Dietary supplements to reduce symptom severity and duration in people with SARS-CoV-2: a double-blind randomised controlled trial

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ABSTRACT

Background COVID-19 has caused morbidity, hospitalisation and mortality worldwide. Despite effective vaccines, there is still a need for effective treatments, especially for people in the community. Dietary supplements have long been used to treat respiratory infections, and preliminary evidence indicates some may be effective in people with COVID-19. We sought to evaluate whether a combination of vitamin C, vitamin D₃, vitamin K₂ and zinc could improve overall health and decrease symptom burden in outpatients diagnosed with COVID-19.

Methods Participants were randomised to receive either vitamin C (6 g), vitamin D₃ (1000 units), vitamin K₂ (240 μg) and zinc acetate (75 mg) or placebo daily for 21 days and were followed for 12 weeks. An additional loading dose of 50,000 units vitamin D₃ (or placebo) was given on day one. The primary outcome was participant-reported overall health using the EuroQol Visual Assessment Scale summed over 21 days. Secondary outcomes included health status, symptom severity, symptom duration, delayed return to usual health, frequency of hospitalisation and mortality.

Results 90 patients (46 control, 44 treatment) were randomised. The study was stopped prematurely due to insufficient capacity for recruitment. The mean difference (control–treatment) in cumulative overall health was −37.4 (95% CI −157.2 to 82.3), p=0.53 on a scale of 0–2100. No clinically or statistically significant differences were seen in any secondary outcomes.

Interpretation In this double-blind, placebo-controlled, randomised trial of outpatients diagnosed with COVID-19, the dietary supplements vitamin C, vitamin D₃, vitamin K₂, and zinc acetate showed no clinically or statistically significant effects on the documented measures of health compared with a placebo when given for 21 days. Termination due to feasibility limited our ability to demonstrate the efficacy of these supplements for COVID-19. Further research is needed to determine clinical utility.

Trial registration number NCT04780061.

INTRODUCTION

COVID-19, caused by the novel SARS-CoV-2, has caused hospitalisations, morbidity and deaths worldwide. There are currently 11 vaccines granted emergency use listing by the WHO.1 Despite this, effective treatments are still needed. Vaccination is not 100% effective at preventing infection or adverse outcomes, and vaccine-acquired immunity wanes over time.2-4 There are also challenges to achieving high vaccination coverage, including access to vaccines, underlying conditions preventing vaccination and vaccine hesitancy.5 In high-income countries, only 74% of people are vaccinated and in low-income and middle-income countries, where access is limited, less than 40% of people are vaccinated.6

Treatments for COVID-19 are currently limited. The WHO recommends a handful of medications for patients with severe illness, or who are at the highest risk for hospitalisation.7 The use of natural health products (NHPs), including vitamins, minerals and herbal products to treat COVID-19 infections, has received both academic and public attention.8-9 Various NHPs have undergone clinical research for a wide variety of other upper respiratory tract infections (URTI).
These trials have mainly focused on symptom management, including reducing the duration and severity of the illness. Some of the most intensively researched NHPs include andrographis,8 9 quercetin,10 vitamin C,11–13 vitamin D11–13 and zinc.14 Additionally, there is limited evidence to support certain NHPs for the treatment of COVID-19, such as vitamin D and vitamin K.15–17

Research into community treatments of COVID-19 continues to be important and has the potential to contribute to global public health management of this pandemic and its associated societal burden. To date, there are no published double-blind, placebo-controlled randomised controlled trials (RCTs) evaluating the effects of NHPs for the treatment of COVID-19 specifically in the community. It is estimated that 98% of people who are diagnosed with COVID-19 will remain as outpatients,18 thus, these products could provide a low-cost, safe treatment option for the vast majority of people diagnosed with COVID-19.

In this RCT, we evaluated the effectiveness of vitamin C, vitamin D3, vitamin K2 and zinc acetate versus placebo in improving the overall health of people in the community diagnosed with COVID-19. We additionally compared health status, symptom severity and duration, delay in return to usual health, frequency of hospitalisations and mortality between arms.

