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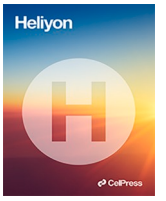

Research article

Evaluating the therapeutic effects of isotretinoin on patients with coronavirus disease 2019 (COVID-19): A controlled open-label clinical trial

Maria Shirvani [a], Siavash Vaziri [a], Mohammad Reza Akrami [b], Azar Sarmasti [c], Kamyab Hassanpour [d], Ali Akrami [b,*,1]

[a] Department of Infectious Diseases, Kermanshah University of Medical Sciences, Kermanshah, Iran
[b] Department of Neurosurgery, Kermanshah University of Medical Sciences, Kermanshah, Iran
[c] School of Nursing, Shahid Beheshti Medical University, Tehran, Iran
[d] School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is still a global health issue with no certain treatment option. So far, various treatments have been suggested among which one can mention isotretinoin. The aim of the present study was to investigate the potential of this medication as a side treatment for COVID-19. This open-label controlled clinical trial with the approval ID of IRCT20190624043993N3 was conducted in Farabi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran. Considering the inclusion and exclusion criteria, 52 patients diagnosed with COVID-19 were enrolled. The control group only received standard of care (SOC) treatment while the intervention arm received 40 mg per day of isotretinoin along with the SOC. The patients were followed until discharge. The results showed no death among the groups. The hospitalization duration in the intervention and SOC groups were 5.1 ± 2.29 and 5.1 ± 3.44 days, respectively with no statistical difference ($P = 0.98$). Moreover, the SpO_2, pulse rate, respiratory rate, and blood pressure also showed no statistical difference neither at admission nor upon discharge ($P > 0.05$). The laboratory investigations showed that white blood cells, absolute lymphocyte count, hemoglobin value, and platelet count did not differ between the groups at admission or upon discharge ($P > 0.05$). According to the results, it seems that isotretinoin didn't act as a potent side therapy in patients with COVID-19. However, due to the small sample size, we suggest further investigations.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global emergency imposing notable pressure on healthcare systems [1]. This disease, with the main manifestation of pneumonia [2], involves different organs and causes numerous serious conditions such as acute respiratory distress syndrome (ARDS) [3] as well as cytokine

* Corresponding author.
E-mail address: akramiali7@gmail.com (A. Akrami).
[1] Postal address: School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Parastar Blvd, Kermanshah, Iran. P.O. Box 67145–1673.

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storm [4]. These two might in turn result in the failure of various organs [4]. Unfortunately, so far, no specific treatment has been developed for this disease while mutations are still producing new variants [5].

According to the findings, SARS-CoV-2 could infect different cells through a receptor named angiotensin that converts enzyme 2 (ACE2) [6]. This receptor is not only expressed in the respiratory system but also in various other sites [7]. Accordingly, SARS-CoV-2 infection has also been observed in other cell types such as endothelial cells causing thromboembolic events which is the main cause of death in a notable proportion of these patients [8]. Expectedly, targeting this receptor and inhibiting its entrance and the consequent infection of different cell types has been gaining a lot of attention as a potential therapeutic option.

Isotretinoin, also known as 13-cis retinoic acid, is a retinoid approved by the United States Food and Drug Administration (FDA) for treatment for acne vulgaris [9]. According to the literature, isotretinoin decreases ACE2 expression, hence, could be suggested as a possible treatment for COVID-19 [10].

Considering the role of ACE2 in the pathogenesis of COVID-19 and potential of isotretinoin in downregulating the mentioned receptor, this study aims to investigate the potential of isotretinoin for the treatment of COVID-19.

2. Methods and patients

2.1. Setting and ethics

This single-blind non-randomized open-label controlled clinical trial was conducted in the Farabi Hospital, Kermanshah, Iran, between April 2021 and September 2021 and after getting the approval of Medical Ethics Committee of Kermanshah University of Medical Sciences with IRIB number of IR.KUMS.REC.1399.288. Also, the study was approved and registered in the Iranian Registry of Clinical Trials (IRCT) with the approval number of IRCT20190624043993N3.

