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Protocol

Effectiveness of metabolic modulation in treating post-vaccination syndrome: study protocol for a prospective and randomized controlled trial

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ABSTRACT

Background: Post-acute COVID-19 vaccination syndrome (PACVS) emerged as a rare complication of the COVID-19 vaccination campaigns, which began in late 2020, when the first trials were underway, and continued to the present day, when COVID-19 vaccines are available for use. While their uptake peaked in the years of 2021 and 2022, a rare side-effect was the presence of a myalgic encephalitis/chronic fatigue syndrome (ME/CFS) phenotype. This population has limited treatment options available, and surveys show that many are trying poorly validated treatment protocols with limited success.
Methods: One hundred patients presenting with PACVS with a lab-confirmed diagnosis will be enrolled for a 3-month study. Patients are randomized to intervention and placebo groups and provided with a combined metabolic modulator, called ViTAL SCAN (vitamin C, taurine, acetyl L-carnitine, serine/sarcosine, creatine/citrulline, acetylcysteine/arginine, and NMN) in the intervention group, and unflavoured rice protein powder with vitamin C in the placebo group. Baseline measurements of a combined biomarker panel, including metabolic and inflammatory markers, as well as heart rate variability, physical performance, and self-rated quality of life.
Conclusions: Treatment of PACVS currently has a lack of evidence for the efficacy of treatment interventions for the disease. While several interventions have been proposed, their prospective clinical usefulness relies on arguments from mechanism or analogy from related disorders (e.g., long COVID-19, ME/CFS, acute COVID-19 infection). Limited data exists on the clinical efficacy of treatments for PACVS. This research proposal tests a combined nutraceutical for the purpose of improving metabolic parameters.
Trial Registration: Clinical Trials Gov NCT number will be obtained.

Keywords: Post-acute COVID-19 syndrome, Metabolic modulation, Spike protein, Nutraceuticals, Supplement protocol

INTRODUCTION

Vaccine recipients may experience post-acute COVID-19 vaccination syndrome (PACVS), a condition with severe morbidity and persistence.[1] There is inadequate information on PACVS, and advocates for patients and researchers have had trouble getting the clinical and scientific professions to acknowledge the condition.[2] Currently, little is known about the pathological state, which restricts the treatment options available to patients with PACVS. Either the analogous condition of post-acute COVID-19 syndrome (PACS), a closely associated pathology, or mechanistic arguments - which typically focus on the modified SARS-CoV-2 spike (S) protein found in the COVID-19 vaccines as the pathogenic factor driving PACVS—have been employed in efforts to formulate therapies.[3-5]

Since the persistent spike protein is frequently detected in the tissues and fluids of patients with post-vaccine problems in both acute as well as chronic cases, there exists scientific research linking the spike protein to disease progression.[6,7] Studies have shown biomarker profiles linked to both conditions that could be useful for both diagnosis and treatment planning. Therapeutic procedures are available, and several treatments have been found for the treatment of PACVS.[7,8] Even though there exist clinical findings to support each, there is a scarcity of clinical evidence regarding the treatment of individuals with PACVS. Owing to this urgent lack of prospective, controlled trial evidence to substantiate the effectiveness of metabolic-modulating treatment options and nutraceuticals, medical professionals and patients are consequently forced to navigate uncertainties and make therapeutic decisions without substantial and reliable evidence. It is therefore essential to conduct a thorough, randomized, prospective clinical trial since it is the only method to go beyond anecdotal claims, provide recommendations that are supported by scientific findings, and provide patients with PACVS with truly evidence-based, compassionate care. This study protocol presents a prospective, randomized controlled trial to test the effects of a combined nutraceutical product on the symptomology of PACVS. The trial is a combined nutraceutical product, which is reflected given by independent organizations for the management of PACVS.

Objectives

Objective of the study was to determine the effectiveness of a combined metabolic modulator (ViTAL SCAN) for the treatment of PACVS.