METHODS
Design
This was a two-arm, parallel-group, double-blind, placebo-controlled RCT. Consented patients were randomised to receive vitamin C, vitamin D3, vitamin K2 and zinc acetate supplements or placebo daily for 21 days. Participants completed validated questionnaires assessing their overall health, health status and symptom severity while taking study products. Follow-up for health status and long-term COVID symptoms continued up to 12 weeks postrandomisation. This study followed Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials, and we used the CONSORT checklist when writing our report.19 The original protocol for this trial was published in 2022.20

Participants
Patients were included in the study if they were diagnosed with COVID-19 by reverse transcriptase PCR (RT-PCR) at an outpatient test centre in Ottawa, Canada and had access to the internet. Patients were excluded if their symptoms began more than 7 days prior to enrolment, were supplementing regularly with >500 mg vitamin C, >1000 units vitamin D (any form), >120 µg vitamin K (any form) or >15 mg zinc, had end stage kidney disease or a history of kidney stones, hypercalcaemia or hypervitaminosis D, active granulomatosis, or were taking vitamin K antagonist anticoagulants, cephalaxin, or tetracyclines. Enrolment began in October 2021 and was terminated prematurely in June 2022 as public access to PCR tests was restricted by the Ontario government in December 2021, with further restrictions added in April 2022. The date of last follow-up was 4 July 2022.

Investigational product
Participants randomised to the treatment arm received:
1. Vitamin D3 50000 units orally once on day 1 of the study (capsule).
2. Vitamin K2/D3 120 µg/500 units orally twice per day for 21 days (liquid).
3. Vitamin C/Zinc acetate 2 g/25 mg orally three times daily for 21 days (capsule).

Participants randomised to the control arm received equivalent capsules of microcrystalline cellulose and equivalent liquid doses of medium chain triglyceride oil. All investigational products were provided by New Roots Herbal under the brand name Vitazan Professional. Further detail on the selection of the investigational products is described in the published protocol.20

Setting
Participants were enrolled from outpatient COVID-19 test centres associated with The Ottawa Hospital. The primary site for enrolment and coordination of the study was The Centre for Health Innovation in Ottawa, Canada with support from the Ottawa Hospital Research Institute. All contact with participants was done remotely. Participants received questionnaires electronically through the Research Electronic Data Capture platform and follow-up was conducted by phone or email.

Regulatory adherence
Study activities adhered to guidelines for Good Clinical Practice, Part C Division 5 of the Canadian Food and Drug Regulations, and Part 4 of the Canadian Natural Health Product Regulations.

Primary outcome
The primary outcome of this study was participant-reported overall health measured using the EuroQol Visual Assessment Scale (EQ-VAS),21 which evaluates overall health on a scale of 0–100 where a score of 100 is described as the best possible health and a score of 0 is the worst possible health. The EQ-VAS was completed daily for 21 days.

Secondary outcomes
Secondary outcomes included health status measured using the EQ 5-Dimension 5-Level (EQ5D) questionnaire,22 symptom severity measured using an internally developed questionnaire (section 1, online supplemental materials S1), symptom duration, incidence of prolonged symptomatic COVID-19 (symptoms 4–12 weeks postonset) and post-COVID-19 syndrome (symptoms greater than 12 weeks postonset), frequency of emergency room visits, acute care admissions, and intensive care unit admissions, and all-cause mortality. Symptom severity was measured daily for 21 days and the EQ5D was administered at baseline and weeks 1,
2, 3, 4, 8 and 12. The study team conducted follow-up phone calls at weeks 1, 2, 3, 4, 8 and 12 to assess all other outcomes, support compliance and monitor adverse events (AEs).

Randomisation and blinding
Randomisation was conducted using a web-based system created and maintained by the Ottawa Methods Centre. Participants were randomised in a 1:1 ratio using variable permuted blocks of 4 and 6. Study products, information materials, and a thermometer were mailed directly to participants by New Roots Herbal. Product bottles were identical in appearance except for the lot number. Liquids and capsules were identical in size, smell and taste. Participants, investigators and research staff were blinded to treatment allocation. Participants were asked to guess which group they were assigned to at the end of the study as a proxy measure to test the effectiveness of blinding.

