse events reported by control volunteers for intramuscular saline solution injection. As a result, parallel adverse events caused by the treatments are often discounted because of adverse events are also occurring in the control volunteers.

**Methods**

Adverse events associated with intramuscular injection of saline solution were downloaded from the Centers for Disease Control and Prevention (CDC) for the Pfizer BioNTech COVID-19, Moderna COVID-19, and Janssen COVID-19 vaccine product reactogenicity web pages ([www.cdc.gov/vaccines/covid-19/infor-by-product](http://www.cdc.gov/vaccines/covid-19/infor-by-product)). Datasets for placebo controls matched with dose 1 and dose 2 of both COVID-19 mRNA Spike vaccines (Pfizer and Moderna) were downloaded. The adverse events with available information included “any systemic”, fatigue, headache, myalgia (muscle aches and pain), arthralgia (joint stiffness), and chills. Microsoft Excel was used to create Fig. 1 and compute Pearson correlation coefficients.

**Results**

The observed frequencies for each of the reported adverse events are consistent across the five intramuscular saline injection volunteer control datasets (Fig. 1). The standard deviation across the five control datasets are “any systemic”: 3.8%, fatigue: 3.7%, headache: 2.6%, myalgia (muscle aches and pain): 2.7%, arthralgia (joint stiffness): 3.5%, and chills: 1.1%, see Table S1. Comparing each set of percentage volunteers with the average value using Pearson correlation coefficient has r values for Pfizer placebo 1: 0.974, Pfizer placebo 2: 0.978, Moderna placebo 1: 0.998, Moderna placebo 2: 1.000, and Janssen placebo: 0.995.

**Discussion**

High consistency of adverse event frequencies were observed across all five intramuscular saline solution injections across five independent sets of control volunteers (Fig. 1 and Pearson correlation coefficients - Table S1). This demonstrates scientific reproducibility of adverse events results for intramuscular saline solution injections. If these adverse events were only due to nocebo effects, then higher variability should be expected than that observed. When saline injections were used as a control for osteoarthritis, the effect of saline injection is always greater than no treatment [6]; the authors note that variations in tissue osmolarity are well known and these variations and that sodium concentration is often of physiological importance [6]. Hence, it is plausible to consider the possibility that there can be immune responses to injections of foreign substances, including saline solution.
The reported adverse events by control volunteers of fatigue, headache, myalgia, arthralgia, and chills all overlap with known histamine intolerance symptoms [4, 5, 7]. It is possible that intramuscular injection of saline solution can trigger innate immune responses in some volunteers. Innate immune granulocytes and mast cells release inflammatory molecules including histamine as part of innate immune responses. Herein, it is hypothesized that histamine released from the proposed innate immune response can temporarily exceed the histamine tolerance level for some volunteers for a period of a few days while the elevated amounts of histamine are being metabolized.

Two systematic review of SARS-CoV-2 vaccine randomized trials compared the adverse events reported between the vaccine and placebo groups concluding that the reported control group adverse events could be traced to nocebo effects where negative treatment-related expectations favor their occurrence [8, 9]. These reviews assumed that saline solution intramuscular injections are inert and are not associated with adverse events. Herein, an alternative hypothesis is advanced that saline solution intramuscular injections are triggering innate immune response adverse events in roughly one third of the volunteers and the conclusion that these are nocebo effects by both systematic reviews is rejected.

Summary

Reproducible patterns of adverse events are observed associated with intramuscular injection of saline solutions. For some volunteers, it is hypothesized that elevated histamine levels from innate immune response to the saline injection is temporarily exceeding the tolerance level for some volunteers for a few days. Furthermore, the adverse events reported by volunteers are associated with innate immune responses to saline injection and not placebo or nocebo effects. This has implications for interpreting adverse events reported in clinical studies including saline solution intramuscular injections.

Declarations

Acknowledgements

None

Conflict of interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent statement/ethical approval

Not required.

Funding

None
References


Figures
Figure 1. Intramuscular saline control adverse events from COVID-19 vaccine trials. Volunteer controls are paired with dose 1 (Placebo1) and dose 2 (Placebo2) for COVID-19 vaccine treatments.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CDCCOVID19vaccineadversereactions.xlsx