METHODS

Trial design

A prospective, single-center, case-controlled trial testing for the superiority of a combined nutraceutical protocol over a non-intervention group.

Study setting

The primary care practice of the study author (JV) is based in Houston, Texas.

Eligibility criteria

Patients must present a plausible diagnosis for post-acute vaccination syndrome with a chronic fatigue syndrome/ myalgic encephalitis phenotype.

Inclusion criteria

The beginning of symptom onset must be within 2 weeks following COVID-19 vaccination. This is in accord with the reported durations from patient surveys.[9] SARS-CoV-2 infection could not have occurred during the 14-day post-vaccination window, as symptoms may be due to PACS in that case. Patients will need to have persistent symptoms for ≥6 months without substantial resolution prior to enrolment.

The patients must meet the ME/CFS criteria per the Institute of Medicine criteria.[10] Patients must meet all three core diagnostic components.

Substantial functional impairment

≥50% reduction in pre-illness occupational, educational, social, or personal activities.

Post-exertional malaise (PEM)

Prolonged symptom exacerbation (physical, cognitive, or emotional) lasting ≥24 hours after exertion.

Unrefreshing sleep

Persistent fatigue unrelieved by rest or extended sleep.

Patients must also have one of the following (moderate-to-severe intensity, occurring ≥50% of the time).

Cognitive impairment

Deficits in memory, executive function, or information processing can be exacerbated by exertion, stress, or upright posture.

Orthostatic intolerance

Symptom worsening upon standing (e.g., light-headedness, tachycardia) validated by heart rate increase ≥30 BPM within 10 minutes of standing or abnormal head-up tilt test.

Exclusion criteria

Exclusion criteria included have not received a COVID-19 vaccine. Active SARS-CoV-2 infection or prior COVID-19 diagnosis within 14 days post-vaccination. Alternative explanations for symptoms (e.g., untreated hypothyroidism, anemia, major depressive disorder) and pregnancy or lactation.

Ethical considerations

Human subject ethics review

This study protocol is currently under a second round of review with the Institute for Pure and Applied Knowledge Institutional Review Board (IPAK-IRB).

Informed consent

Patients will receive an information package detailing the rationale for the study, which will include a link to this

protocol. The rationale for the study will be explained in terms of amino acids and other metabolites being depleted in PACS and/or PACVS.

We hypothesize that the two conditions are similar enough that various therapeutic items may work for both cases. The informed consent form includes information on the potential adverse effects. This study protocol is currently under a second round of review with the Institute for Pure and Applied Knowledge Institutional Review Board (IPAK-IRB).

Privacy and confidentiality

Data is anonymized when shared with researchers outside the clinic. All identifying characteristics from the data (names, birthdates) are removed, and the patient is given a unique identifier for the purpose of data analysis.

Compensation details

Compensation will not be given for trial participation. The study protocol and accompanying tests will be provided by the study, free of charge. Participants will be required to transport themselves to the clinic, at their own expense, for the follow-up visits and to receive the trial protocol.

Interventions

Intervention description and rationale

Interventions with dosages are shown in Table 1.

Table 1: Composition of the ViTAL-SCAN intervention and control formulations with comparison to established LOAEL values.

Control		Intervention (ViTAL SCAN)		LOAEL (g/day)
Component	Mass (g)	Component	Mass (g)	
Standard amino acids				
Aspartic acid	4.29			
Threonine	2.45			
Serine	1.73	L-Serine	4	12[11]
Glutamic acid	6.94	L-Glutamine	13	14[12]
Glycine	0.78			
Alanine	2.07			
Valine	2.36			
Methionine	0.93			
Isoleucine	2.52			
Leucine	4.52			
Tyrosine	1.29			
Phenylalanine	1.38			
Lysine	3.84			
Histidine	0.74			
Arginine	1.1	L-Arginine	3	>10[13]
Proline	2.48			
Cystine/cysteine	0.81	N-Acetylcysteine	1.2	Not established
Tryptophan	0.67			
		L-Citrulline	5.75	15[14]
Other components				
Vitamin C	0.5	Vitamin C	0.5	3[15]
		Creatine	6.3	10[16]
		NMN	0.25	1[17]
		L-Carnitine	2	2[18]
		Taurine	1.5	4[12]
		Sarcosine	2	2[19]

