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Pentoxifylline effects on hospitalized patients with COVID19: A randomized, double-blind clinical trial

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ABSTRACT

Pentoxifylline (PTX) has broad-spectrum properties such as anti-inflammatory, anticoagulant, and antiviral effects. The aim of this study was to evaluate the efficacy and safety of PTX in hospitalized patients with COVID-19.

This double-blind, placebo-controlled randomized clinical trial was conducted on hospitalized patients with COVID-19. The recruited patients were randomly (1:1) assigned to the PTX group and the placebo group. The intervention group received PTX capsules at a dose of 400 mg three times a day for 10 days along with the national regimen, including interferon plus lopinavir/ritonavir and hydroxychloroquine. The primary outcome was the improvement of clinical scores. The secondary outcomes, on the other hand, were improvement in inflammatory and oxidative stress factors and hospital complications.

From a total of 102 patients who met the inclusion criteria, 72 individuals completed the study and were analyzed. No significant differences were shown in demographics and baseline clinical characteristics. Clinical scores was not significant between the two groups ($P = 0.31$ and 0.07 for day 5 and 11, respectively). Although the mean serum levels of interleukin-6 (IL-6) and glutathione changed significantly after 5 days in the PTX group ($P = 0.03$ and $p = 0.04$), ICU admission, intubation, and hospital stay did not differ between the two groups.

The results of our study did not show any superiority of PTX over placebo in improving the clinical outcomes of patients with COVID-19. Although PTX had a beneficial effect on IL-6 and showed an acceptable safety profile, it did not offer any clinical benefit for COVID-19 complications.

1. Introduction

Corona virus is a known pathogenic virus that primarily causes respiratory infections. In December 2019, a novel corona virus 2019 (2019-nCoV), starting from Wuhan, China, rapidly spread around the world. In February 2020, the World Health Organization (WHO) declared it a 21st-century pandemic, and named the disease coronavirus disease 2019 (COVID-19) [1–3].

Most infected patients have mild to moderate illness; however, some are severely ill [4]. Cytokines storm appear to play an important role in progression of the disease and the occurrence of critical conditions [5]. Immunological studies have demonstrated that elevated serum levels of proinflammatory cytokines such as interleukin-6 (IL-6), IL-1β, IL-2, IL-8, IL-17, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, and tumor necrosis factor α (TNF) cause a cytokine storm in most patients with severe COVID-19 [6].

To date, remdesivir has been recommended for the treatment of COVID-19, and it is the only FDA-approved drug to treat hospitalized patients [7]. However, one of the most urgent challenges of our present time is to find an effective, safe, and accessible therapeutic agent against COVID-19. Pentoxifylline (PTX) is a phosphodiesterase-4 (PDE-4) inhibitor used for human vascular diseases [8]. PDE-4 is a major regulator of cyclic adenosine monophosphate (cAMP) metabolism in pro-inflammatory and immune cells [9]. PTX could activate protein kinase A (PKA) by increasing cAMP levels, which reduces the synthesis of pro-inflammatory cytokines—such as interleukin-1 (IL-1), IL-6, and tumor

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necrosis factor- alpha (TNF-α)—and increases the levels of IL-10 and anti-inflammatory cytokines [10–12]. Animal and human studies of the PTX support its beneficial effects on ameliorating inflammatory conditions like sepsis, bronchopulmonary dysplasia, meconium aspiration, post-radiation pulmonary fibrosis, and acute respiratory distress syndrome (ARDS) in patients with advanced cancer and hypoxic ischemic encephalopathy [12–15]. Besides its anti-inflammatory properties, PTX has been shown to have significant antiviral effects on herpes simplex virus, vaccinia virus, rotavirus, tick-borne encephalitis virus, and human immunodeficiency virus (HIV) [16,17]. PTX has improved endothelial dysfunction in HIV patients, and has shown beneficial effects on short-term survival in alcoholic and non-alcoholic patients with hepatitis [18–20].