Sample size calculation
With respect to the primary outcome of participant-reported overall health, a sample size calculation was conducted based on between-group differences at a single time point (21 days) using Cohen’s guideline for a small effect size of 0.3. A sample size of 176 (88 per arm) would provide 80% power to detect a difference at an alpha of 0.05. To account for an expected 10%–15% non-compliance rate, we planned to enrol 200 participants (100 per arm).

Statistical methods
All analyses used an intention-to-treat approach and were conducted using SPSS StatisticsV.28.0.1.1. Continuous and quasi-continuous variables (overall health, health status and symptom severity) were compared between arms using unadjusted two-sample t-tests. Dichotomous outcomes (incidence of severe symptoms, ongoing symptomatic COVID-19, post-COVID-19 syndrome and hospitalisations) were
compared between arms using $\chi^2$ tests. Symptom duration was displayed graphically with a Kaplan-Meier curve and differences between arms were compared with the log-rank test. Participants were included in the analysis of overall health, symptom severity and symptom duration if they completed the 21-day intervention period, completed at least 11 (52%) daily assessments and did not miss more than three assessments sequentially. An area under the curve approach was used to analyse cumulative overall health and symptom burden, whereby participants’ scores for each assessment were summed over the 21-day period. For missing values, we imputed the mean of the most recent and first subsequent measurement or carried the last observation forward if there was no subsequent measurement.

**Patients and public involvement**

Patients and the public were not involved in the design and conduct, the collection and interpretation of data, or the dissemination plans of this research.

**RESULTS**

**Participant characteristics**

There were 90 of a planned 200 participants (46 control, 44 treatment) who were enrolled in this study between September 2021 and April 2022 (figure 1).
Four participants (two control, two treatment) withdrew before starting any intervention. Baseline health status and demographics of participants are presented in table 1. Mean age at enrolment was 39.9±14.9 (mean±SD) years in the control arm and 38.0±12.7 years in the treatment arm. There were no significant differences in sex, race, comorbidities or COVID-19 variant of concern (VOC) between arms at the time of randomisation. Most participants received the Pfizer-BioNTech vaccine (70% control, 79% treatment). The AstraZeneca vaccine was the least prevalent (4% control, 4% treatment). Over 95% of both populations received at least two vaccine doses. A significant proportion of participants in the treatment arm received a second booster vaccine compared with the control arm (88% vs 68%). The mean time from symptom onset to starting the investigational product was 7.7±2.4 days in the control arm and 7.9±2.7 days in the treatment arm.

**Primary outcome**

Figure 2 shows the average daily EQ-VAS score for both arms. The mean cumulative EQ-VAS score in the control arm was 1752.6±220.7 (mean±SD) compared with 1790.0±226.6 in the treatment arm (scale 0–2100), resulting in a mean difference of −37.4 (95% CI −157.2 to 82.3), p=0.53. This corresponds to an absolute difference of 1.8%. Seventy-one per cent of analysed participants in the control arm had an average daily score of 80/100 or above compared with 79% in the treatment arm, p=0.45.

**Secondary outcomes**

The mean cumulative symptom score in the control arm was 192.9±153.6 compared with 166.3±92.3 in the treatment arm (scale 0–2100), resulting in a mean difference of 26.7 (95% CI −38.6 to 91.1), p=0.42. This corresponds to an absolute difference of 1.3%. Of 44, 6 (14%) participants reported a severe symptom in the control arm compared with 12/42 (29%) in the treatment arm, p=0.09. Table 2

<table>
<thead>
<tr>
<th>Interval</th>
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<th>Treatment</th>
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<tr>
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<td>Mean±SD</td>
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<td>Mean±SD</td>
</tr>
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<td>Week 2</td>
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<td>0.95±0.07</td>
</tr>
<tr>
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<td>0.94±0.08</td>
</tr>
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</tr>
<tr>
<td>Week 12</td>
<td>0.96±0.07</td>
<td>26</td>
<td>0.96±0.07</td>
</tr>
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EQ5D, EuroQol 5-dimension; N, number of participants.
shows the mean EQ5D health status values for both arms, and we note that there was increasing non-response at each successive measurement time. The largest absolute difference seen between arms was 3% at 3 weeks, with all other time points showing differences between 0% and 2%. No comparisons were statistically significant. Figure 3 shows a Kaplan-Meier curve depicting time to symptom resolution. Median symptom duration in the control arm was 12.5 days compared with 13.0 days in the treatment arm, p=0.81. When analysing the incidence of delayed return to usual health, 5/29 (17%) participants reported symptoms at 4 weeks in the control arm compared with 6/35 (17%) in the treatment arm, p=0.99; 4/30 (13%) in the control arm reported symptoms at 8 weeks compared with 3/35 (9%) in the treatment arm, p=0.54; 3/29 (10%) in the control arm reported symptoms at 12 weeks compared with 3/33 (9%) in the treatment arm, p=0.87.

