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Effect of vitamin A supplementation on the outcome severity of COVID-19 in hospitalized patients: A pilot randomized clinical trial

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Abstract

Introduction: Vitamin A is one of the vitamins that is suggested as adjuvant therapy in viral infections due to its immune enhancing role. In the present clinical trial, we intended to assess the effect of vitamin A supplementation on Coronavirus disease-2019 (COVID-19) in hospitalized patients. **Methods:** The present pilot randomized controlled clinical trial was conducted on 30 hospitalized patients with COVID-19. Patients in the intervention group received 50000 IU/day intramuscular vitamin A for a maximum of two weeks. Patients in the control group continued their common treatment protocols. All participants were followed up until discharge from the hospital or death. The primary outcome of the study was time to achieve clinical response based on the six classes of an ordinal scale. Time to clinical response was calculated based on the days needed to improve two scores on the scale or patient's discharge. **Results:** The time to clinical response was not significantly different between the two groups (7.23 ± 2.14 vs. 6.75 ± 1.85 days, respectively, $p = 0.48$). There was no significant difference between the groups regarding clinical response (hazard ratio: 1.76 [95% CI: 0.73, 4.26]). There were no significant differences between groups regarding the need for mechanical ventilation, duration of hospitalization, or death in the hospital. **Conclusion:** The results of this pilot clinical trial showed no benefit of vitamin A compared with the common treatment on outcome severity in hospitalized patients with COVID-19. Although the results are negative, there is still a great need for future clinical studies to provide a higher level of evidence.

Keywords

COVID-19, clinical severity, respiratory sign, vitamin A, clinical trial, clinical response

Introduction

Coronavirus disease-2019 (COVID-19), which originated in Wuhan China in late 2019, has been spreading very fast around the world and declared a pandemic (Cucinotta and Vanelli, 2020). The challenge is that the novel coronavirus can vary from a simple upper tract respiratory system disease to a multiorgan failure disease (Esakandari et al., 2020). It is believed that angiotensin-converting enzyme-2 (ACE2) is the pathological pathway of severe acute respiratory syndrome coronavirus-2 (SARS-COV2) infection in the host, but unfortunately, there is not yet a specific vaccine or fully effective antiviral drug for its treatment (Zhang et al., 2020). In some patients, Covid-19 progresses rapidly, leading to intensive care, intubation, or death (Martins-Filho et al., 2020). This may be partly related to the nutrition status of patients. It has been indicated that low micronutrient status, such as vitamin A and zinc deficiency, has been associated with a higher risk of severe

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viral infections (Stephensen, 2001). Vitamin A is one of the vitamins that is suggested as adjuvant therapy in viral infections and pneumonia (Stephensen, 2001). Vitamin A and its metabolites are immune enhancers in different ways, such as increasing lymphocyte proliferation and their response to antigens, and they can improve the development of T and B cells (mostly T-helper cells) (Stephensen, 2001). Previously, most of the studies have focused on the effect of vitamin A deficiency in pneumonia, especially in younger ages and children, and provided mixed results (Fawzi et al., 1998; Iddir et al., 2020; Nacul et al., 1998; Zhou et al., 2016). Some of these studies have reported the positive effect of vitamin A supplementation on the risk of severe diseases via an immunomodulatory and anti-inflammatory effect (Li et al., 2020; Zhou et al., 2016); however, others did not show any effect (Nacul et al., 1998).

Now that Covid-19 is a public health emergency around the globe and presently, there is no effective treatment for it, some studies are emphasizing the use of simple adjuvant therapies without side effects, such as bioactive compounds (Carr, 2020). Considering the immune enhancing role of vitamin A, we intended to assess the effect of vitamin A supplementation on the severity of Covid-19 in hospitalized patients with Covid-19.

Methods

The present parallel-arm, randomized, controlled clinical trial was conducted on patients with COVID-19 who were admitted to the Imam-Reza hospital in Tabriz-Iran. The patients were included if they were aged >18 years, had a confirmed diagnosis of COVID-19 with RT-PCR, and were ventilator independent. The patients were excluded if they were pregnant, lactating mothers, or using high-dose vitamin A in the last month.

The sample size was calculated based on the Whitehead study (Whitehead et al., 2016), which recommended 15 samples per arm in pilot clinical trials considering 90% power, two-sided 5% significance, and medium effect size (0.5). To allow drop-outs, 18 patients in each arm were recruited.