In addition to all these benefits, PTX is an inexpensive medication with few side effects such as dizziness, headache, nausea, flushing, and stomach discomfort [21].

Considering the positive impact of PTX on inflammatory and pro-thrombotic pathways as well as antiviral function and its limited side effects, this study was performed to evaluate the efficacy and safety of PTX in the clinical improvement of hospitalized patients with COVID-19.

2. Method

2.1. Setting and study registration

This double-blind, placebo-controlled randomized clinical trial was conducted in hospitalized COVID-19 patients at Ibne Sina Hospital, Sari, Iran. The study was approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1399.744) and was also registered in the Iranian Registry of Clinical Trials (IRCT20190804044429N4). The study was done in accordance with the Declaration of Helsinki. All patients or their caregivers were informed about the objectives and procedure of the study. Subsequently, they signed the consent form before the intervention, and their privacy rights were observed.

2.2. Blinding and randomization

The patients were randomized (ratio 1:1) to receive PTX or placebo for 10 days. PTX (made by Arya company) and placebo capsules were exactly the same in color, shape, and packaging. The clinicians and clinical pharmacists responsible for evaluating the study outcomes as well as the patients were blind to the intervention.

2.3. Setting and patients

All patients over 18 years old with COVID-19 symptoms beginning within the last 14 days, according to the WHO proposed definition [22,23]. were enrolled in the study. The disease was confirmed by the reverse transcription polymerase chain reaction (RT-PCR) or chest computed tomography (CT) scan in all the patients. On the other hand, patients with a history of PTX use, cerebral or ocular bleeding, renal impairment (GFR $<$ 30 ml per minute), hepatic impairment (Child-Pugh C), and hypersensitivity to PTX, in addition to breastfeeding and pregnant women were excluded.

2.4. Study intervention and outcome measurement

The intervention group received PTX capsules at a dose of 400 mg three times a day for 10 days. The other group received placebo capsules in the same way and for the same period. According to the official national policy for COVID-19 treatment at the time of this study, as an antiviral regimen, all the patients received Hydroxychloroquine 400 mg (one dose), Lopinavir/Ritonavir (200/100) tablets every 12 h for five days, and interferon beta 1b 250 mcg administered subcutaneously every other day for three doses. Furthermore, antibiotics, corticosteroid therapy, prophylactic dose of anticoagulant (unfractionated heparin or low molecular weight heparin), and the standard supportive care were considered for all the patients.

Demographic characteristics including age, sex, underlying diseases, medications history, and clinical manifestations were recorded. Laboratory tests including complete blood count(CBC) with differential, electrolytes, coagulation test, urea and creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and albumin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and lactate dehydrogenase (LDH) were evaluated during the study. Serum levels of IL-6 and factors related to cellular oxidation pathways (glutathione and lipid peroxidation) were measured for all patients at baseline and on the fifth day of the study. All patients were evaluated daily for any possible drug interactions and side effects during hospitalization.

2.5. Outcomes

The primary outcome was the clinical response of patients, which was evaluated using an eight-point ordinal scale [24]. A score$<$3 was considered as a response to treatment. The scores of this scale were defined as follows: 1, not hospitalized and no activity limitation; 2, not hospitalized with activity limitation or needing home oxygen, or both; 3, hospitalized, no need for supplemental oxygen nor continuous medical care (applied in case hospitalization was prolonged for infection control or other nonmedical reasons); 4, hospitalized, no need for supplemental oxygen yet requiring continuous medical care (because of COVID-19 or other medical conditions); 5, hospitalized, needing supplemental oxygen; 6, hospitalized, needing noninvasive ventilation or high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death.

Hospital duration, mortality, intensive care unit (ICU) admission, and intubation rate were also considered as secondary outcomes. Furthermore, serum levels of IL6 and oxidative stress indices LPO and GSH were evaluated as secondary outcomes. The side effects of PTX were assessed and reported as safety outcomes. In the case of any life-threatening adverse drug reaction (ADR), the intervention was discontinued and all necessary treatment measures were considered.