There were no known acute or intensive care unit admissions in our population. Of 44, 4 (9%) participants in the control arm reported to the emergency room during study follow-up compared with 2/42 (5%) in the treatment arm, p=0.43. There were no deaths reported in our population.

**Compliance and blinding**

While on-study, investigational product compliance was 93% in the control arm compared with 91% in the treatment arm. Eighteen participants guessed they were in the intervention arm and 37 guessed they were in the control arm, with 29/55 (53%) correctly guessing their assignment (11/30 treatment; 18/25 control). Most participants guessed they were in the control arm with the main rationale being a lack of improvement to health and a lack of side effects. Conversely, the most common reasons participants gave for guessing they were in the treatment arm were an improvement to health and experiencing side effects. Of participants giving one of these reasons, 8/11 accurately guessed their assignment.

**Safety**

Twenty-three AEs were reported in total (control: n=7; treatment: n=16). Four AEs possibly related to the investigational products were reported in the control arm vs 15 in the treatment arm, p=0.003. All AEs related to the investigational product were classified as grade 1 or 2, gastrointestinal, and were expected based on clinical experience and previous literature. No serious AEs were reported in the treatment arm. A full list and description of AEs is available in online supplemental table S1.

**DISCUSSION**

In this trial, we compared 21-day supplementation of vitamin C, vitamin D₃, vitamin K₂ and zinc acetate versus placebo for the treatment of outpatients diagnosed with COVID-19 in Ottawa, Canada. We assessed overall health, health status, symptom severity, symptom duration, incidence of delayed return to usual health, frequency of
hospitalisation and mortality. Recruitment was terminated prematurely due to restrictions placed on PCR testing by the Ontario government, which severely limited the number of eligible patients. The products were well tolerated with mild side effects. No clinically or statistically significant differences were seen in any measured outcome. Participants in the control arm were slightly less vaccinated compared with the treatment arm. Our method of blinding was effective, as evidenced by only 53% of the population able to correctly guess their treatment allocation.

Overall health using the EQ-VAS was chosen as the primary outcome as it is a validated tool and easily interpretable. Although research on other URTIs focuses heavily on symptom severity questionnaires, at the time there were no validated tools for assessing COVID-19 symptom burden. The clinical significance of symptom severity in a non-validated tool is much more difficult to assess and open to differing interpretations. The symptom questionnaire developed by our team was largely based on recommendations from the US Food and Drug Administration guidance document for investigators conducting community clinical trials for COVID-19 prevention or treatment and commonly reported COVID-19 symptoms in both the hospital and community setting. An area under the curve approach was used to analyse overall health and symptom severity as opposed to focusing on specific symptoms as it is not feasible to accurately and objectively rank one symptom as more debilitating than another, especially in an illness where the symptom profile is diverse and inconsistent among individual patients.

Data generally supports the use of vitamin C, vitamin D and zinc in the treatment of URTIs. Moderate doses of vitamin D have been shown to reduce the duration and severity of URTIs. Reductions in ascorbate levels have been observed and may be due to increases in reactive oxidation species during the immune response. Proposed mechanisms for zinc and the treatment of the common cold include inhibiting binding of the rhinovirus in the nasal mucosa, inhibiting proteolysis during the rhinovirus cell cycle and inhibiting rhinovirus replication. Evidence for the use of these products in people with COVID-19 is limited. Observational research indicates a correlation between the risk, seriousness and mortality of COVID-19 and maintaining appropriate levels of vitamin D and vitamin K. To our knowledge, this was the second clinical trial studying the effects of dietary supplements on COVID-19 for patients in the community and the first to be blinded and placebo controlled. In a study by the Cleveland Clinic, usual care plus high-dose vitamin C and zinc did not significantly reduce the duration of symptoms compared with usual care alone.

