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Evaluation of Preventive Pentoxifylline Effect on Acute Respiratory Distress Syndrome (ARDS) Incidence in Traumatic Patients: A Randomized Triple-Blind Placebo-Controlled Trial

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Abstract

Background: Inflammation is important in the pathophysiology of acute respiratory distress syndrome (ARDS). Traumatic injuries have been assumed to be primary ARDS causes. Recently, pentoxifylline, a phosphodiesterase inhibitor (PEI), was shown to have anti-inflammatory effects and reduce the incidence of ARDS. The present study investigated the impact of preventive pentoxifylline administration in trauma patients prone to ARDS development.

Methods: A total of 62 trauma patients admitted to the Kamyab Hospital in Mashhad,Iran, with ARDS risk who fulfilled the inclusion and exclusion criteria were included in this study. The patients were randomly divided into treatment and placebo groups. The treatment group received 400 mg pentoxifylline 3 times a day, while the control group received placebo tablets thrice for 1 week. Before the intervention and during the study, factors such as heart rate, blood pressure, respiration rate, continuous pulse oximetry, CRP, PO_2, PCO_2, and PH were assessed. Finally, the obtained data were analyzed using SPSS Version 26 via a generalized estimating equations model and an independent t test.

Results: The heart rate was significantly lower in the treatment group than in the placebo group ($P = 0.036$). In addition, PO_2 levels were remarkably higher in the treatment group ($P = 0.040$). Changes in respiratory rate ($P = 0.064$), CRP ($P = 0.341$), PH ($P = 0.910$), PCO_2 ($P = 0.892$), HCO_3 ($P = 0.172$), systolic blood pressure ($P = 0.302$), and SPO_2 ($P = 0.350$) were not significantly different between the 2 groups. In addition, no significant difference was observed in the incidence and severity of ARDS between the 2 groups.

Conclusion: The findings of this study revealed that pentoxifylline administration to trauma patients had no beneficial effects on ARDS but improved some vital signs and laboratory variations.

Keywords: Acute Respiratory Distress Syndrome, Pentoxifylline

Conflicts of Interest: *None declared*
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Introduction

Acute respiratory distress syndrome (ARDS) is an acute, diffuse, inflammatory lung injury leading to increased pulmonary vascular permeability, enhanced lung weight, and loss of tissues in the gas exchange process (1). It can develop due to an exaggerated immune response of the lungs to acute, locally or systemically applied inflammatory stimuli (2). Traumatic injuries are one of the most common causes of ARDS after sepsis, pulmonary infec-

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↑What is "already known" in this topic:
Acute respiratory distress syndrome (ARDS) is an acute, diffuse, inflammatory lung injury that leads to hospitalization and death. Based on ARDS pathophysiology, targeting the cyclic adenosine monophosphate (cAMP) signaling pathway may be a promising method for ARDS therapy. Pentoxifylline is a phosphodiesterase inhibitor (PEI) that exhibits anti-inflammatory effects through different mechanisms.

→What this article adds:
This study reports the beneficial effect of pentoxifylline in traumatic ARDS patients and suggests establishing more clinical trials to reach a more accurate conclusion.

