

Finasteride in hospitalized adult males with COVID-19: A risk factor for severity of the disease or an adjunct treatment: A randomized controlled clinical trial

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Abstract

Background: There is controversy about the efficacy of 5-alpha-reductase inhibitors in COVID-19 patients. Some assumed that finasteride might be a risk factor for deterioration and others proposed it as a possible adjunct treatment for moderate to severe COVID-19 infection in the elderly.

Methods: We performed a randomized controlled clinical trial (registration ID IRCT20200505047318N1) on 80 hospitalized male patients aged ≥ 50 years diagnosed with COVID-19 pneumonia in a tertiary hospital in Qazvin (Iran) from April to July 2020. The patients were randomized into one of the 2 treatment groups using simple randomization. Treatment group patients underwent routine drug therapy and 5 mg finasteride once daily for 7 days. The primary endpoint was mortality rate and length of hospital stay (LOS), and secondary endpoints were peripheral capillary oxygen saturation, respiratory rate, and inflammatory markers changes. The study protocol was approved by the medical ethics committee of Qazvin University of Medical Sciences (registration ID IR.QUMS.REC.1399.080). Data were analyzed by statistical tests and SPSS version 25. Also, $p < 0.05$ was considered to be statistically significant.

Results: We found a significant difference on O_2 saturation among the 2 study groups on fifth day compared with the admission time ($p = 0.018$). The results did not show significant differences in mortality rate (2.5% vs 10%; $p = 0.166$) and LOS ($p = 0.866$) between patients in the finasteride and the control group.

Conclusion: A short course of finasteride administration partially improves O_2 saturation but does not influence other outcomes in hospitalized male patients aged ≥ 50 years with COVID-19 pneumonia. Further research in a large scale with longer follow-up is required to help clarify the role of finasteride in this setting.

Keywords: Finasteride, Adult, Male, Therapy, COVID-19 Infection

Conflicts of Interest: None declared

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Introduction

In 2020, COVID-19 pneumonia has become a leading cause of morbidity and mortality in many countries

worldwide, particularly among the elderly (1). Since COVID-19 was first reported, a worldwide pandemic has

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↑What is “already known” in this topic:

There is controversy about the efficacy of 5 α -reductase inhibitors in COVID-19 patients. Some assumed they might be a risk factor for deterioration and others proposed it as a possible adjunct treatment for moderate to severe COVID-19 infection in the elderly.

→What this article adds:

This study is the first and only interventional research on COVID-19 pneumonia outcome in hospitalized male patients aged ≥ 50 years. A short course of finasteride administration partially improves peripheral capillary O_2 saturation.

ensued affecting more than 24 000 000 people as of September 2020. Only oxygen and other supportive care may help improve outcomes in patients with COVID-19 pneumonia and rare progress has been made in the treatment of COVID patients (2).

During the Covid-19 pandemic, epidemiological reports unveiled a disproportionate high rate of severe cases and disease outcomes among adult males compared to adult females (with short-term follow-up, males have 65% higher mortality). Also, convalescence from COVID-19 among the elderly takes longer, and complications and death are also more frequent than in younger adults (3, 4).

Research to date has not yet clearly determined the reason for differences of COVID-19 infection severity and outcome between adult females and males. This issue was discussed theoretically in 4 earlier studies (5-8). These studies have introduced the hypothesis that finasteride has a beneficial or harm effect on clinical outcomes in adults with COVID-19 pneumonia. Hoffmann et al propose that the lower rate of severe COVID-19 infection in female patients may be attributed to the molecular mechanism required for SARS-CoV-2 infectivity (ie, lower androgen receptor (AR) expression in females). SARS-CoV-2 cell entry depends on priming of a viral spike surface protein by transmembrane protease serine 2 (TMPRSS2) present in type II pneumocytes (9). TMPRSS2 expression is associated with an increase in AR expression, specifically connecting AR expression to SARS-CoV-2 due to AR-regulated TMPRSS2 gene promoter (7, 10). Angiotensin-converting enzyme 2 (ACE2) is the attachment molecule to the viral spike surface protein "receptor of SARS-CoV-2". ACE2 activity has been shown to be reduced by the decrease of androgen hormones, possibly due to decreased expression of ACE2 (6). The US Food and Drug Administration (FDA) approved that 5-alpha reductase inhibitor (finasteride) demonstrated reduction of activation of AR in multiple tissues.

