

Original Article

An open-label, exploratory documentation of proving-symptoms of CVN01 (Coronavirus nosode from the clinical sample) in healthy volunteers

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Abstract

Introduction: Homeopathic Pathogenetic Trials (Proving) are human studies to examine the pathogenetic effects of investigational drugs in high dilution on healthy volunteers. As a part of the new coronavirus nosode development process for prophylactic use, the phase 1 study was conducted. The documentation of proving symptoms for a fast-track nosode development for a pandemic condition was the objective of this study. **Materials and methods:** An open-label trial to evaluate the safety and proving symptoms of Coronavirus nosode given orally to 10 volunteers (18-65 years age and of both genders). Volunteers were administered 6 doses of nosode as 6 pills twice daily in 30c dilution (size 30 globules) for 3 consecutive days. Pre and post-examination (physical), vital signs, and laboratory investigations were done on days 0, 17, 34. Symptoms experienced by the volunteers were recorded. **Results:** Symptoms reported by volunteers were analyzed. The symptoms reported were mild to severe but reversible and matching with the symptoms produced by the viral infection. There were no serious/fatal adverse events during the study. The basic biochemistry and Liver Function tests were not affected by the Nosode. **Conclusion:** New nosode developed during a pandemic condition produced specific symptoms in the homeopathic pathogenetic trial as a part of the Phase 1 study.

Keywords: SARS-CoV-2, COVID-19, nosode, homeopathic pathogenetic trial, drug proving

Introduction

Homeopathic pathogenetic trials [1], traditionally called Drug Proving, are human studies to examine the pathogenetic effects of investigational drugs in high-dilution on healthy human volunteers. The induction of subjective and objective symptoms and signs is essentially considered the primary actions of the drug substance that are carefully documented and used to determine their clinical indications. As per the fundamental homeopathic principle of similarity, the substance capable of producing symptoms (and signs) may also be used to treat similar symptoms and signs if administered in ultra-dilute, potentized form.

Literature survey of about 1500 approved drugs listed in Indian, British, German, and American Pharmacopeias based on the major textbooks of Materia Medica, such as those by Samuel Hahnemann (MMP) [2], TF Allen[3], and C Hering[4], suggests that major drug provings made in the olden days (from 1796 to 1820) were un-blinded, single-arm, without placebo-control, and on a few healthy volunteers. For example, Alumina (9 provers) [5], Calcarea carbonica (8 provers) [6], Causticum (8 provers) [7], Pulsatilla (5 provers) [8], and Sulphur (3 provers) [9,10].



As the research systems evolved, placebo-controlled homeopathic pathogenetic trials became acceptable. Relatively, very few new homeopathic drugs, which include drugs from the Central Council for Research for Homeopathy (CCRH) and new nosodes such as HIV Nosode [11] and Hepatitis C Nosode [12], underwent placebo-controlled homeopathic pathogenetic trials in the recent past. Many new homeopathic drugs in the recent past did not opt for placebo-controlled drug-provings [13,14]. Placebo-controlled pathogenetic trials are of high importance, particularly for the use of drugs for therapeutic, if not as prophylactic.

There has been limited experience in the homeopathic profession in developing new drugs, particularly nosodes for epidemic or pandemic situations. Dengue Nosode [15], Leptospirosis Nosode [16], and Influenza Nosode [17] were developed in the recent past and used based on not the drug proving but the homeopathic rationale.

Epidemic and pandemic situations requiring the development and exploration of new nosodes may call for separate regulation or waivers for the faster approval process for prophylactic and therapeutic measures yet not compromising the ethics, safety, and efficacy criteria.

SARS-CoV-2 viral infection leading to the COVID-19 pandemic offered such experience of developing Coronavirus nosode on a fast-track. Our team developed three variants of Coronavirus Nosode from the clinical sample (an oropharyngeal swab of positive corona patient), inactivated strains, and spike glycoprotein [18]. The nosodes were developed and studied during the lockdown situation in Mumbai (the most affected city in India then) with limited mobility, scarce resources, and social distancing. We decided to conduct a Phase 1 study of the CVN01 (coronavirus nosode from the clinical sample) on 10 healthy volunteers for its safety evaluation (meeting the regulatory requirement).

For future prophylactic use in the COVID-19 pandemic, the circumstances motivated us to combine a homeopathic pathogenetic trial (drug proving) and Phase 1 study (safety and efficacy) in the same experiment. The objective of the study is to document and evaluate the proving-symptoms of CVN01 in the healthy volunteers in the Phase I trial of a fast-track development of a new drug in a pandemic condition.