In the present study, the patients were selected randomly from newly admitted patients in inpatients wards of patients with Covid-19. The patients were randomly allocated to vitamin A or the control groups. A person who was not involved in other processes of the study assigned the patients to the groups by a simple random allocation using a computer program.

Patients in the intervention group received a daily dose of 50000 IU intramuscular vitamin A (OSVE-VITAMIN A 50,000U/1ML AMP) for a maximum of two weeks in addition to their common treatments. The dose of vitamin A was selected based on a previous study on adults (Said et al., 2020). Patients in the control group continued their common treatment protocols (Hydroxychloroquine, Antiviral regimen, Corticosteroid, and Antibiotic). Considering the nature of the study, neither the doctors and nurses nor the patients were blind to their study group.

The demographic data, baseline characteristics, and clinical laboratory data were collected using questionnaires by a trained physician. All participants were monitored daily in terms of vital signs, medical interventions, and clinical conditions. They were followed up until discharge from the hospital or death. The national early warning score (NEWS) 2 was used for determining the severity of diseases. It is calculated by summing the predetermined values regarding each of seven parameters: respiration rate, oxygen saturation, oxygen supplement, systolic blood pressure, pulse, body temperature, and level of consciousness. NEWS2 (score: 0–20) was categorized into four risk groups: low (0–4), low-medium (an extreme variation of 3 in a single parameter), medium (5–6), and high ($\geq$7) risk (Physicians RCo, 2017).

The need for respiratory support was evaluated by the physician, and according to the physician's decision, the patients were considered in one of the six classes of the ordinal scale (Peterson et al., 2017).

The primary outcome of the study was time to achieve clinical response based on the six classes of an ordinal scale (Peterson et al., 2017). Based on this scale, the patients were categorized into six classes: 1) discharged, hospital admission: 2) without the need for supplementary oxygen, 3) with the need for supplementary oxygen, 4) with the need for noninvasive positive pressure ventilation, 5) with the need for invasive mechanical ventilation, and 6) death. Time to clinical response was calculated based on the days needed to improve two scores on the scale or patient's discharge (Peterson et al., 2017). In addition, the need for invasive mechanical ventilation (IMV), noninvasive positive-pressure ventilation (NIPPV), and duration of ICU stay and hospitalization were recorded.

Statistical analysis

SPSS version 22.0 was used for statistical analysis. The continuous variables are presented as the mean (SD) for normally distributed data, and median (IQR) for no normally distributed data. The nominal and categorical variables are presented as numbers (%). The between-group comparisons were performed using independent sample t-tests and Mann-Whitney U test for continuous variables and chi-square tests for nominal variables. The Kaplan-Meier plot and log-rank test were used to compare the number of days needed to reach the clinical response between groups. Cox regression was used to estimate the hazard ratio considering age, sex, smoking, and comorbidities as confounding factors. The significance level was considered a P-value ≤ 0.05.

Results

In the present clinical trial, 45 patients were assessed for eligibility, of whom 36 patients were selected

according to our eligibility criteria. Three participants in each group were not included in the final analysis (figure 1).

The patients' mean age was 60.21 ± 13.61 years, and 63.3% of them were male. As shown in Table 1, there were no significant differences between the vitamin A and control groups regarding demographic characteristics, symptoms on admission, initial vital signs, disease severity, and laboratory data.

The patients were received the vitamin A supplements 7.33 ± 2.31 days. Table 2 indicates the supportive care interventions and medications stratified by groups. There were no significant differences between the vitamin A and placebo groups in terms of ICU admission rate, respiratory support, and treatment strategies.

Figure 2 depicts the Kaplan-Meier plot for time to clinical response. As a primary endpoint, the time to clinical response was not significantly different between the two groups (7.23 ± 2.14 vs. 6.75 ± 1.85 days, respectively, $p = 0.48$). The log-rank test indicated that there was no significant difference between the groups regarding time to clinical response (hazard ratio: 1.76 [95% CI: 0.73, 4.26].

Table 3 presents the secondary outcomes of the study. As illustrated, there were no significant differences between groups regarding the need for IMV, duration of hospitalization, and death in the hospital.

No adverse effects were reported in the intervention group.