2.6. Statistical analysis

Statistical analysis was carried out in SPSS 24.0. (IBM Corp., Armonk, NY). Kolmogorov-Smirnov test was used to examine the normality of data distribution. Standard deviation was used to describe normally-distributed quantitative data, and median and interquartile range to describe quantitative data with no normal distribution. On the other hand, qualitative data were described using frequency and percentage. Besides, *t*-test and Mann-Whitney test were used to compare quantitative data between the two groups. Finally, Chi-square test and Fisher's exact test were used to compare qualitative data between the two groups. $P < 0.05$ was considered statistically significant.

3. Results

From November 2020 to April 2021, 197 patients were admitted to the COVID-19 wards, of whom 102 individuals met the inclusion criteria. Finally, 72 patients completed the study and were analyzed. A CONSORT diagram is shown in Fig. 1.

The mean age of the patients was 58.87 (SD=± 15.04) years, and 65.3% of them (n = 47) were female. Moreover, almost all patients had at least one underlying disease (75%), and diabetes mellitus was the most common comorbidity. Baseline demographic and clinical characteristics of patients are shown in Table 1, suggesting no statistical difference between the two groups. Likewise, baseline vital signs and laboratory tests showed no significant difference between the two

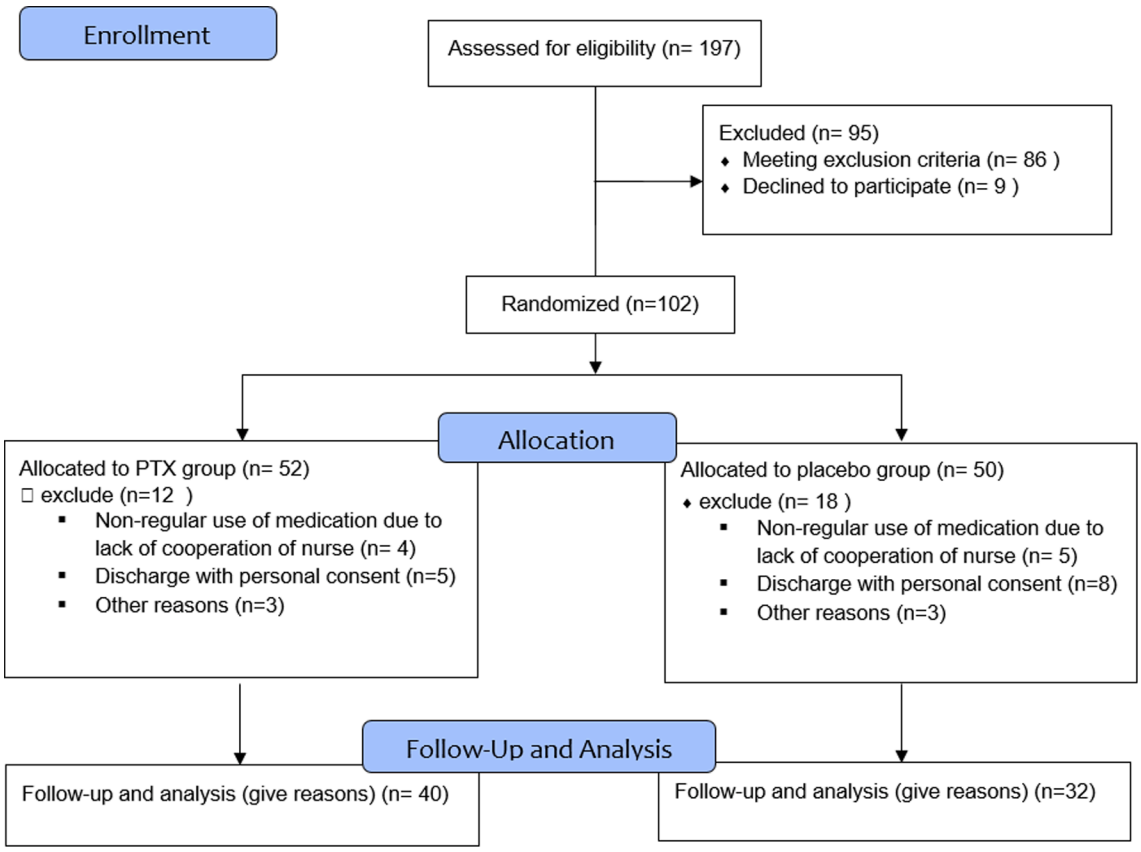

Fig. 1. consort diagram of the study.

groups (Table 2).

Clinical response was based on patients' scores of the eight-point ordinal scale on days 5 and 11 (Table 3, Fig. 2). The comparison revealed no significant differences between the two groups (P = 0.31 and 0.07).

Although the median time for hospital duration was shorter in the PTX group than placebo group, the difference was not significant (P = 0.55, Table 3). Four patients in the PTX group and two patients in the placebo group were admitted to the ICU without any significant difference (P = 0.69). Moreover, in the PTX group, two patients were intubated and three patients died, whereas in the placebo group, one patient was intubated and no one died. However, this observed difference was not statistically significant (P = 0.25, Table 3).

In the case of inflammatory biomarkers, the mean levels of IL6 were similar at baseline, but after 5 days the mean level significantly decreased in the PTX group and increased notably in the placebo group (P = 0.03, Table 4). Also, the changes from baseline to day 5 were significant between the two groups (P = 0.01, Table 4). Regarding indicators of oxidative stress, LPO and GSH serum levels and the observed changes from baseline were not statistically significant (Table 4).

