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Abstract

Background: Incomplete data are often presented for determining the role of vitamin A supplement therapy for improving treatment outcomes in patients with COVID-19.

Aims: We compared treatment effects between a group that received vitamin A added to the standard COVID-19 treatment and another group that received the standard drug treatment alone.

Methods: Participants in this triple-blind controlled trial comprised 182 COVID-19 outpatients in Saveh City, Markazi Province, Islamic Republic of Iran, in 2020. Patients were randomly divided into experimental (n = 91) and control (n = 91) groups. Patients in the control group received the national standard treatment for COVID-19 (hydroxychloroquine), and those in the intervention group received 25 000 IU/d oral vitamin A for 10 days in addition to the standard treatment recommended by the national protocol. We evaluated the clinical symptoms, paraclinical criteria, and hospitalization status before and after 10 days of interventions.

Results: The treatment groups did not differ significantly in clinical and paraclinical symptoms before the intervention. However, clinical symptoms such as fever, body ache, weakness and fatigue, paraclinical symptoms, white blood cell count, and C-reactive protein showed significantly greater decreases in the experimental group 10 days post-intervention compared with the standard treatment alone (P

Conclusion: Vitamin A supplementation demonstrated efficacy in improving some clinical and paraclinical symptoms in patients with COVID-19. Future studies should evaluate vitamin A supplementation with a larger sample size and compare different dosages, especially in hospitalized patients.

Keywords: COVID-19, vitamin A, treatment, hydroxychloroquine

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Introduction

In December 2019, an epidemic emerged in Wuhan, China, and drew the attention of the world (1). The virus rapidly spread to other countries and soon became a pandemic (2). On 30 January 2020, the World Health Organization declared the disease a public health emergency of international concern that threatened not only China, but also all countries (3,4). The evolutionary analyses based on genes indicated that the virus belongs to the family of beta-coronaviruses (5).

Beta-coronaviruses cause a wide range of viral diseases, including more severe illnesses such

as the Middle East respiratory syndrome coronavirus (MERS- CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) (6,7). In the novel coronavirus (nCoV-2019) COVID-19, the incubation period lasts about 7 days when the antibodies are not yet developed. The asymptomatic period is from the time of infection until the fifth day; and the period of onset of clinical symptoms is from the fifth to the eighth day (8,9). The most common clinical symptoms of infection are fever (87.9%), cough (67.6%), fatigue (38.1%), diarrhoea (3.7%), and vomiting (5%), and therefore COVID-19 is similar to other coronaviruses.

Vitamin and mineral dietary supplements are typically safe and can be used to supply or supplement nutrients essential for bodily processes, especially immune system functioning. For instance, vitamin A reduces the risk of viral infections and has beneficial effects on the lungs and immune system function. It is an anti-inflammatory substance (10) and plays a considerable role in immunity against infectious diseases (11); its deficiency causes numerous injuries that disrupt the response to infection (12). Recent clinical trials have indicated that vitamin A reduces complications and mortality in various infectious diseases such as measles, diarrhoea, measles-related pneumonia, and human immunodeficiency virus infection (11). Its deficiency is associated with higher susceptibility, severity and duration of infection (13).

Vitamin A is necessary for consistent immunity and plays a role in the growth of T cells, T helper cells (Th cells), and B cells. In particular, vitamin A deficiency decreases the antibody-mediated responses by Th2 cells. Its deficiency disrupts innate immunity by preventing the regeneration of mucosal epithelium damaged by infection and by reducing the function of neutrophils, macrophages and natural killer cells (12,14).

Given that there is no specific treatment for COVID-19 and to our knowledge no studies have evaluated the effects of vitamin A supplementation in the treatment of COVID-19, this study aimed to assess the efficacy of standard treatment plus vitamin A supplementation compared with standard treatment alone on COVID-19 symptoms, hospitalization status and paraclinical criteria.