Recruitment

An advertisement will be posted using the social media channels of the Independent Medical Alliance, the study's sponsor. We will also advertise the trial on social media sites using paid advertisements to reach people outside of our channels. The link will direct prospective patients to an application. They will be required to visit the clinic in person in Houston, TX, USA, and that will be advertised. The application form will record their basic information for administrative purposes, as well as demographic information, including age, race, sex, comorbidities, and medications used. Additionally, a frequently used survey assessing health behaviours will be given during application, alongside the PAC-19QoL Questionnaire, a survey designed for PACS patients to assess their

subjective rating for quality of life and functional independence.[20,21] After a period of recruitment, patients will be randomized into intervention and control arms. Recruitment will occur through the clinic of Dr. Joseph Varon. There is potential for bias, as his media profile attracts PACVS patients, who may be more likely to respond positively to treatments. The patient recruitment will follow a structured format. Patients will have an intake interview and will watch a short explanation video on the basis of the protocol, and what they can expect. However, we take objective measurements and only use subjective measures for a single outcome variable.

Data collection and management

Baseline measurements in physical parameters will be taken during patient recruitment. During an initial consultation, the patient will provide blood and urine samples, perform the 6MWT, and receive a heart rate monitor with the ability to measure heart rate variability. A PAC-19QoL Questionnaire will be administered for the patients to fill out before function tests, so as not to let the performance alter the patient's perception of their quality of life. The 6MWT will be administered indoors on a treadmill setup to reduce the impact of weather variation on patient scores.

A breath test using a Lumen device will determine the fatty acid oxidation percentage prior to the test, and one measurement at the timepoints 2 and 4 minutes during the 6MWT. The heart rate will be recorded during the entire exercise.

Outcome measures

Metabolic markers

Interestingly, long COVID syndrome appears to interfere with mitochondrial function, contributing to the post-exertional malaise symptoms seen in long COVID and PACVS.[9] At a molecular level, the spike protein damages mitochondria.[22-27] Combined with the issues in oxygen delivery owing to coagulopathies, from microclots to more recognizable thromboses, PACVS can be marked by a distinctly reduced metabolic profile. The metabolic profile of long COVID suggests difficulty in utilizing fatty acids, and drastically lowers the level of exertion at which the metabolic transition from fatty acid oxidation to glycolysis occurs.[28]

Metabolic markers may be useful for observing the metabolic changes occurring during PACVS and how they are affected by treatment. The metabolic changes are central to the exercise intolerance, brain fog, and general fatigue experienced by those with PACS, and these may also be relevant to the experience of those with PACVS.

Hemoglobin A1c

Analysis of hbA1c will be done through Roche Cobas B 101 system as per the manufacturer guidelines.

Pre-exercise (basal) blood lactate

The device to measure lactate will be the Arkray Lactate Pro.

Inflammatory and autoimmune markers

Inflammation is a characteristic of persistent PACVS and PACS, sometimes with autoimmune components. Patient condition is associated with the levels of inflammatory markers over longer timescales.

SARS-CoV-2 Spike protein levels

This trial will use the S-PLEX SARS-CoV-2 spike protein kit from MSD to determine spike protein levels.[29]

C-reactive protein

The quantification of CRP will be done by using the Cobas b 101 CRP discs.

Well-being and physical function

PAC-19QoL questionnaire

The PAC-19QoL instrument has previously been validated to assess the quality of life in post-acute COVID-19 patients, 21 participants fill out the survey as a PDF document, and their scores are recorded.