During our study, nausea was the only dominant ADR that patients reported. Nevertheless, the differences between the groups was not significant and the symptom severity was mild and tolerable (PTX: 19 vs placebo:10, P = 0.16).

4. Discussion

The results of our study showed the effects of PTX on clinical scores improvement, ICU admission, length of hospital stay, and mortality were not superior to those of placebo in hospitalized patients with COVID-19. Although PTX led to a significant decrease in IL-6 levels as an inflammatory biomarker as well as a significant increase in GSH levels as an antioxidant, no differences were found in LPO, LDH and CRP. Regarding safety, no significant difference was seen in the PTX group compared with the placebo group, suggesting that PTX is as safe as the placebo.

PTX is a well-known a cardiovascular drug that is generally used for treating human vascular diseases; in addition, it could reduce IL-6 levels through inhibiting the synthesis of pro-inflammatory cytokines [10–12], thus restoring the balance of the immune response and reducing endothelial and alveolar damage[10]. PTX also has significant antiviral effects [16,17], improves blood circulation, and produces anticoagulant effects [25,26]. In line with the anti-inflammatory effects of PTX, we noticed the beneficial effects of PTX on COVID-19.

Maldonado et al. conducted an open label pilot study [27] among 38 moderate-to-severe COVID-19 patients. PTX was prescribed 400 mg every 8 h from admission to discharge. The survey results, similar to our findings, demonstrated PTX could not significantly reduce the length of hospital stay, the need for intubation, and mortality. They also showed PTX reduced LDH levels and increased lymphocyte counts significantly without any ADR in comparison with the control group. Small sample size, open label nature of the study, and lack of matching groups due to other antiviral agents were major limitations that should be considered while interpreting the results of this study.

In a retrospective study, the effects of PDE inhibitors including pentoxifylline or theophylline on hospitalized COVID-19 patients requiring oxygen support were evaluated. The authors reviewed 209 patients, 58 of whom had received PDE inhibitors. PTX was administered 400 mg orally three times a day for a maximum of 7 days. They reported partial decrease in mortality and CRP level, in addition to an increase in clinical response (ROX score) in the PDE group. No serious ADR was detected [28]. The antiviral regimens, co-administered drugs, and underlying disease were not matched appropriately; hospital duration and rate of ICU admission were not reported; and disease

Table 1
Baseline demographic and clinical characteristics of the patients.