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tions, and aspiration (3). More than 200,000 cases of ARDS are diagnosed every year in the United States, accompanied by >3.6 million days of hospitalization (4). Predictive models show that the presence of blunt trauma, pulmonary contusion, extensive blood transfusion, and injury leading to a flail chest increases the incidence of trauma-induced ARDS (5). The prognosis of trauma-induced ARDS is better than that of ARDS induced by other causes (6). Clinical signs of ARDS usually appear within 6 to 72 hours after injury. Generally, patients present with diffuse dyspnea, cyanosis, crackles, and respiratory distress. In addition, arterial blood gas analysis mainly exhibits hypoxemia with acute respiratory alkalosis. Therefore, most patients require supplemental oxygen. Moreover, chest x-rays in these patients revealed bilateral alveolar infiltration and lung computed tomography scans showed diffuse and patchy opacities (7). Recently, it was demonstrated that ARDS results from an immune system disorder that disrupts the balance between regulatory T cells (Tregs) and interleukin (IL)-17-producing T helper lymphocytes (Th17) (8). Th17 cell levels are elevated in the lungs of mice with ARDS. IL-17 can also cause edema by increasing the permeability of the epithelial alveoli (9). Forkhead box P3 (Foxp3) is a Treg marker. Tregs are differentiated by transforming growth factor (TGF)-β1 stimulation. TGF-β1 can be suppressed through cyclic adenosine monophosphate (cAMP) signaling and can reduce Treg concentration (10, 11). Therefore, targeting the cAMP signaling pathway to rectify the Treg/Th17 imbalance may be a promising method for ARDS therapy. Pentoxifylline is a phosphodiesterase inhibitor (PEI) that exhibits anti-inflammatory effects through different mechanisms. One of the main mechanisms is an increase in cAMP levels. Pentoxifylline can inhibit the chemotaxis of neutrophils and their activation by inhibiting TNF-α secretion from macrophages in response to endotoxins in animal sepsis models. In a study, the preventive administration of pentoxifylline in rats with cecal ligature and puncture-induced ARDS significantly increased cAMP concentration, reduced IL2, IL6, IL10, IL17, and TGF-β secretion, decreased Foxp3 levels, and reduced the mortality rate and lung damage (12, 13). Based on these data and the lack of human studies, the present study aimed to investigate the effect of preventive pentoxifylline administration on the incidence of ARDS in patients with trauma.

Methods

Study Design

This study was a triple-blind, randomized, placebo-controlled clinical trial from May 2021 to October 2022 at the Kamyab Hospital, affiliated with Mashhad University of Medical Sciences, Mashhad, Iran. The CONSORT (Consolidated Standards of Reporting Trials) guidelines were used to report this clinical trial (14).

Study Population

Traumatic patients prone to ARDS, aged 20 to 40 years with a lung injury prediction score ≥4 were included in the study (Table 1) (15). The exclusion criteria are as follows: (1) adrenal insufficiency; (2) blood vessel inflammation; (3) intolerance to methylxanthine and pentoxifylline; (4) patients with end-stage liver or renal disease or bleeding (16); (5) patients who could not be prescribed orally; (6) life-threatening side effects from drug consumption; (7) unwillingness of the participant or their guardian to continue taking part in the study; and (8) patient's or legal guardian's lack of consent to continue participating in the study

Study Protocol

Eligible patients were randomly assigned to treatment and control groups. Patients in the treatment group received tablets of pentoxifylline (400 mg) in 3 doses per day for 1 week with standard treatment. Patients in the control group received similar-looking tablets in 3 doses per day for 1 week plus standard treatment. All the patients included in the study were monitored at the baseline and during the study period. Heart rate, breathing rate, blood pressure, blood gas variables (PaO_2, $PaCO_2$, and PH), and hs-CRP were recorded. The results of the treatment and placebo groups were then statistically compared, and changes relative to the baseline were examined.

Outcome

The primary outcome of this study was the severity and incidence of ARDS in patients during the follow-up, which was assessed on days 1, 3, and 7. We also monitored the heart rate, breathing rate, blood pressure, blood gas variables (PaO_2, $PaCO_2$, PH, and HCO_3), and hs-CRP as a secondary outcome during the study. Secondary outcomes were assessed every day for 1 week. In addition, the degree of patient compliance with therapy and the frequency of adverse pharmacological effects were inves-

Table 1. Lung Injury Prediction Score

Predisposing conditions	Score
Shock	2
Aspiration	2
Sepsis	1
Pneumonia	1.5
High-risk surgery*	
Orthopaedic spine	1
Acute abdomen	2
Cardiac	2.5
Aortic vascular	3.5
High-risk trauma	
Traumatic brain injury	2
Smoke inhalation	2
Near drowning	2
Lung contusion	1.5
Multiple fractures	1.5
Risk modifiers	
Alcohol abuse	1
Obesity (BMI>30)	1
Hypoalbuminaemia	1
Chemotherapy	1
FiO_2 >0.35 (>4 L/min)	2
Tachypnoea (RR>30)	1.5
SpO_2 <95%	1
Acidosis (pH<7.35)	1.5
Diabetes mellitus **	-1

*In case of emergency surgery, 1.5 score is added
** Only if sepsis

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tigated.