In another paper, authors assumed finasteride might increase androgen concentration in lungs hampering their regeneration. It might result in impairment of spontaneous regeneration capacity and prolonged or deteriorated recovery prognosis. According to the presented hypothesis, patients receiving 5-alpha-reductase inhibitors (5-ARIs) might be vulnerable to COVID-19 infection with poorer prognosis (5).

However, no observational or interventional studies on the effect of finasteride on the treatment of COVID pneumonia was found in our literature review. Taken together, the evidence warrants further studies to elucidate the role, if any, of the AR on the severity of COVID-19 infection. The study aim was to assess the influence of adjunctive treatment with finasteride on the outcomes of hospitalized adult male patients with COVID-19 pneumonia.

Methods

Study Design

We conducted a clinical randomized controlled trial in hospitalized male patients aged 50 years or older, who are predisposed to higher AR expression and may also be suffering from benign prostatic hyperplasia (BPH), with

COVID-19 pneumonia. Patients were prospectively enrolled between May and June 2020 at BouAli Sina hospital (a tertiary referral center during the COVID-19 outbreak), Qazvin, Iran. Patients were considered eligible if they met the following criteria: (1) provided informed consent; (2) had clinical symptoms suggestive of COVID-19 pneumonia, including cough (with or without sputum), fever, pleuritic chest pain, or dyspnea; (3) chest computed tomography (CT) scan findings compatible with COVID-19 or positive real time reverse transcription polymerase chain reaction RT-PCR of COVID-19; (4) male patients aged 50 years and older; and (5) moderate and severe disease.

Patients were excluded from the study if one of the following criteria applied: the presence of severe immunosuppression (eg, use of immunosuppressants); malignancy; any likely infection other than COVID-19 pneumonia; and indications that the patient was unable and/or unlikely to comprehend and/or follow the protocol; liver function abnormalities (as finasteride is metabolized extensively in the liver); and a positive drug history of finasteride medication or hypersensitivity to any component of this medication. If there was any violation of the protocol, the patient was excluded from the final analysis.

We calculated that 40 patients were needed in both groups to detect a mean difference of 2 days LOS (5 ± 1.7 vs 7 ± 1.7 days) between finasteride and control groups, with a power of 80% and an alpha level of 0.05 (by statistics and sample size calculator). Formula:

$$n \geq \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 \left(\sigma_1^2 + \frac{\sigma_2^2}{r} \right)}{(\mu_1 - \mu_2)^2}$$

Patients were randomly allocated into 2 therapeutic groups in a 1:1 ratio to receive either only common care based on "Iranian Guideline of Hospitalized COVID-19 Patients' Management (V 5)" or common care plus finasteride (as adjuvant). The randomization sequence was generated using Statistics and Sample Size application version 1.0. A simple randomized list was produced for a sample size of 80 and the participants were placed into 2 groups of case and control with numeric sequential unique identifiers (simple or unrestricted randomization). Forty patients in case group received a film coated tablet containing 5 mg finasteride (Aburaihan pharmaceutical Co, Iran) once daily for 7 days.

This study was a partial double-blind study. During the treatment phase, the investigators could ascertain the patients' study-drug assignment (only in the event of an emergency). During the study, to minimize possible sources of bias (ie, report more favorable outcomes or even reporting subjective efficacy endpoints or adverse effects in patients with previous experience of finasteride and reporting treatment responses or adverse events by the observer), patients and health care professionals who were undertaking the outcome assessment of the primary outcome were blinded to the group to which the subject was

assigned.

Clinical data were measured at enrolment. Hypertension was defined as an average systolic blood pressure (SBP) greater than or equal to 140 mmHg or an average diastolic blood pressure (DBP) greater than or equal to 90 mmHg, or currently using blood pressure (BP)-lowering medication. A generalized formula of the mean arterial pressure (MAP) is as follows:

$MAP = DP + 0.01 \times \exp(4.14 - 40.74/HR) (SP - DP)$, where HR is the heart rate (11).