Methods

Study design and participants

In this triple-blind clinical trial, the sample comprised patients of Saveh Health Centre, in Islamic Republic of Iran and all of them had COVID-19. The sample size was estimated to be 64, with confidence level 0.95, power 0.80, and the probable mean difference (Cohen's d) of the dependent variable before and after the intervention [i.e. predicted change in probability, mean score for creatinine (Cr) 0.5] using the formula proposed by Lehr (16/d2) (15). Given the possibility of sample attrition, 91 individuals were included in the study for each group (n = 182)

(Figure 1).

The inclusion criteria were: receiving outpatient care for COVID-19 from the health centre in Saveh, age 18–75 years, agreeing to participate in the study and completing the informed written consent forms. The exclusion criteria included: having any autoimmune diseases (lupus, multiple sclerosis, etc.), having chronic infectious disease, having concomitant or previous viral infections, being a current consumer of vitamin A supplement, pregnant and breastfeeding women, having renal failure, underlying liver disease, having heart failure and having chronic pulmonary disease.

We recruited patients who visited the COVID-19 outpatient centre of Saveh, which is the only medical centre in the city, from 1 May to 1 September 2020 and had positive PCR results for COVID-19. After patients were screened for inclusion/exclusion criteria and completed informed consent, they were then randomly assigned to the 2 treatment groups using the random allocation table.

Randomization and blinding

The method of blinding was as follows: the main researcher packed the drugs in 2 packages A and B and placed them in the pharmacy with the pharmacist. Package A included national standard treatment for outpatients (hydroxychloroquine) in addition to vitamin A (Zahravi Pharmaceutical Company), and package B included the national standard treatment of COVID-19 for outpatients (hydroxychloroquine) in addition to placebo. The placebo was made to look and feel like the original vitamin A, but the active ingredient was an ineffective substance (glycerin). Patients diagnosed with COVID-19 were referred to a pharmacy by the physician; and the pharmacist assigned the patients to one of the groups A or B based on the random numbers table. The pharmacist was a research assistant who did not take part in the enrolment of participants. Using permuted block randomization with a block size of 2 and an allocation ratio of 1:1, patients were allocated to the intervention

and control groups. A random sequence of “intervention” and “control” was generated using a random numbers table. After installing the tables in the clinic, the intervention or control was designated as the first experimental group for the first eligible person by the sampler. It is clear that based on the random sequence method, the next word can be used. Therefore, the patients, laboratory technicians, therapists involved in prescribing, sample recipient and questionnaire responders were blind to the treatment group. The main researcher was not blind to the groups. Participants were not allowed to use any other medication during the 10 days of the study. Patients were trained to follow the prescribed treatment. They were followed up by telephone on the third and sixth days to check their health and general condition and adherence

to the recommended treatment regimens, and on the eleventh day they were visited in person.

Supplement administration

Ninety-one patients in the control group received only the standard national treatment, and 91 patients in the intervention group received 25 000 IU/d vitamin A for 10 days in addition to the standard treatment recommended in the national protocol.

Outcome measurements

We examined the dependent variables before and after the treatment intervention in both groups. The clinical improvements (in combination) up to 10 days after treatment were measured using a self-report questionnaire and patient examination. Clinical improvement was defined as normal body temperature (≤ 37.2° oral), improved cough (lack of cough that was sustained for at least 24 hours and based on the patient report on a physical scale), chills, shortness of breath, headache, body ache, hyposmia, fatigue, anorexia and diarrhoea. A therapist examined the symptoms at baseline and 10 days after the treatment. The cellular count and biochemical parameters of patients were tested by trained constant operators in the reference laboratory of Saveh University of Medical Sciences (17) according to international guideline. Paraclinical improvement was defined as changes in C-reactive protein (CRP) and lymphocytes before and after the treatment, and normal ranges of: white blood cells (WBCs), erythrocyte sedimentation rate (ESR), creatine phosphokinase (CPK), Cr test, liver function tests [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)]. A turbidimetric method was used to determine CRP; CPK quantified by an ultra violet kinetic method using a special kit; WBC was measured with flow cytometry counters using a haematology analyser (ADVIA 2120) for AST and ALT via a photometric method and autoanalyser. We did not evaluate alkaline phosphatase and did not perform the liver and bile duct ultrasonography because no jaundice occurred in any of the patients. The paraclinical variables were evaluated at the beginning and on the tenth day of study. The proportion of patients who were hospitalized due to COVID-19 was examined and compared between the 2 groups.