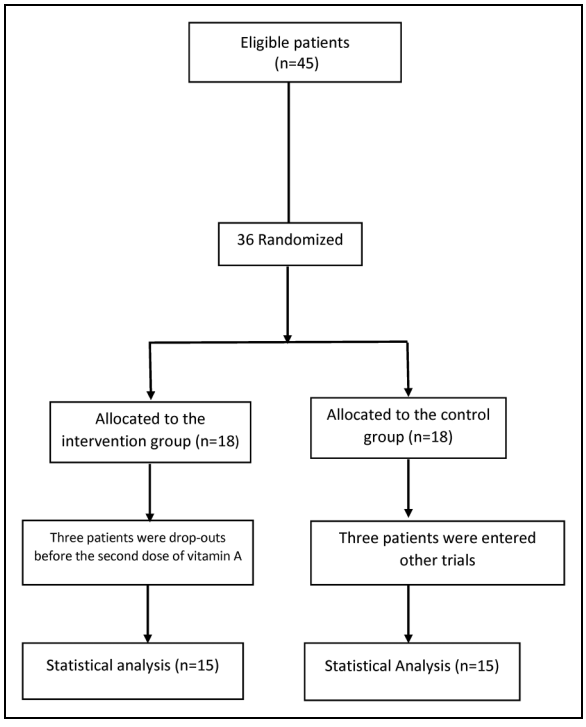

Figure 1. Flow chart of patients' recruitment and analysis.

Discussion

Considering the lack of a specific drug or vaccine for COVID-19, studies have focused on different adjuvant therapies or supplements during this disease. Accordingly, in this study, we investigated the impact of using vitamin A as adjuvant therapy on hospitalized COVID-19 patient outcomes. Our results showed no significant differences between the vitamin A and placebo groups in terms of clinical response, ICU admission rate, and respiratory support. To the best of our knowledge, this is the first study that evaluated the effect of vitamin A supplementation in patients with COVID-19. Previously, different studies focused on the effect of vitamin A on pneumonia. The results of our study were in line with some of the previous studies. In a meta-analysis study, Agrawal et al. concluded that vitamin A has no protective effect on the pneumonia rate (Sommer et al., 1995). In another meta-analysis study, Ni et al. concluded that high doses of vitamin A have no favorable effect on acute lower respiratory tract infections (Wu et al., 2005). However, some other studies have shown that high-dose supplementation with vitamin A can shorten the recovery period, especially in the course of pneumonia in children (Si et al., 1997). The observed controversy among the studies can be attributed to the differences in the included population, (children vs. adults), serum vitamin A status, studied disease (pneumonia vs COVID-19), and supplementation dosage. Earlier studies have suggested that in patients with sufficient vitamin A stores, supplementation with high doses of vitamin A may cause a malfunction in the regulation of immune function that may lead to an increased susceptibility to infectious diseases (Grotto et al., 2003). However, in the present study, we used moderate doses of vitamin A that have been shown to have a favorable effect on pneumonia in children with a sufficient amount of serum vitamin A (Rodríguez et al., 2005). The probable reason for this lack of significant difference between the experimental groups in the present study is the low sample size of the study.

The results of the present study should be interpreted considering the study limitations. This study was a single-center pilot study, with only 15 patients per arm. Moreover, we did not follow-up the patients after they were discharged from the hospital to detect long-term mortality, as we focused on in-hospital mortality. In addition, clinicians and patients were not blind to treatment allocation. Moreover, we did not measure the serum level of vitamin A, so, we could not be confident that the injected vitamin A raises the serum vitamin A sufficiently. However, previous studies showed that vitamin A supplementation increases the serum retinol level(Madatuwa et al., 2007; Soekarjo et al., 2004).

Conclusion

In conclusion, the results of this pilot clinical trial showed no benefit of vitamin A compared with the common

Table 1. Demographic and clinical characteristics of the patients at baseline.