Materials and methods

Coronavirus nosode

A Coronavirus nosode (coded as) CVN01 was prepared from the clinical sample (oropharyngeal swab) of a patient having confirmed infection of SARS-Cov-2 at Haffkine Institute in Mumbai in the second half of May 2020, by following various biosafety and ethical guidelines and protocols. [19, 20]. The nosode was prepared in the BSL-2 facility modified to BSL- 3 practices to process the clinical samples. First 1c to 4c potencies were prepared using water for injection, and 5c onwards 91% alcohol was used as a vehicle [18].

Study Design

As a part of Phase I, an open-label and non-randomized Homeopathic Pathogenetic trial was designed to examine the response of Coronavirus nosode (CVN01) administered orally to healthy volunteers. The study was planned to examine the safety in terms of clinical effects and blood parameters at baseline and time points day 17, day 34, and the document proving symptoms experienced by the volunteers in response to the nosode.

This study was conducted at a single center in Mumbai, India. The first volunteer was enrolled on June 6, 2020, and the last volunteer visit was completed on August 12, 2020. The study protocol,



amendments, and informed consent forms were reviewed and approved by the institutional ethics committee. Written informed consent was obtained from each volunteer before the performance of any study-specific procedures. The study was conducted following the Good Clinical Practice guidelines and the ethical principles outlined in the Declaration of Helsinki 2008.

Study Population

10 eligible volunteers (18 – 65 years, 4 males and 6 females) with a healthy status, no major untreated diseases, and routine laboratory parameters during screening, who voluntarily signed informed consent forms, were enrolled in the trial. The volunteers having current or recent COVID-19 infections were excluded from the study. Full inclusion and exclusion criteria are included in the Supplementary Materials.

Interventions

A variant of nosode prepared from the clinical sample coded as CVN01 30c (pill size 30) was administered six doses, six pills twice daily for three consecutive days.

Approval

The trial protocol was reviewed by the Scientific Advisory Board and approved by an Institutional Ethics committee. The trial was registered at the Clinical Trial Registry of India (CTRI) with Trial registration number: CTRI/2020/05/025496

Study End Points and Assessments

The endpoint of the study was the recording of clinical symptoms and changes in the biochemistry observed in the volunteers.

Safety Assessments

Safety assessments included monitoring volunteers for any unexpected symptoms, adverse events, serious adverse events, clinical and laboratory investigation results, blood pressure, physical examination findings, and general well-being.

The government did not permit the RT-PCR tests for diagnosing COVID-19 for the healthy persons (due to the shortage of kits in the country during the study period), however, the status of the COVID-19 total antibodies was investigated at different time points, confirming that the volunteers were not infected.

Symptom recording

The symptoms experienced by the volunteers during the study period were recorded in a specific format.

- All symptoms were reported with the location, sensation, duration, frequency, and concomitants, if any. For example, a dull headache with the heaviness of the head all over the head < 1-4 p.m. is associated with sleepiness. (Volunteers: 1).
- Every symptom described by the volunteers has been graded as + (mild), ++ (moderate), +++ (severe), and ++++ (very severe). This method allowed qualification grading.

- Volunteers who exhibited some symptoms before this study duration (as per the history) were eliminated if the volunteer also exhibited the same or similar symptoms after consuming study medication.
- Symptoms experienced by more than one volunteer were recorded in bold text and considered as characteristic.

Study method

Volunteers were administered six doses of nosode coded as CVN01 30c (pill size 30) as six pills twice daily for three consecutive days. Pre and post-examinations, such as physical, vital signs, and laboratory investigations, were done at baseline. On day 17 (14 days after the last dose), a few investigations were repeated on day 34.

Results

Six volunteers exhibited definite subjective symptoms (Table 1). Detailed biochemistry report of the volunteers is published separately and provided as supplementary data [21]. As the symptoms reported by the volunteers in the study were short-lasting, mild to severe, self-limiting, and not requiring medical intervention, they did not qualify as serious adverse events. This pathogenetic trial was conducted for a fast-track nosode development in a COVID-19 pandemic condition.

Discussion

The Phase 1 study with CVN01 nosode from the clinical sample in 30c potency also included a pathogenetic trial. It is interesting how the homeopathic drug substances in potentized form retain properties of inducing primary action in terms of symptoms and signs comparable and relevant with those produced in the physiological doses without producing the actual disease. Vaccines are also known to induce some symptoms as an immune response to the weakened microbial material. These are two different techniques of transforming the microbial material into immunomodulatory agents which could be explored for prophylaxis, the former being less reconnoitered.