Statistical methods

The data collected from the patients were given to the statistical evaluator in codes because the statistical evaluator was blinded to the treatment groups. Statistical analysis was conducted using SPSS, version 20.0. All measurement data were reported as mean and standard deviation. Treatment groups were statistically compared using independent sample t-tests. The intra-group comparisons were performed using paired t-tests. Enumeration data were reported as case numbers and percentages and these outcomes were compared using chi-squared. Alpha level was set at P **Ethics**

Written informed consent was obtained from all the patients in the study. All participants were

given an information sheet together with the consent form and advised that they could revoke their consent at any time without giving any reasons. The study protocol was approved by the ethics committee of Saveh University of Medical Sciences (IRSAVEHUMSREC1399.003) and registered on the Iran Clinical Trial database (IRCTID: IRCT 46974). The required permission was obtained from the hospital authorities.

Results

Two out of 91 patients in the experimental group did not complete the post-intervention evaluation 10 days after treatment, therefore the final analysis was performed on 91 patients in the control group and 89 in the experimental group. Mean age was 39.4 (SD 15.6) years in the experimental group and 40.8 (SD 17.3) years in the control group. Fifty-three individuals (59.5%) in the experimental group and 51 (56%) in the control group were male. Most of the patients (n = 122, 67.8%) were married, and 56 (31%) had a high school diploma. A total of 15 patients (8.3%) were drug addicts, and 81 (45%) reported moderate economic status. Forty-eight patients (26.6%) had underlying diseases, and 49 (27%) had family members with COVID-19. The chi-square test did not show any significant difference between the experimental and control groups in terms of demographic variables (P > 0.05) (Table 1).

Evaluation of the patients' clinical symptoms indicated that there was no significant difference between the groups in terms of fever, chills, cough, shortness of breath, headache, body ache, decreased sense of smell, weakness, and fatigue, anorexia and diarrhoea before the therapeutic intervention. However, the proportion of those reporting fever, body ache, and weakness and fatigue was significantly lower in the group that received the vitamin A supplement plus hydroxychloroquine 10 days after the intervention (P Table 2).

There was no statistically significant difference between the experimental and control groups in terms of paraclinical criteria - WBC, CRP, AST, ESR, CPK and Cr - before the therapeutic intervention, but there was a significantly greater reduction of CRP and WBCs in the group receiving the vitamin A supplement in comparison with the control group after the therapeutic intervention (P Table 3). The results of the paired t-tests indicate that all paraclinical criteria significantly changed in the experimental group after the treatment intervention (P 0.05).

Discussion

In this study, we aimed to determine whether vitamin A supplementation along with standard treatment was more efficacious in reducing COVID-19 symptoms and improving outcomes than standard treatment alone in patients presenting to an outpatient health centre. We found that some clinical symptoms (fever, body ache and fatigue) were significantly more improved 10

days after treatment in the group that received the vitamin A supplement in comparison with the control group. The results for other clinical symptoms also indicated improvements over time for chills, cough, shortness of breath, hyposmia, anorexia, and diarrhoea in the vitamin A group, but these findings were not statistically significant compared with the control group. This was consistent with a study by Kahbazi et al., who found that vitamin A could reduce fever in patients with acute pyelonephritis (10). In a study on neonates, Shenai et al. found that taking vitamin A was effective in reducing the infection in breathing pathways (16). Aluisio et al. found that vitamin A supplement led to a reduction in mortality in patients with Ebola virus disease (17). In a study on very-low-birth-weight infants, vitamin A reduced the symptoms of patients with diarrhoea, fever, lethargy, acute respiratory infections, rubella and ear infections (18). In a similar study among schoolchildren, a vitamin A supplement reduced mortality rates and complications of infectious diseases of the gastrointestinal and respiratory tracts (19).