All patients were treated according to "Iranian Guideline of Hospitalized COVID-19 Patients Management (version 5)". This comprised a heparin prophylaxis in combination with a supplemental oxygen and intravenous or oral fluid therapy. To avoid exaggerated estimates of treatment effect, baseline and follow-up clinical and para-clinical data measurement and recording were performed by nurses with adequate experience. The investigators did not influence decisions concerning discharge.

The primary endpoint was death/alive status and length of hospital stay (LOS) and secondary endpoints were peripheral capillary oxygen saturation, respiratory rate, and inflammatory markers changes. A CURB-65 severity score was calculated, and 1 point was given for each feature present (range, 0–4 points) (12, 13). All patients were observed and subsequently asked about adverse events. Renal function assessment was performed on presentation.

Assessment of gas exchange requires knowledge of fractional inspired oxygen tension (FiO_2) unless the patient is breathing room air. Hence, all peripheral capillary oxygen saturation was measured in breathing room air at rest.

This trial was registered with the Iranian Registry of Clinical Trials website (registration ID IRCT20200505047318N1). The study protocol was approved by the medical ethics committee of Qazvin University of Medical Sciences (registration ID IR.QUMS.REC.1399.080). All participants were provided with information about the study's purpose and gave informed consent to participate in the study, according to the principles of medical ethics of the World Health Organization and the seventh revision of the Declaration of Helsinki 2008.

Statistical Analysis

The data were summarized as frequencies or percentages for categorical variables and as medians and inter-quartile ranges (IQR) (all the variable distributions were skewed). We compared continuous variables using the Mann-Whitney test and proportions using the χ^2 test or Fisher's exact test. Moderation analyses were conducted using the SPSS macro-PROCESS V 3.5. The PROCESS macro produces bootstrapped unstandardized regression output as well as estimates of the effect of the focal predictor variables (LOS and death/alive status) at values of the moderator variables (ie, diabetes melitus) (14). $P \leq 0.05$ was considered statistically significant. The Statistical Package for Social Sciences software, version 25.0 (SPSS®, Armonk, NY, USA) was used for data management and statistical analysis.

Results

In this study, of the 90 hospitalized male patients diagnosed with COVID-19 pneumonia who met the inclusion criteria, 8 were unwilling to continue the study. The remaining 82 patients were randomized, and 2 patients, one in each group, were excluded due to a positive drug history of finasteride. Data from the final 80 randomized patients were analyzed (Fig. 1). Demographic Information is presented in Table 1.

Patients were evenly distributed in the 2 groups, except those with diabetes mellitus history; (5 [12.5%] vs 15 [37.5%] patients; $p=0.020$). Other clinical and paraclinical features, such as Glasgow coma scale, peripheral capillary oxygen saturation, white blood cell and platelet count, and erythrocyte sedimentation rate, were not significantly different between the 2 groups (Table 1).

The results did not show significant differences in mortality rate (1 [2.5%] vs 4 [10.0%]; $p=0.166$) and LOS ($p=0.866$) between patients in the finasteride and the control groups (Table 2).

We found a significant difference in peripheral capillary O_2 saturation on the fifth day among the 2 study groups ($p=0.016$) (Fig. 2).

The results of the binary logistic regression analysis and linear regression analysis showed diabetes is not a significant predictor of the outcome variables (for death/alive status [model 1 Hayes: $Y = \text{death/alive status}$, $X = \text{group}$ and $W = DM$; $p=0.989$] and for LOS [model 1 Hayes: $Y = \text{LOS}$, $X = \text{group}$ and $W = DM$; $p=0.398$]).

Two patients developed hospital-acquired pneumonia and were treated in the intensive care unit (one patient in each group). Other patients in the finasteride group and in the control group did not have any treatment-related adverse events.