Variable	Vitamin A group (n = 15)	Control Group (n = 15)	P-value
Age (years)	59.20 ± 14.65	61.28 ± 4.94	0.68*
Male Sex n (%)	10 (66.6)	9 (60.0)	0.60**
Current smoker n (%)	2 (0.13)	2 (0.13)	-
Coexisting condition n (%)			
Diabetes	3 (20)	4 (26.6)	0.68**
Cerebrovascular diseases	6 (40.0)	10 (66.6)	0.08**
Cancer	0 (0.0)	1 (6.6)	-
Chronic respiratory diseases	1 (6.6)	1 (6.6)	-
Symptoms at admission n (%)			
Cough	12 (80.0)	13 (86.6)	0.31**
Fever	11 (73.3)	9 (60.0)	0.70**
Dyspnea	12 (80.0)	13 (86.6)	0.31**
Myalgia	11 (73.3)	13 (86.6)	0.16**
Initial vital sign and laboratory data n (%)			
Temperature (°C)	37.57 ± 0.53	37.42 ± 0.60	0.48**
Heart rate	87.0 ± 8.41	90.80 ± 12.03	0.33**
RR	27.46 ± 3.73	28.14 ± 3.65	0.62**
RR>24	14 (93.3)	13 (86.6)	0.98**
SBP<90	0 (0.0)	0 (0.0)	-
O_2 saturation (%)	88 (10)	87 (2.25)	0.45***
White-cell count (× 1000/µl)	7.49 ± 4.88	8.02 ± 2.91	0.84*
Lymphocyte count (× 1000/µl)	0.55 ± 0.14	0.43 ± 0.11	0.67*
Serum creatinine (mg/dl)	1.08 ± 0.26	1.10 ± 0.34	0.16*
ALT (IU/liter)	29 (10.25)	25 (42)	0.22***
AST (IU/liter)	46.78 ± 20.85	42.53 ± 25.31	0.63*
Hemoglobin (g/dl)	12.68 ± 2.0	13.51 ± 2.04	0.28*
BUN (mg/dl)	19.05 ± 11.75	15.65 ± 3.90	0.31*
INR	1.05 ± 0.11	1.09 ± 0.09	0.30*
ESR(mm/h)	40.77 ± 23.16	58.81 ± 30.45	0.16*
LDH (U/liter)	581.71 ± 293.37	640.27 ± 288.54	0.65*
NEWS2	7.66 ± 0.72	7.42 ± 1.34	0.55*
Lung CT scan findings –n (%)			-
Ground-Glass pattern	15 (100)	15 (100)	
Consolidation pattern	0	1 (6.6)	
Bilateral lesion	15 (100)	14 (93.3)	

RR: respiratory rate; ALT: Alanine amino transferase; AST: Aspartate amino transferase; BUN: blood urea nitrogen; INR: International normalized ratio; ESR: Erythropoietin sedimentation rate; LDH: lactate dehydrogenase; NEWS2: National Early Warning Score

*p-value of independent t-test

**p-value of chi-square

*** p-value of Mann-whitney U test

Table 2. Supportive care interventions and medications.

Variables	Vitamin A group (n = 15)	Control Group (n = 15)	P-value *
ICU admission	3 (20)	4 (26.6)	0.66
Respiratory support			
Supplementary Oxygen	12 (80)	11 (73.33)	0.94
NIPPV	0 (0)	1 (6.66)	0.29
IMV	3 (20)	3 (20)	-
Medications			
Hydroxychloroquine	15 (100)	15 (100)	-
Antiviral regimen	7 (46.66)	4 (26.66)	0.17
Corticosteroid	6 (40)	3 (20)	0.21
Antibiotic	6 (40)	5 (33.3)	0.45

ICU: intensive care unit; NIPPV: noninvasive positive-pressure ventilation; IMV: invasive mechanical ventilation