Variables	PTX (n = 40)	Placebo (n = 32)	P value
Age, year; mean ± SD	58.45 ± 13.67	59.41 ± 16.80	0.791
Gender, female; n(%)	26 (65)	21 (65)	0.956
Body mass index, kg/m2; mean ± SD	28.12 ± 4.55	27.57 ± 4.31	0.602
Symptom onset, day; mean ± SD	5.75 ± 2.11	6.03 ± 3	0.584
Symptoms, n(%)			
Cough	18 (45)	17 (53.1)	0.493
Fever	19 (47.5)	16 (50)	0.833
Chilling	9 (22.5)	10 (31.3)	0.403
Chest pain	6 (15.1)	1 (3.1)	0.123
Dyspnea	16 (40)	16 (50)	0.396
Fatigue	2 (5)	1 (3.1)	1.000
Headache	11 (27.5)	7 (21.9)	0.584
Weakness	12 (30)	16 (50)	0.084
Myalgia	11 (27.5)	9 (28.1)	0.953
Dizziness	4 (10)	0	0.124
Dyspepsia	12 (30)	7 (21.9)	1.000
Diarrhea	8 (20)	6 (18.8)	0.894
Nausea	12 (30)	7 (21.9)	0.437
Vomiting	8 (20)	4 (12.5)	0.396
Anorexia	13 (32.5)	11 (34.4)	0.867
Anosmia	3 (7.5)	2 (6.3)	1.000
Ordinal Score on day 1;	4.68 ± 0.47	4.63 ± 0.49	0.660
Past medical history; n(%)			
Diabetes mellitus	14 (35)	9 (28.1)	0.534
Hypertension	8 (20)	5 (15.6)	0.632
Cardiovascular disease	3 (7.5)	6 (18.8)	0.151
Cerebrovascular disease	2 (5)	2 (6.3)	1.000
Thyroid dysfunction	3 (7.5)	3 (9.4)	1.000
Psychiatric disease	0	2 (6.3)	0.194
Gastrointestinal disease	1 (2.5)	1 (3.1)	1.000
Medications used during hospitalization			
High dose corticosteroid	10 (25)	6 (18.8)	0.526
Corticosteroid	22(55)	18(56.3)	0.916
Ceftriaxone	12 (30)	14(44)	0.227
Metronidazole	2 (5)	1(3.1)	1.000
Meropenem	4 (10)	4(12.5)	0.737
Vancomycin	0	3(7.5)	0.249

PTX: Pentoxyfylline, SD: standard deviation

severity was not determined in the study groups. Considering these limitations besides the retrospective design of this study, one must interpret its results with due caution.

In a prospective, open label, nonrandomized study, 110 patients were included to evaluate the effects of different anti-oxidant regimens on patients with moderate-to-severe COVID-19. PTX was administered 400 mg orally two times a day for five days alone or in combination with other antioxidants (vitamin E, C, N- acetyl cysteine (NAC) and melatonin (MT)). The authors evaluated oxidative stress (OS), biomarkers including LPO, total oxidative capacity (TAC), and nitrites (NO_2^-), along with survival scores and inflammation markers (IL6, CRP, and pro-calcitonin). The results showed a significant decrease for IL-6 and CRP in both moderate and severe groups. Similarly, they supported beneficial effects on OS factors for the group receiving PTX along with the other antioxidants as opposed to patients receiving PTX alone. No adverse effects were reported [29]. Despite the synergic effects of different anti-oxidant combinations on OS and inflammation markers, clinical outcomes such as length of hospital stay, ICU admission, and intubation rate were not compared. In addition, antiviral agents and other co-administered medications were not examined. Besides these limitations, this study had a short follow-up.