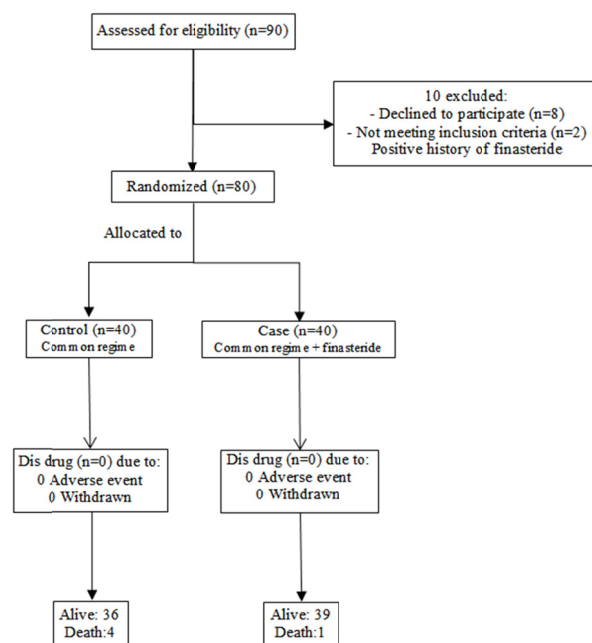


Fig. 1. Design Trial

Table 1. Baseline Characteristics and Severity Score in the Study Groups

Characteristics	Group		Total (n=80)	p
	Finasteride + Common regimen (n=40)	Common regimen (n=40)		
Age (year)	71 [62- 81]	72 [65- 77]	72 [64- 78]	0.904
Diabetes mellitus (%)	5 (12.5)	15 (37.5)	20 (25.0)	0.020*
Hypertension (%)	24 (60.0)	29 (72.5)	53 (66.3)	0.344
Cardiac disease (%)	17 (42.5)	14 (35.0)	31 (38.8)	0.646
Chronic obstructive pulmonary disease	3 (7.5)	7 (17.5)	10 (12.5)	0.310
Respiratory rate (breath/min)	18 [18- 20]	19 [18- 20]	19 [18- 20]	0.189
Systolic blood pressure (mmHg)	120 [120- 135]	130 [120- 140]	128 [120- 140]	0.265
Diastolic blood pressure (mmHg)	80 [70- 80]	80 [70- 90]	80 [70- 90]	0.426
Mean Arterial Pressure (mmHg)	96 [92- 103]	97 [91- 109]	96 [91- 106]	0.453
Pulse rate (beats/min)	90 [78- 100]	85 [81- 90]	88 [80- 95]	0.205
Temperature (°C)	36.8 [36.5- 37.8]	36.9 [36.5- 37.2]	36.8 [36.5- 37.4]	0.877
Peripheral capillary O ₂ saturation	90 [84- 92]	89 [86- 92]	90 [85- 92]	0.806
Glasgow Coma Scale (GCS)	≤10	0 (0.0)	3 (3.9)	0.136
	11-12	3 (7.5)	4 (5.1)	
	13-14	4 (10.0)	12 (15.0)	
	15	30 (75.0)	61 (76.3)	
White blood cells (per mL)	8.0 [4.6- 11.4]	8.9 [6.8- 11.7]	8.4 [6.3- 11.6]	0.187
Absolute Lymphocyte count per µl)	1063 [797- 1441]	1144 [851- 1455]	1116 [821- 1455]	0.498
Platelets count (per µl)	159 [117- 234]	183 [134- 211]	162 [130- 223]	0.557
Erythrocyte sedimentation rate (mm/h)	29 [9- 45]	28 [15- 44]	28 [14- 44]	0.952
C-Reactive Protein (mg/dL)	23 [10- 40]	22 [6- 43]	23 [7- 42]	0.704
Blood Urea Nitrogen (mg/dL)	22 [17- 29]	23 [19- 29]	22 [18- 29]	0.512
Creatinine (mg/dL)	1.0 [0.9- 1.3]	1.1 [0.9- 1.3]	1.1 [0.9- 1.3]	0.615
Risk class (CURB-65)	0	1 (2.5)	8 (10.0)	0.443
	1	12 (30.0)	28 (35.0)	
	2	18 (45.0)	41 (51.2)	
	3	3 (7.5)	0 (0.0)	

n (%) or median [IQR]; IQR = Interquartile Range; CURB-65 = Mental Confusion; Urea >20 mg/dL; Respiratory Rate ≥30/min; Low Blood Pressure (diastolic blood pressure ≤60 mm Hg or systolic blood pressure >90 mm Hg); Age ≥65 years; COVID-19 Pneumonia.