Sample Size

To the best of the author's knowledge, no study has been conducted to investigate the preventative efficacy of pentoxifylline in trauma patients with ARDS. We assumed a reduction of 34% in the number of patients with ARDS in the intervention group to be significant based on expert opinion. In addition, a power of 80%, a normalized effect size of 0.05, and the Suleyman study's (17) prevalence of ARDS in patients in intensive care units were used to determine the sample size, which came out to be 29 patients. Each arm consisted of 31 patients.

Randomization and Blinding

Using the randomization.com website, a computer-generated list of sequential, random allocations was created. Afterward, a block randomization technique was employed for an equitable distribution of qualified patients across the treatment and placebo groups. An unrelated study participant (a pharmacist from the teaching pharmacy where we purchased the pentoxifylline tablets) filled identical boxes with pentoxifylline and placebo tablets. The clinical pharmacist labeled the tablets with the letters A (treatment) or B (placebo), and the patient received them. The physician chose the patients who met the inclusion criteria. Based on the randomization list, he randomly divided the patients into 2 groups (A and B) and gave them boxes labeled A or B. The physician conducted patient evaluation during the study period. The clinical pharmacist examined the data. The patients' group assignment was unknown to the physician, the clinical pharmacist, and the patients themselves.

Statistical Methods

The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. If the data distribution was expected, an independent t test was used to compare the means in the 2 studied groups. If the data distribution was not expected, the Mann-Whitney U test was used. Moreover, we used repeated model tests to exclude time as a covariate for the incidence and severity of ARDS in patients during the follow-up. Initially, we converted the paired repeated data from wide to long format. Then, we used generalized estimating equations to compare the effect of intervention between the 2 groups. All analyses were performed using SPSS Software Version 26.

Results

Patients' Characteristics

A total of 62 patients who met the inclusion criteria were divided equally between the treatment and placebo groups in this study. None of the patients were excluded from the study (Figure 1). Table 2 shows the mean and standard deviation of the patient's demographic data in the