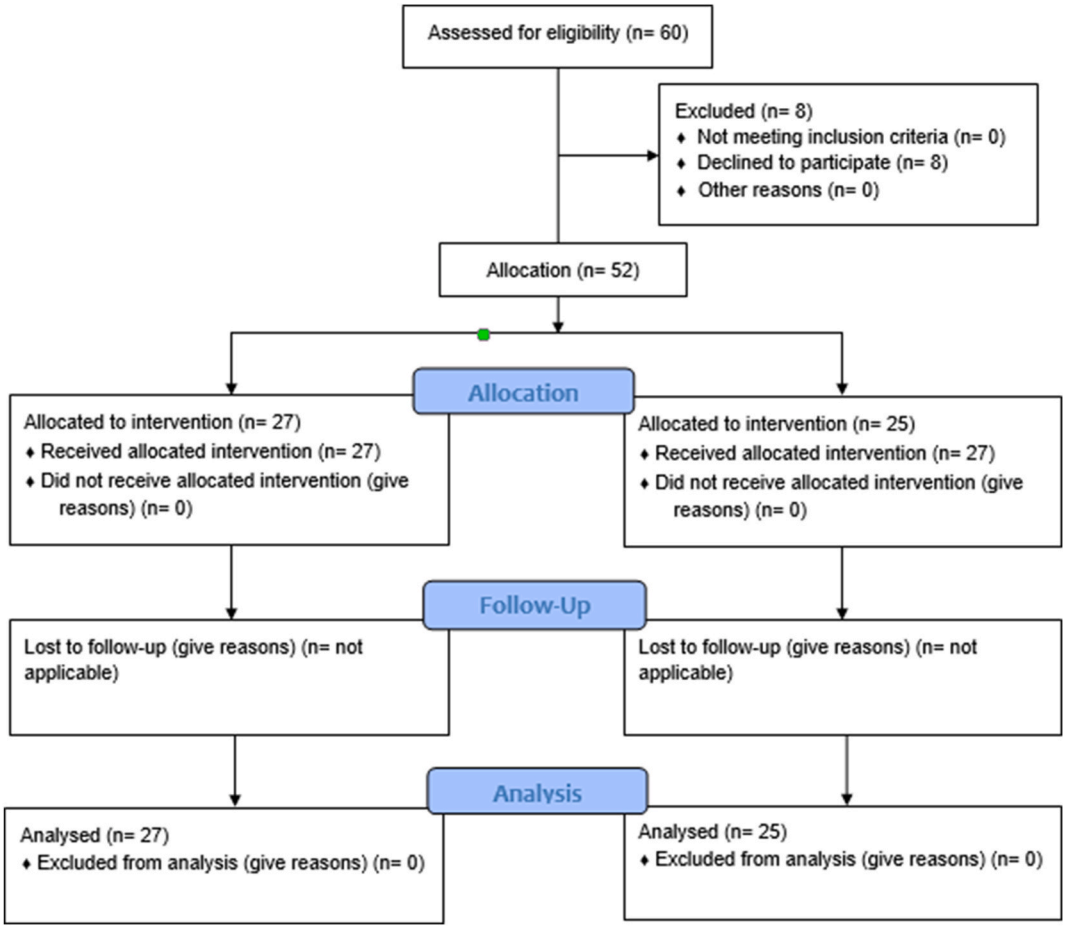

Fig. 1. Study design according to the CONSORT flow diagram.

2.2. Study design

Individuals ≥18 years of age, with confirmed COVID-19 through reverse transcriptase polymerase chain reaction (RT-PCR) and/or chest computed tomography (CT) scan, and symptoms started within the past two weeks of admission were considered eligible for enrollment in the study (inclusion criteria). Also, the exclusion criteria were considered as 1) pregnancy and lactation, 2) already known hepatic disorder, 3) any underlying diseases such as diabetic mellitus, hypertension, chronic kidney disease, and heart diseases, 4) hematologic disorders, 5) triglyceride≥ 600 mg/ml, 6) tetracycline consumption, 7) chronic alcohol consumption, 8) allergy to the isotretinoin, and 9) disagreement to sign the consent form. All the patients were asked to sign a consent form freely to join the trial after being explained the aims and methods according to their level of understanding.

Patients who met the inclusion and exclusion criteria were pooled and divided into the intervention and control arms. The control arm received only the standard of care (SOC) treatment and the intervention group took SOC as well as 40 mg per day (20 mg BID) of isotretinoin for five days. Daily vital signs such as SpO2 and body temperature were recorded and fever was considered as a temperature ≥37.7 °C.