Table 2. Length of Hospital Stay, Outcome and Parameters of Disease Severity in Fifth Day Admission Among Male Adults With COVID-19 Pneumonia.

Characteristics	Group		p
	Finasteride Plus Common regime (n = 40)	Common Regimen (n = 40)	
Respiratory rate (breath/min)	18 [17- 18]	18 [17- 18]	0.940*
Systolic blood pressure (mmHg)	115 [103- 120]	120 [110- 130]	0.090*
Diastolic blood pressure (mmHg)	70 [70- 80]	80 [70- 80]	0.074*
Pulse rate (beats/min)	79 [69- 84]	73 [66- 80]	0.126*
Temperature (°C)	36.7 [36.5- 36.8]	36.7 [36.5- 36.9]	0.731*
Peripheral capillary O ₂ saturation	92 [89- 94]	89 [86- 92]	0.016*†
White blood cells (per µl)	7100 [5000- 9900]	6900 [5900- 8950]	0.773*
Absolute lymphocyte count (per µl)	1057 [630- 1491]	1312 [1062- 1440]	0.229*
Platelets count (per µl)	200 [165- 254]	195 [157- 237]	0.625*
Erythrocyte sedimentation rate (mm/h)	29 [13- 40]	28 [20- 44]	0.676*
C-Reactive Protein (mg/dL)	18 [5- 50]	28 [20- 40]	0.255*
Blood Urea Nitrogen (mg/dL)	18 [15- 31]	21 [15- 29]	0.602*
Creatinine (mg/dL)	1 [1- 1]	1 [1- 1]	0.670*
Length of hospital stay (day)	10 [6- 16]	10 [6- 14]	0.866*
Length of ICU stay (day)	0 [0- 0]	0 [0- 0]	0.902*
Length of intubation (day)	0 [0- 0]	0 [0- 0]	0.539*
Glasgow Coma Scale (GCS)	≤8	2 (5)	0.730**
	9 to 14	8 (17.5)	
	15	31 (77.5)	
Outcome	discharge	39 (97.5)	0.166***
	expire	1 (2.5)	

* Mann-Whitney U test, ** χ^2 for linear trend, *** χ^2 test, † Significant, IQR = interquartile range.

Discussion

To the best of our knowledge, this clinical trial study was the first to examine the effects of finasteride as adjunctive therapy on outcome, hypoxia, and inflammatory biomarkers in hospitalized adult male patients with COVID-19 by assessing clinical and paraclinical parameters. This study may help clinicians to optimize the

COVID infection management to decrease its mortality and morbidity.

Only patient peripheral capillary O₂ saturation on the fifth day was significantly higher in the finasteride compared with the control group. Finasteride could reduce hypoxia-inducible factor-1 α (HIF-1 α), which reduces vascular endothelial growth factor (VEGF), which in turn