Six-minute walking test (6MWT)

This test of physical exercise capacity and endurance merely measures the total distance that a person can walk in a 6-minute duration.[30,31]

Heart rate variability

It has been found that during long COVID, people have reduced heart rate variability (HRV).[32] HRV is measured via a Garmin Premium HRM DualTM Heart Rate Monitor with a chest strap.[33]

Post-exercise Borg category-ratio 10 scale

This test is used to assess the level of perceived exertion after the 6MWT by asking participants to rate their exertion on a scale of 1 to 10.[34] This is useful as a measure of exercise intolerance.

Plans to promote participant retention and complete follow-up

Participants will be required to download a notification which notifies them to take their supplement. They will be able to fill in the times that they take it. Additionally, patients will be able to record the length of their fasting window if they practice intermittent fasting.

Data management

Patient data will be stored in a folder given the patient's unique identifier, with the documents of the test reports, anonymized charts, and demographic data.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use

Sample collection

Upon arrival, the patient is given the PAC-19QoL questionnaire to complete. If the patient has recently been asked about exertion, they are required to wait a minimum of 30 minutes before proceeding, during which time they complete the questionnaire. If not, the patient waits until the survey room and staff are ready, using this time to finish the PAC-19QoL. Once ready, the patient enters the survey room, where a heart rate variability (HRV) measurement is taken using a heart rate monitor. Next, a lactate measurement is performed. Blood samples are then collected sequentially for HbA1c, lipid profile, and C-reactive protein (CRP), with each sample disk labelled with the patient's ID. An additional blood sample is drawn for a serum spike test and labelled accordingly. All sample disks are stored at 2°C, while serum samples are stored at -20°C.

Table 2: Trial summary table.

Title {1}	Effectiveness of metabolic modulation in treating post-vaccination syndrome: A prospective study
Trial registration {2a and 2b}.	ClinicalTrials.gov ID: NCT06967428
Protocol version {3}	Issue date: 01 August 2025, protocol amendment number: 03, author(s): MTJH, JV
Funding {4}	Independent Medical Alliance, Open Source Medicine OÜ
Author details {5a}	MTJH and JV conceived the study, initiated the study design. MTJH developed the intervention
Name and contact information for the trial sponsor {5b}	Trial sponsor: Open Source Medicine OÜ, Pärnu mnt. 139c, 11317, Tallinn, Estonia opensourcemed.info, contact@opensourcemed.info
Role of sponsor {5c}	This funding source had a role in the design of this study and will not have any role during its analyses and interpretation of the data, or decision to submit results

HbA1c, lipid panels, and CRP measurements

At the end of the day, the sample disks will be thawed. The final disk collected must be in the refrigerator for at least ten minutes to minimize any effects of uneven temperature between the disks. Disks will be thawed for 20 minutes and analyzed using the Roche Cobas B 101 and the respective sample disks (HbA1c, lipid profile, and CRP). These values will be recorded in a spreadsheet with the patient identification number. After use, the disks will be discarded in a biohazardous waste bin.

Spike protein levels

Spike protein tests will be performed using the MSD S-PLEX SARS-CoV-2 spike kit using a SECTOR Imager 2400 plate reader.[29]

Storage of samples

We will store the blood samples for further analysis, which may include assays of clotting propensity and observations of clotting progression.

Further experiments may include- association of clinical status with blood parameters and behaviour, such as clotting propensity, proteomics, metabolomics, and genomics of blood contents, developments of clotting assays and monitoring of clotting progression and screening of therapeutics for anticoagulation properties.

Statistical methods for primary and secondary outcomes

Statistical tests

To assess the effectiveness of the intervention, two-tailed statistical tests will be used unless strong directional hypotheses are warranted. The primary method for comparing continuous outcome measures (e.g., PAC-19QoL scores, metabolic markers) between intervention and control groups will be independent samples t-tests or analysis of variance (ANOVA), where appropriate. For repeated measures (e.g., baseline and follow-up), linear mixed-effects models will be employed to account for intra-individual variability and temporal correlation.