2.3. Statistical analyses

Data was reordered from the patients' files and reviewed separately by two of the authors and in the case of a discrepancy, data was checked by a third person within the original file. All data was transferred and saved in a Microsoft Office Excel file until analysis. The analysis was performed using Statistical Package for the Social Sciences (SPSS; SPSS Inc, Chicago, IL, USA) version 25.0. The continuous and categorical variables were presented as mean ± standard deviation (SD) and N (%), respectively. The continuous variables between the groups were compared using student's t-test (parametric) or the Mann-Whitney test (non-parametric). For comparing the categorical variables between the groups, two-sided Chi-square/Fisher's exact tests were used. Any P-value less than 0.05 was considered statistically significant.

3. Results

Following the consideration of both inclusion and exclusion criteria, a total of 52 patients were included in the study (Fig. 1). The intervention and SOC groups consisted of 27 and 25 patients, respectively. The details of age and body mass index (BMI) in each group is shown in Table 1. According to this table, gender prevalence and BMI of the patients did not significantly differ, while the age ($P < 0.001$) was different between the two groups. Furthermore, underlying diseases such as heart diseases, chronic kidney/hepatic disease, asthma, and cancer showed no significant difference between the groups (all $P > 0.05$). However, the prevalence of hypertension in the control group was significantly higher than intervention arm ($P = 0.031$). Also, the duration of fever, cough, weakness myalgia, and chills were not significantly different between the groups (all $P > 0.05$). According to the results, it was shown that baseline levels of SpO2, pulse rate, respiratory rate, blood pressure, and body temperature in each group had no statistically significant difference (all $P > 0.05$). Similarly, no statistical difference for white blood cells (WBC), hemoglobin (Hb), platelet, and absolute lymphocyte count was found between the group (all $P > 0.05$).

According to the results, no deaths occurred in any of the control or intervention groups. Following the intervention, the hospitalization duration was calculated as 5.1 ± 2.29 and 5.1 ± 3.44 days for the control and intervention groups, respectively ($P = 0.98$). Moreover, the discharge levels of SpO2 were not different between the groups ($P = 0.63$). Similarly, WBC, Hb, platelet, and absolute lymphocyte count did not vary between the groups (all $P > 0.05$). Details on the other laboratory results are provided in Table 2.

4. Discussion

This trial investigated the efficacy of isotretinoin + SOC versus SOC alone in patients diagnosed with COVID-19. According to the

Table 1
Demographic and clinical characteristics of patients in both groups.

Variable	Control (n = 25)	Intervention (n = 27)	P-value
Age (years)	64.2 ± 16.22	48.3 ± 15.83	**0.001**
Male	12/25 (48%)	18/27 (66.7%)	0.2
Female	13/25 (52%)	9/27 (33.3%)	0.2
Body mass index (kg/m2)	25 ± 4.39	27.4 ± 6.45	0.13
Fever (days)	5.0 ± 2.14	4.0 ± 2.36	0.22
Weakness (days)	4.8 ± 2.07	5.7 ± 3.97	0.34
Cough (days)	8.5 ± 1.84	7.8 ± 2.49	0.33
Heart diseases	5/25 (20%)	5/27 (18.5%)	0.9
Hypertension	4/25 (16%)	0	**0.03**
Chronic kidney disease	0	1/27 (3.7%)	0.3
Chronic hepatic disease	0	0	–
Asthma	0	1/27 (3.7%)	0.3
Smoking	32%	11/27 (40.7%)	0.5
Cancer	0	0	–

Table 2
Clinical and paraclinical findings of the patients.