This experiment (a part of the Phase 1 study) was conducted during the period of COVID-19 lockdown hence comes with certain limitations, such as a lack of placebo-control arm and a limited number of volunteers. A larger, placebo-controlled study could be carried out in the future. To develop preventative medicine for epidemics and pandemics conditions, an elaborate controlled drug-proving may not be considered mandatory as prophylactic prescribing does not require symptomatic indications. This study combining Phase 1 and drug-proving could help develop such a study model for fast-track homeopathy drug development as the epidemic and pandemic situations present with time constraints, as immediate prophylactic and therapeutic solutions cannot wait for a lengthy process of a new nosode drug discovery.

For using the drugs as prophylactic in endemics and pandemics, the drug-proving may have a limited or no role, as the drug would be administered without matching the symptoms. However, for the therapeutic use of this nosode, drug-proving data will help. The study of the pathogenesis produced by the source material gives much information about its primary action. In the case of the SARS-CoV-2 virus, we have essential information on its pathogenicity. A strategic regulatory process needs to be set up for new drug discovery for epidemic and pandemic situations.

Table 1: Symptoms produced by the volunteers (With severity, duration, and volunteer number) –Onset: The day on which the symptom appeared after taking the first dose.)		
Sr No.	Location	Symptom (Severity of symptoms in ascending order: +, ++, +++, +++++)
1.	Head	1. Frontal headache for 4 days +++, onset day 24 (Volunteer no. 3) 2. Effect on the right side of the head, neck (15 hrs), Sudden severe throbbing pain, < light + with Nausea as a concomitant symptom +++, onset day 3 (Volunteer no. 6) 3. Headache (Right side) for 3 days + (Volunteer no. 6) 4. Frontal and occipital headache ++, onset day 10 (Volunteer no. 6) 5. Heaviness in the head ++, onset day 18 (Volunteer no. 4)
2.	Eyes	6. Itchy eyes +++, onset day 18 (Volunteer no. 6)
3.	Nose	7. Watery discharge +++, onset day 18 (Volunteer no. 3, 6) 8. Sneezing, Severe +++, onset day 18 (Volunteer no. 3, 6) 9. Congestion in the right sinus (sinusitis) (15 hrs) with drowsiness, < sound ++, and brain fog as concomitant symptom +++, onset day 3 (Volunteer no. 6)
4.	Neck and shoulder	10. Effect on the right shoulder, Severe pain, radiating from the neck, shoulder +++, onset day 3 (Volunteer no. 3) 11. Effect on the right neck, cannot lift the right hand ++, onset day 3 (Volunteer no. 3)
5.	Throat	12. Throat pain, < swallowing liquids < swallowing liquids ++, onset day 10 (Volunteer no. 6)
6.	Chest	13. Heaviness in the chest +, onset day 3 (Volunteer no. 4) 14. Shortness of breath +, onset day 20 (Volunteer no. 6) 15. Desire to take a deep breath +, onset day 3 (Volunteer no. 4)
7.	Cough	16. Dry cough +, onset day 24 (Volunteer no. 3)
8.	Abdomen	17. Tightness in the abdomen +, onset day 1 (Volunteer no. 8) 18. Constipation +, onset day 1 (Volunteer no. 8) 19. Eructation for a few hours in the afternoon for 3-4 days +, onset day 12 (Volunteer no. 7)
9.	Sleep	20. Sound sleep +, onset day 1 (Volunteer no. 4) 21. Loss of sleep between 3-6 am for 2 days +, onset day 3 (Volunteer no.2) 22. Drowsiness after 6 pm +++, onset day 2 (Volunteer no. 10, 7)
10.	Fever	23. Fever (99.5 F) for 3 hours with fatigue < sleep and > warm clothes, with overwhelmed feeling +++++, onset day 18 (Volunteer no. 6)
11.	Heart	24. Palpitation on slight exertion +, onset day 3 (Volunteer no. 4)
12.	Mind	25. Anxiety +++, onset day 3 (Volunteer no. 6)
13.	Generalities	26. Body pain affecting full body +, onset day 3 (24 hrs) (Volunteer no. 6) 27. Increased appetite +++, onset day 2 (Volunteer no. 7, 8)

Conclusion

New CVN01 nosode developed during a pandemic condition produced specific symptoms in the homeopathic pathogenetic trial as a part of the Phase 1 study.

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Statement of ethics

The study complies with the guidelines for human studies, and it was conducted ethically following the World Medical Association Declaration of Helsinki. The Independent Ethics committee approved the study protocol (Protocol reference number: LFFT/SS1/2020) and the written informed consent form. The trial was registered on the central clinical trial registry of India, reference number: CTRI/2020/05/025496.

Conflict of interest statement

One of the authors (RS) has a pending patent for nosodes prepared from corona-related viruses.

Funding sources

None

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