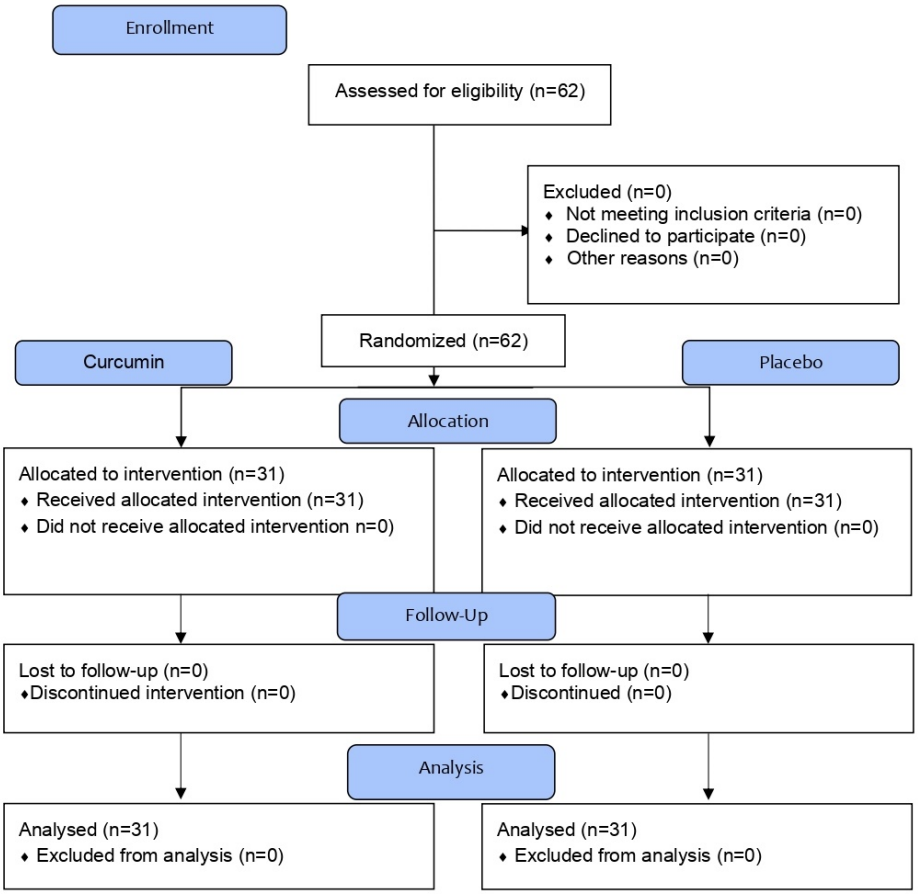

Figure 1. Flow diagram of the trial

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Table 2. The Baseline characteristics of the participants

Characteristics	Group		†*P* Value
	Pentoxifylline (n=31) Mean ± SD	Placebo (n=31) Mean ± SD	
Age (year)	32.16 ± 5.29	31.16±6.06	0.492
BMI (kg/m^2)	25.60±3.24	24.81±3.54	0.365
LIPS	11.48±2.03	11.69±1.97	0.682
HR	99.35±13.67	101±17.2	0.678
RR	20.25±3.48	20.74±2.95	0.558
SP	120.48±20.39	126.12±24.63	0.330
DP	69.83±16.64	74.16±11.84	0.243
WBC	11.19±4.11	9.91±2.82	0.158
Hg	12.39±2.38	11.24±2.30	0.057
PLT	159.83±42.98	170.0±49.57	0.392
SPO^2	92.48±2.86	92.35±2.66	0.855
pH	7.30±0.09	7.33±0.09	0.226
PO^2	55.7±25.15	50.53±24.57	0.410
PCO^2	43.83±8.95	42.00±7.94	0.398
HCO^3	22.01±3.17	21.45±2.87	0.468
CRP	36.20±29.94	40.33±33.20	0.608

BMI, Body Mass Index; LIPS, Lung Injury Prediction Score; HR, Heart Rate; RR, Respiratory Rate; SP, Systolic pressure; DP, Diastolic pressure; WBC, White blood cell; Hg, Hemoglobin; PLT, Platelet; SPO2, Oxygen saturation; HCO3, Bicarbonate; CRP, C-reactive protein
†Calculated by the independent T test.

2 groups. There were no significant differences in patient's baseline characteristics between the treatment and control groups.

The Pattern of Vital Signs Variations During the Follow-up

The 7-day variations in heart rate characteristics in the 2 study groups are shown in Figure 2. The mean heart rate in the medication group was consistently lower than in the control group. A statistically significant difference was reported ($P = 0.036$) after the analysis. Figure 2 (B) shows the variations in breathing rate characteristics during 7 days in the 2 study groups. The average breathing rate in the treatment group was lower than in the placebo group on most days (except for the first and second days). However, there were no significant differences between the 2 groups h ($P = 0.064$). The SPO_2 level fluctuations throughout the study are shown in Figure 2 (C) for the 2 study groups. The average SPO_2 level in the medicine group was higher than in the placebo group on all days (except on day 3). However, this difference was not statistically significant ($P = 0.350$). Similarly, as represented in Figure 3 (D), the mean systolic blood pressure in the treatment group was lower than in the placebo group on all trial days. Nevertheless, this difference was not statistically significant ($P = 0.302$).

The Pattern of Laboratory Variations During the Follow-up

The pH levels in the 2 study groups changed over 7 days (Figure 3 E). The average blood pH in the treatment group was lower than in the placebo group until the third day of the trial. However, it was higher than that in the placebo group until the last day of the study (the seventh day). Altogether, the differences in blood pH between the 2 study groups were not statistically significant ($P =$ 0.910). (Figure 3 F) represents the variations in PO_2 levels over 7 days in the 2 study groups. The average PO_2 in the drug group was greater than in the placebo group on all the trial days. A statistically significant difference ($P = 0.040$) was reported in the statistical analysis. During the 7 days of monitoring, the average PCO_2 level differed between the 2 groups on days 2 and 4 of the study (Figure 4 G). However, this difference was not statistically significant ($P = 0.892$). The variations in HCO_3 levels over 7 days in the 2 study groups are presented in Figure 4 H. The average HCO3 level was higher in the treatment group than in the placebo group, except the first day of the trial. However, the difference was not statistically significant ($P = 0.172$). The hs-CRP levels in the 2 study groups changed throughout the study (Figure 4 I). The average hs-CRP level was lower in the treatment group than in the placebo group during the entire study period. However, this difference was not statistically significant ($P = 0.341$).