Our study has some limitations too. Due to restricted resources, it was not possible to administer remdesivir as a part of the antiviral regimen at the time of the study. Small sample size and lack of longer follow-up are the other limitations.

Table 2
Baseline vital signs and laboratory tests.

variables	PTX, mean ± SD	Placebo, mean ± SD	P value
Temperature, ℃	37.25 ± 0.68	37.14 ± 0.56	0.679
Systolic blood pressure, mmHg	120.78 ± 19.62	122.56 ± 17.92	0.612
Diastolic blood pressure, mmHg	77.03 ± 12.07	75 ± 9.16	0.554
Respiratory rate, per minute	18.58 ± 1.03	20.16 ± 9.20	0.923
Heart rate, per minute	85.75 ± 12.64	85.53 ± 16.76	0.950
Oxygen saturation, %	94.10 ± 4.66	94.44 ± 3.03	0.891
Lactate dehydrogenase, U/l	497.63 ± 201.59	491.90 ± 270.72	0.919
Blood sugar, mg/dl	156.50 ± 96.21	140.41 ± 74.09	0.825
Urea, mg/dl	31.03 ± 15.17	30.39 ± 11.63	0.826
Creatinine, mg/dl	0.88 ± 0.2	0.84 ± 0.18	0.311
Sodium, mg/dl	138.95 ± 3.76	139.72 ± 4.39	0.427
Potassium, mg/dl	4.10 ± 0.33	4.03 ± 0.36	0.371
Albumin, g/dl	3.70 ± 0.56	3.6 ± 0.51	0.450
Calcium, mg/dl	8.67 ± 0.72	8.75 ± 0.54	0.227
Phosphorus, mmol/l	3.25 ± 0.57	3.31 ± 0.6	0.696
Magnesium, mg/dl	2.04 ± 0.32	2.08 ± 0.31	0.624
Wight blood cell, cells/μl	6726.27 ± 2527.28	6108.44 ± 2339	0.290
Neutrophil, cells/μl	4605.71 ± 2571.15	4183.30 ± 2080.35	0.454
Lymphocyte, cells/μl	1224.03 ± 867.41	1401.67 ± 621.48	0.333
Red blood cell, cells/μl	4.55 ± 0.67	4.40 ± 0.59	0.339
Hemoglobin, g/dl	12.07 ± 1.71	12.18 ± 1.69	0.758
Platelet, cells*10^3	221.34 ± 105.17	223.97 ± 97.71	0.914
Alanine aminotransferase, U/l	28.01 ± 13.14	38.88 ± 26.70	0.106
Aspartate aminotransferase,U/l	40.62 ± 15.63	48.91 ± 25.03	0.108
Alkaline phosphatase, U/l	196.38 ± 78.89	192.74 ± 80.12	0.862
INR	1.06 ± 0.18	1 ± 0.04	0.144
PTT, second	35.05 ± 5.25	35.69 ± 13.29	0.474
Erythrocyte sedimentation rate, mm/h	63.03 ± 31.82	62.37 ± 33.74	0.934

PTX: Pentoxifylline, SD: standard deviation, INR: international normalized ratio, PTT: Partial thromboplastin time.

Table 3
Clinical outcomes comparison between two study groups.