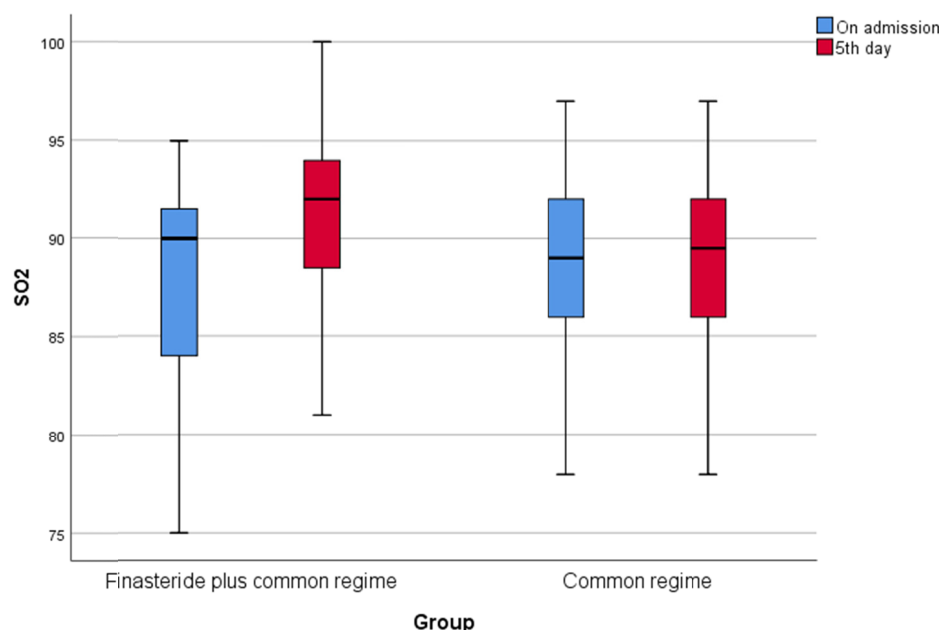


Fig. 2. Box Plot of the peripheral capillary O₂ saturation trends during hospital admission for the 2 study groups

reduces micro vessel density (MVD). Finasteride administration in BPH results in a statistically significant suppression of hypoxia marker in BPH (HIF-1 α expression) (15).

Although a trend towards improved clinical outcomes was observed in the finasteride group, these differences were not statistically significant at day 5. Reduction in LOS is an important goal in the treatment of patients with COVID-19 pneumonia. In our study, the finasteride group patients had not shorter LOS than control patients.

One hypothetical study assumed finasteride might be a risk factor for deterioration of COVID-19 pneumonia in the elderly (5) and 2 others proposed finasteride administration as a possible adjunctive treatment (6, 16). Based on our result, a short course administration of finasteride does not seem to deteriorate outcomes of COVID-19 pneumonia in male adults but even improves peripheral capillary O₂ saturation. Two recent reports are compatible with our study. In a recent retrospective cohort analysis on male participants with laboratory confirmed SARS-CoV-2 infection, it was demonstrated that males using the 5-ARIs display drastically reduced symptoms of COVID-19 disease in an outpatient setting (17). Another prospective cohort study was conducted from the data of men hospitalized due to COVID-19. The participants were categorized into 2 cohorts: those taking antiandrogens for at least 6 months or those not taking antiandrogens prior to hospitalization. The participants were followed for a period of 60 days from the date of hospitalization. The relative risk for ICU admission for those taking antiandrogens compared with the age-matched group was RR 0.19 (16).

Adverse events related to treatment with finasteride in our study were low and did not differ from the control group. Adverse effects such as decrease in sexual and genitourinary complications were reported with long-term finasteride consumption; however, at recommended dos-

ages and duration, finasteride is well-tolerated. Finasteride is generally well tolerated; adverse reactions are usually mild and transient (18).

There are a number of limitations in the present study. A limitation of the present study was that the finasteride and dihydrotestosterone levels in our study population was not directly assessed. The lack of a placebo group necessitated a single-blind design, which may have influenced the study outcomes. To prevent bias in parameter estimates, health care professionals who were undertaking primary outcome assessment did not have a priori knowledge of group assignment (ie, partially blinded). In addition to, patients took numerous medications. Also, the follow-up period was short and in conditions such as COVID-19, much longer periods are warranted to evaluate lasting treatment effects. Furthermore, the follow-up period lacked a control group because of funding constraints. Additionally, although patients were usually discharged when they reached the discharge criteria listed in the national COVID-19 guidelines, various comorbid disease of patients and their socioeconomic status might influence the decision-making of physicians.

Conclusion

A short course of finasteride administration partially improves peripheral capillary O₂ saturation but does not influence other outcomes in hospitalized male patients aged 50 years and older with COVID-19 pneumonia. Further research in a large scale with longer follow-up is required to help clarify the role of finasteride in the treatment of COVID-19 pneumonia. Until then, we should be cautious and not recommend routine administration of finasteride for COVID-19 treatment.

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Conflict of Interests

The authors declare that they have no competing interests.

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