Previous research has suggested that vitamin A plays an important role in maintaining the health of the mucous membranes and skin covering the nose, sinuses and mouth; immune system function; T and B lymphocytes; macrophages; and the production of antibodies (20,21). It helps in adjusting the secretion of IL-10: IL-10 is produced by T helper 2 (TH2) cells and inhibits the synthesis of the pre-inflammatory cytokines, including IFN-γ and IL-2, in both natural killer- and T-cells. This mechanism is important in limiting inflammatory responses to certain pathogens (22).

In our study, the CRP rate further decreased in the vitamin A supplement group; CRP is known as an attractive biomarker of inflammation because its concentration increases rapidly within a few hours of infection, and even before any clinical symptoms develop (23). Shaker et al. conducted a study evaluating the effectiveness of zinc and vitamin A supplement in treating and reducing upper respiratory tract infections in children (23). Consistent with our findings, they found a significant reduction in CRP in patients. This was expected because vitamin A inhibited CRP production (24). This biomarker is widely used in clinical diagnoses as a non-specific acute phase indicator of inflammation. It responds to infection through its rapid production by the liver and its release into the bloodstream and stimulation by several cytokines, including IL6, IL1β, and TNFα. (24,25).

Our findings indicates that the WBC level in the group receiving vitamin A supplement showed a greater decrease than in the control group. Similarly, the rate for WBCs showed a significant reduction in recipients of vitamin A and zinc in a study on upper respiratory tract infections in children (23). In a similar study, the WBC level significantly decreased in tuberculosis patients who received vitamin A (26). In our study, the level of lymphocytes significantly increased in the experimental group, while there was no significant change in the control group. Previous studies have shown the beneficial effects of vitamin A supplement in children with viral diseases through the increase of lymphocyte proliferation (22,27). Vitamin A deficiency disrupts the innate

immunity by preventing the natural regeneration of mucosal barriers damaged by infection and reducing the function of neutrophils, macrophages and natural killer cells. Vitamin A is necessary for consistent immunity and is involved in the growth of T helper (Th) and B cells. In particular, its deficiency decreases the antibody-mediated responses by Th2 cells (12,14).

Our findings did not show any significant difference in Cr levels of patients in the experimental and control groups before and after the intervention. However, in-group comparison indicated a significant decrease in Cr in the experimental group. Creatinine level is a sign of kidney function. As none of our participants had kidney failure or dysfunction, the therapeutic intervention likely had no effect on their Cr levels.

Our findings indicate that liver enzymes were less than 1.5 times the normal amount (normal: 20 in women and 30 in men) in both control and experimental groups, and they were unchanged by the pharmacological intervention. In the case of liver inflammation and hepatocellular hepatitis, the amount of transaminase increased by more than 5 times (28).

The research limitation was that, because this study used a sample from an outpatient health centre and these patients were quarantined at home, all conditions of the patients were not directly supervised.

Conclusion

Our results suggest that vitamin A supplement is efficacious in improving some clinical (fever, body ache, weakness and fatigue) and paraclinical symptoms (reduction of WBC and CRP) in patients with COVID-19. We suggest future studies examine outcomes with a larger sample size and compare dosage of vitamin A, especially in hospitalized patients.

Funding: None

Competing interests: None declared.

Évaluation de la supplémentation en vitamine A et comparaison avec les thérapies standard dans le traitement des patients atteints de COVID-19

Résumé

Contexte : Les données présentées pour déterminer le rôle de la supplémentation en vitamine A dans l'amélioration des résultats du traitement des patients atteints de COVID-19 sont souvent incomplètes.

Objectifs : Nous avons comparé les effets thérapeutiques entre un groupe qui recevait de la vitamine A en complément du traitement standard contre la COVID-19 et un autre groupe qui recevait uniquement le traitement médicamenteux standard.