Outcomes	PTX , n (%)	Placebo, n (%)	P value
Ordinal Score at day 5:			
2;Not hospitalized with activity limitation or needing home oxygen, or both	25(62.5	24 (75)	0.26
3;Hospitalized, no need for supplemental oxygen and continuous medical care	6 (15)	3 (9.4)	0.47
4;Hospitalized, no need for supplemental oxygen yet requiring continuous medical care	7 (17.5)	5 (15.6)	0.83
8; Death	2 (5)	0	0.5
Ordinal Score at day 11;			0.117
1; Not hospitalized and no activity limitation;	16 (40)	13 (40.6)	
2; Not hospitalized with activity limitation or needing home oxygen, or both;	17 (42.5)	17 (53.1)	
3; Hospitalized, no need for supplemental oxygen and continuous medical care	2 (5)	1 (3.1)	
4; Hospitalized, no need for supplemental oxygen yet requiring continuous medical care	0	1 (3.1)	
5; Hospitalized, needing supplemental oxygen	2 (5)	0	
8; Death	3 (7.5)	0	
Hospital duration, day; median (IQR)	3 (2)	6 (1.75)	0.55
Death; n(%)	3(7.5%)	0 (0%)	0.25
ICU admission, day; mean ± SD	4 (10%)	2 (6.3%)	0.69
ICU duration, day; mean ± SD	10.75 ± 5.85	4.5 ± 0.71	0.23
Intubation; n(%)	1 (25%)	0 (0%)	1.00

SD: standard deviation, IQR: interquartile range, ICU: Intensive Care Unit

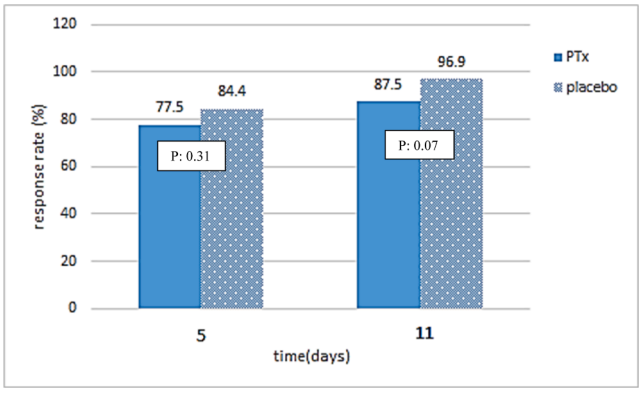

Fig. 2. Clinical response rate between groups of the study.

Table 4
Inflammatory and oxidative stress biomarkers comparison.

Biomarkers[+]	PTX	Placebo	P-value*	P-value[#]
C- reactive protein (mg/dl), day 1	40.15 ± 38.9	46.53 ± 37.87	0.39	–
Interleukin-6 (pg/ml), day 1	73.92 ± 45.49	69 ± 41.43	0.640	–
LPO (μg/ml) ,day 1	8.70 ± 25.45	6.71 ± 16.84	0.90	–
GSH (μg/ml), day 1	122.95 ± 55.57	109.17 ± 49.94	0.28	–
Interleukin-6 (pg/ml) day 5 ; mean ± SD,	71.76 ± 46.93	100.14 ± 59.64	0.03	0.01
LPO (μg/ml), day 5	5.13 ± 13	17.32 ± 37.13	0.32	0.07
GSH (μg/ml), day 5 ;	126.45 ± 57.80	98.73 ± 49.71	0.04	0.15
C- reactive protein (mg/dl), day 5	26.45 ± 26.17	33.40 ± 33.57	0.24	

[+] Values shown by mean ± SD, *: The differences were compared between two groups, [#]: The amount of changes from baseline was compared, LPO: lipoperoxidation, GSH: Glutathione.

5. Conclusion

The results of our study did not show any significant benefits for PTX versus placebo on improving the clinical outcomes of hospitalized patients with COVID-19. Nevertheless, PTX exerted a beneficial effect on inflammatory biomarkers and caused no specific adverse effect.

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Ethics approval

This study follows the declaration of Helsinki and was approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1399.744).

CRediT authorship contribution statement

Hanieh Azizi: Data curation, Investigation, Writing – original draft. **Nima Rouhani:** Data curation, Investigation. **Fatemeh Shaki:** Data curation, Investigation. **Elahe Karimpour-razkenari:** Data curation, Writing – original draft. **Monireh Ghazaeian:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Ebrahim Salehifar:** Validation, Writing – review & editing. **Majid Saeedi:** Resources. **Sahar Fallah:** Formal analysis.

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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