Variable		Control	Intervention	P-value
Hospitalization duration (days)		5.1 ± 2.29	5.1 ± 3.44	0.98
Body temperature (°C)	Admission	37.2 ± 0.27	37.2 ± 0.31	0.61
	Discharge	37 ± 0.38	37 ± 0.38	0.14
Pulse rate (/minute)	Admission	77.9 ± 11.83	80.7 ± 10.46	0.37
	Discharge	78.3 ± 5.82	78.8 ± 9.44	0.83
Respiratory rate (/minute)	Admission	22 ± 2.14	23.8 ± 4.15	0.05
	Discharge	20.8 ± 1.58	20.7 ± 2.16	0.81
SpO2 (%)	Admission	88 ± 5.50	88.3 ± 5.08	0.90
	Discharge	93.7 ± 2.24	93 ± 5.55	0.63
Systolic Blood pressure (mmHg)	Admission	122 ± 19.39	120 ± 16.07	0.67
	Discharge	118 ± 13.12	113 ± 10.02	0.11
Leukocyte × 103/mm3	Admission	11.5 ± 10.97	11.3 ± 5.77	0.94
	Discharge	13.3 ± 9.90	11 ± 3.70	0.27
Lymphocyte to Leukocyte ratio (%)	Admission	17 ± 17.51	15.5 ± 10.68	0.7
	Discharge	14.7 ± 11.49	15.5 ± 9.84	0.78
Neutrophil to Leukocyte ratio (%)	Admission	83 ± 17.51	84.5 ± 10.68	0.7
	Discharge	85.3 ± 11.76	84.5 ± 9.84	0.82
Platelet × 103/mm3	Admission	208.7 ± 111.69	228.3 ± 80.48	0.47
	Discharge	211.5 ± 93.62	252.5 ± 124.94	0.21
Hemoglobin (gr/dL)	Admission	13 ± 1.78	13 ± 2.01	0.75
	Discharge	12.6 ± 1.81	12.7 ± 2.14	0.85
Creatinine (U/L)	Admission	1.3 ± 0.53	1.2 ± 0.52	0.46
	Discharge	1.1 ± 0.45	0.9 ± 0.13	0.07

results, there was no significant difference between the groups in terms of hospitalization duration as well as discharge SpO2, WBC, Hb, platelet, and absolute lymphocyte count. Also, the laboratory variables of the two groups didn't exhibit any significant differences.

About isotretinoin and COVID-19, there are two hypotheses; the first implicates that systemic consumption of isotretinoin could increase the vulnerability of SARS-CoV-2 infection through affecting nasal mucosa [11]. On the other hand, considering the effects of isotretinoin on ACE2 receptors as well as its immunomodulatory effect and potential to increase CD4 T cells, this agent has been suggested as a possible treatment for COVID-19 [10]. Regarding the first hypothesis, Gundogdu and Dere have investigated whether systemic isotretinoin could increase the risk of COVID-19 infection in comparison to its topical consumption. According to their study, no statistically significant difference was found between the two groups regarding the rout of consumption (topical vs. systemic) and a confirmative polymerase chain reaction (PCR) test for SARS-CoV-2 infection [12]. Considering this finding, we aimed to test the other hypothesis stating the therapeutic potential of isotretinoin for COVID-19. It has been mentioned that isotretinoin could suppress the SARS-CoV-2 replication in the Vero E6 cells. Moreover, according to a hypothesis, isotretinoin could attach to the fatty acid residues on SARS-CoV-2 spike protein and possibly affects its binding to the cell surface receptor [13]. Also, it has been shown that the reduced plasma levels if vitamin A were significantly correlated with increased C-reactive protein (CRP) and ferritin levels. Moreover, patients with critically ill condition had a significant lower plasma levels of vitamin A compared with moderately ill group [14]. Regarding the safety issues, we didn't observe any serious side-effect, however, a study has mentioned that using isotretinoin in patients with recent history of COVID-19 or its vaccination should be carefully watched [15].

To our knowledge, this controlled clinical trial is the first study to ever investigate the therapeutic aspect of isotretinoin on COVID-19. The main limitation to this study was the low population of each group. The other minor limitations were being open-label (not blinded), not randomized, and differences in age as a very important demographic feature between the groups.

5. Conclusion

According to our results, isotretinoin was not able to reduce the hospitalization duration and improve the clinical and laboratory variables following the treatment between the groups. Considering these results, isotretinoin does not seem to be a proper choice as a side treatment for COVID-19; however, for a certain decision, the authors suggest further randomized controlled double-blind clinical trials with a greater number of patients to assess this conclusion.

Ethics

This study was approved by Medical Ethics Committee of Kermanshah University of Medical Sciences with IRIB number of IR.KUMS.REC.1399.288. Also, the study was approved and registered in the Iranian Registry of Clinical Trials (IRCT) with the approval number of IRCT20190624043993N3.

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Data availability statement

Data will be made available on online request.

CRediT authorship contribution statement

Maria Shirvani: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Siavash Vaziri:** Writing – review & editing, Writing – original draft, Investigation. **Mohammad Reza Akrami:** Writing – review & editing, Writing – original draft, Investigation. **Azar Sarmasti:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Kamyab Hassanpour:** Writing – review & editing, Writing – original draft, Investigation. **Ali Akrami:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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