This trial had many strengths and limitations. A major strength is the rigorous design, including blinding, randomisation and placebo control, which gives the trial high internal validity. The similarity between both arms at baseline demonstrates effective randomisation and little likelihood for confounding factors on the outcomes assessed. A major limitation is the delay in receiving the study products. In an ideal setting, patients would begin taking therapeutic interventions immediately after noticing symptoms. In our study, the average time from symptom onset to starting the investigational product was nearly 8 days due to delays in testing, reporting of results, enrolment and the shipment of product. The median time to symptom resolution for COVID-19 patients has been reported to be 4–8 days. In addition, participants generally had a low symptom burden when starting the investigational product. Thus, it is likely that the majority of the participants had almost fully recovered before starting treatment. The delay in treatment highlights the difficulty of conducting such a study remotely while relying on institutional registry data, compounding further delay. Another major limitation is that most participants in this study were young, had few comorbidities and had excellent self-rated health at baseline (EQ-VAS: control: 74.5±15.4, treatment: 70.2±16.5, scale 0–100). This relatively healthy population offers less room for improvement by an experimental intervention. There may have been inherent selection bias toward patients with better overall health as those with more severe symptoms may have been less likely to participate due to the additional burden of the study.

Other minor limitations were present. A challenge with a trial exploring the impact of commonly available supplements is the potential for contamination. In this scenario, it is conceivable that participants may have chosen to access the same NHPs used in the trial from sources at home or easily purchased at a local health food store or drugstore; however, participants were asked about concomitant supplementation weekly while taking the study product, and exogenous usage was not reported. We attempted to address the issue of contamination prior to study onset by excluding people who were already taking relatively high doses of the study NHPs. Furthermore, dietary intake of these nutrients was not assessed. Although the recommended dietary allowance of these nutrients is substantially smaller than the study dosages, some contamination could be present. Another related limitation is that we did not obtain blood levels of these nutrients, particularly vitamin D, which would have been important given most research shows adequate vitamin D levels being the hypothesised reason for improved outcomes. The reason for this is that outpatients with COVID-19 were mandated to self-isolate on receiving a positive diagnosis; thus, obtaining blood samples was not possible in this population. Although VOC sequencing was not done in all participants, most participants with an unknown VOC likely had the Omicron variant of COVID-19 as it was the dominant variant in Ottawa when regular sequencing ended.

is reported to be more virulent but less severe than its delta counterpart. Finally, our statistical power was significantly reduced due to a lack of recruitment and a low compliance rate with completing daily questionnaires. In order to effectively address these limitations in future studies, researchers would likely need to conduct RT-PCR tests, consent and prerandomise patients during a single visit. This could help decrease the lag time between symptom onset and starting patients during a single visit. This could help decrease

In summary, a combination of vitamin C, vitamin D₃, vitamin K, and zinc acetate in outpatients with COVID-19 showed no beneficial effects for overall health or symptom burden when compared with a placebo. Due to the major logistical and participant-related limitations relevant to this study, we cannot make a definitive conclusion on the effectiveness of these nutrients.

REFERENCES

20. Legacy M, Seely D, Conte E, et al. Dietary supplements to reduce symptom severity and duration in people with SARS-CoV-2: study

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Contributors DS conceived of the study and serves as the guarantor for the study. DS, KW, ML, EC, AP, SK, TR and DAF designed the study. ML, EC, AP and CK recruited patients and were responsible for data collection and follow-up. JS confirmed eligibility for all participants. TR and ML contributed to statistical analysis. All authors contributed to data interpretation and the writing of this manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and this study was approved by the Research Ethics Boards of the Ottawa Health Sciences Network (20210072-01H) and Canadian College of Naturopathic Medicine (CCNMREB0306). Seely Wilson. No study activities took place before approval by both organisations. Each participant signed an informed consent form approved by both organisations prior to participation in the study. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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