Multiple comparisons

Given the presence of multiple secondary outcome variables, adjustments for multiple comparisons will be made. For primary endpoints, a Bonferroni correction will be applied to maintain a family-wise error rate of 0.05. For secondary and exploratory outcomes, the Benjamini-Hochberg procedure will be used to control the false discovery rate (FDR), thereby balancing type I error control with statistical power.

Confounding variables

Multivariable analyses will be conducted using general linear models to adjust for potential confounders, including age, sex, baseline health status, and other

relevant clinical covariates. Stratified analyses may also be performed on key subgroups (e.g., sex and age cohorts).

Missing data

To handle missing data, multiple imputation by chained equations (MICE) will be employed under the assumption of data missing at random (MAR). Sensitivity analyses will be conducted using complete case analysis and last observation carried forward (LOCF) where appropriate. The extent and patterns of missingness will be reported in full.

Software

All analyses will be conducted using R (v4.3.1), Python, Microsoft Excel, or IBM statistical package for the social sciences (SPSS) statistical software.

DISCUSSION

The study is currently in process to receive Institutional Review Board Approval from IPAK-IRB. The prospective trial evaluates the therapeutic utility of metabolic modulation using a combined nutraceutical product (ViTAL-SCAN) for the treatment of PACVS. We hypothesize that the nutraceutical will improve measures of function and independence, as measured by the PACS-19QoL instrument, as well as performance on the 6MWT, a measure of exercise tolerance and endurance.[21,30] The intervention will be compared against a rice protein powder with some vitamin C and follows a double-blinded design, where clinical staff and patients do not know group assignments. The trial aims to recruit 100 people, with 50 in each trial arm. We hypothesize that the ViTAL SCAN supplement group will see a superior improvement in symptoms when compared to the control group.

The study has strengths in that it is evaluating treatments validated for a related condition, and the clinical translation may lower the potential for a non-superior outcome (compared to placebo). The study will be the first of its kind to evaluate treatment for a new condition, and it is useful from that perspective.

One possible limitation is the potential for subtle differences in the flavour, color, and texture of the product between the control and experimental group, such that participants can tell which group they are in. One risk is that participants in the trial meet each other and compare products, which may allow them to make an educated guess about which group they are in. Participants will be forbidden from comparing the product with another participants, but this may still happen. Another limitation is that the amino acids in the placebo group may not be inert, as is intended for a placebo. It is doubtful that a non-protein supplement could be passed off as protein, and this is our reasoning for including protein powder. Additionally, vitamin C has a characteristic acidity and taste, which is why it is included in the control group as well.

It is possible that individuals may make an educated guess as to which group they are assigned to base on the appearance and taste of the product. Another limitation is that if an effect is observed, it will not be known which agent contributed. Generally, we will assume that observed effects are a product of the nutraceutical combination, and not an individual ingredient. Additionally, targeting PACVS by "metabolic modulation" is broad in terms of mechanism, but the focus of the trial is more for clinical utility rather than an intimate understanding of the disease and treatment mechanism.

CONCLUSION

A single-center trial aiming to recruit 100 people will evaluate a combined nutraceutical (ViTAL-SCAN) for its efficacy in treating PACVS via metabolic modulation. The trial will evaluate quality of life indices, physical performance, as well as metabolic and inflammatory markers. The interventions, a combination of vitamin C, taurine, acetyl l-carnitine, serine/sarcosine, creatine/citrulline, acetylcysteine/arginine, and NMN, may modulate host metabolism to counteract the symptoms of PACVS, based on the mechanisms of action of the components and their performance on the related conditions PACS and COVID-19. This trial may improve the lives of those suffering from PACVS currently in the USA.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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