Méthodes : Les participants à cet essai contrôlé en triple aveugle comprenaient 182 patients COVID-19 ambulatoires dans la ville de Saveh, province de Markazi, République islamique d'Iran, en 2020. Les patients ont été répartis aléatoirement en groupes expérimental (n = 91) et témoin (n = 91). Les patients du groupe témoin ont reçu le traitement standard national contre la COVID-19 (hydroxychloroquine) et ceux du groupe d'intervention ont reçu 25 000 UI/j de vitamine A par voie orale pendant 10 jours parallèlement au traitement standard recommandé par le protocole national. Nous avons évalué les symptômes cliniques, les critères paracliniques et le statut d'hospitalisation avant et après 10 jours d'interventions.

Résultats : Il n'y avait pas de différence significative entre les groupes de traitement en ce qui concerne les symptômes cliniques et paracliniques avant l'intervention. Cependant, des symptômes cliniques tels que la fièvre, les douleurs corporelles, la faiblesse et la fatigue, les symptômes paracliniques, la numération des globules blancs et la protéine C-réactive ont montré des diminutions significativement plus importantes dans le groupe expérimental 10 jours après l'intervention par rapport au traitement standard seul (p

Conclusion : La supplémentation en vitamine A a prouvé son efficacité dans l'amélioration de certains symptômes cliniques et paracliniques chez les patients atteints de COVID-19. Les futures études devraient évaluer la supplémentation en vitamine A avec un échantillon plus vaste et comparer différents dosages, notamment chez les patients hospitalisés.

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: غالبًا ما تقدم بيانات غير كاملة لتحديد دور العلاج بمكملات فيتامين (أ)الخلفية
لتحسين نتائج العلاج بين مرضى كوفيد -19.

: هدفت هذه الدراسة الى مقارنة آثار العلاج بين مجموعة تلقت فيتامين (أ)الأهداف
بالإضافة إلى علاج كوفيد -19 المعياري ومجموعة أخرى تلقت العلاج بالأدوية المعيارية
وحدها .

: ضم المشاركون في هذه التجربة المضبوطة بتعمية ثلاثية 182 مريضًا من مرضطرق البحث
كوفيد -19 المراجعين للعيادات الخارجية في مدينة سافيه بمحافظة مركازي في جمهورية
إيران الإسلامية في عام 2020. ووزَّع الباحثون المرضى عشوائيًّا إلى مجموعة تجريبية
(العدد = 91) ومجموعة ضابطة (العدد = 91). وتلقى المرضى في المجموعة الضابطة العلاج
المعياري الوطني لكوفيد -19 (الهيدروكسيكلوروكين) ، وتلقى المرضى في مجموعة التدخل
25000 وحدة دولية / يوميًّا من فيتامين (أ) عن طريق الفم لمدة 10 أيام، بالإضافة إلى
العلاج المعياري الموصى به في البروتوكول الوطني . وقد قيَّمنا الأعراض السريرية
والمعايير اللاسريرية وحالة إدخال المستشفى قبل التدخلات وبعدها بمدة 10 أيام .

: لم تختلف مجموعتا العلاج اختلافًا مهمًّا في الأعراض السريرية واللاسريرية**النتائج**
قبل التدخل . ومع ذلك، تراجعت الأعراض السريرية، مثل الحمى وآلام الجسم والضعف والتعب
والأعراض اللاسريرية وتعداد خلايا الدم البيضاء والبروتين المتفاعل سي، تراجعًا أكبر
كثيرًا في المجموعة التجريبية بعد 10 أيام من التدخل، مقارنةً بالعلاج القياسي وحده
(القيمة الاحتمالية أقل من 0.05).

: أثبتت مكملات فيتامين (أ) فاعليةً في تحسين بعض الأعراض السريريةالاستنتاجات
واللاسريرية عند مرضى كوفيد -19. وينبغي للدراسات المستقبلية تقييم مكملات فيتامين (أ)
بعينات أكبر حجمًا ومقارنة الجرعات المختلفة، وخاصة مع المرضى نزلاء المستشفيات .

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