*p-value of chi-square test

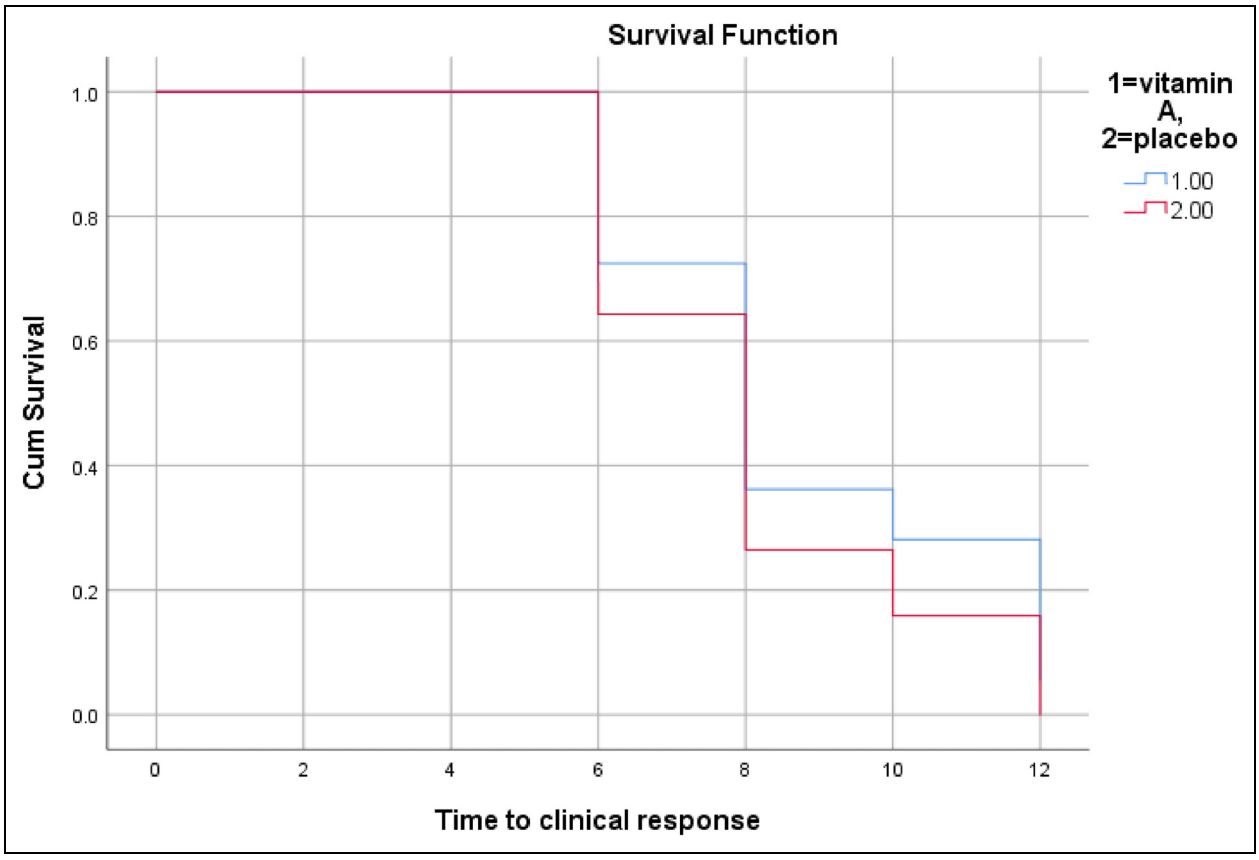

Figure 2. Kaplan-Meier plot for time to clinical response. Hazard ratio was calculated as 1.76 with 95% CI of 0.73, 4.26.

Table 3. Outcomes of the study.

Outcomes	Vitamin A (n = 15)	Placebo (n = 15)	p-value
Time from starting intervention to clinical response*	7.23 ± 2.14	6.75 ± 1.85	0.48*
Required IMV	3 (20)	3 (20)	-
Duration of hospital stay	7.33 ± 2.31	6.78 ± 1.84	0.49*
Death in hospital	3 (20)	2 (13.3)	0.68**
Death in general wards	0	0	-
Death in ICU	3 (20)	2 (13.3)	0.68**

ICU: intensive care unit; NIPPV: noninvasive positive-pressure ventilation; IMV: invasive mechanical ventilation
*p-value of independent t-test
**p-value of chi-square
Clinical response was defined based on the six classes of an ordinal scale

treatment on outcome severity in hospitalized patients with COVID-19. Although the results of this study are negative, there is still a great need for future randomized, controlled, and double-blinded clinical studies to provide a higher level of evidence for the efficacy of vitamin A in COVID-19 patients.

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Abbreviations

COVID-19	Coronavirus disease-2019
ACE2	angiotensin-converting enzyme-2
SARS-COV2	severe acute respiratory syndrome coronavirus-2
IRCT	Iranian registry of clinical trials
NEWS	national early warning score
ICU	intensive care unit
NIPPV	noninvasive positive-pressure ventilation
IMV	invasive mechanical ventilation
SD	standard deviation

Availability of data and materials

The datasets supporting the conclusions of this research will be available on request for the corresponding author, Dr Zeinab Nikniazare.

Authors' contributions

ZN & MHS were responsible for the conception and design of the study. SA, MFD, AT, and MV were responsible for the acquisition of data. ZN & ESM was responsible for data analysis. SA and ESM drafted the manuscript; MHS, MFD, ZN, AT, and MV revised and commented on the draft, and all authors read and approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethics code: IR.TBZMED.REC.1398.1305). Written informed consent was obtained from all participants. In addition, the protocol of the trial was registered in IRCT (IRCT20170117032004N3).

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