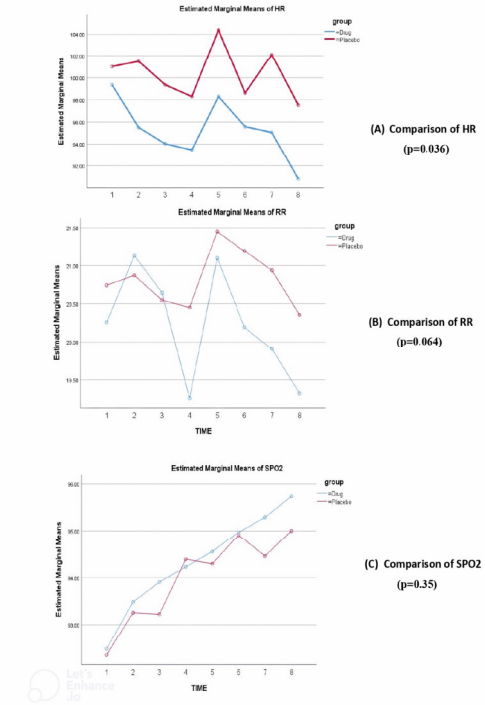

Figure 2. Comparison of (A) Heart rate, (B) Respiratory rate, (C) SPO_2 in two case and control groups

Incidence and Severity of ARDS in Patients During the Follow-up

The incidence and severity of ARDS (18) were compared between the treatment and placebo groups (Table 3). Although the incidence of ARDS in patients taking the medication was much lower than that in the placebo group on the seventh day, we observed no statistically significant difference between the 2 groups during the 7 follow-up days ($P = 0.995$). In the treatment and placebo groups, recovery was observed in 60% and 67% of the patients with mild ARDS, respectively. Moreover, there was no

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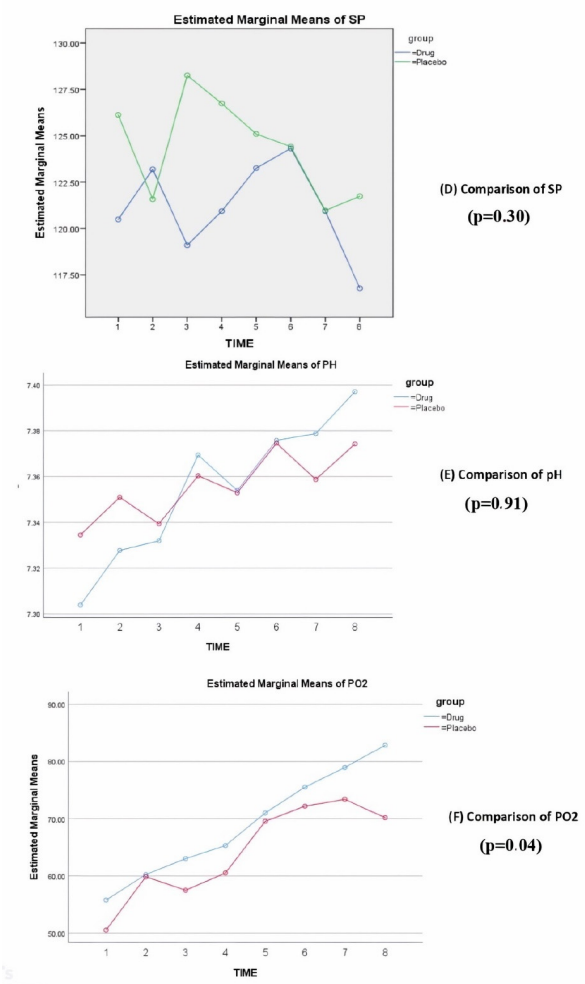

Figure 3. Comparison of (D) Systolic blood pressure, (E) pH, (F) PO_2 in two case and control groups

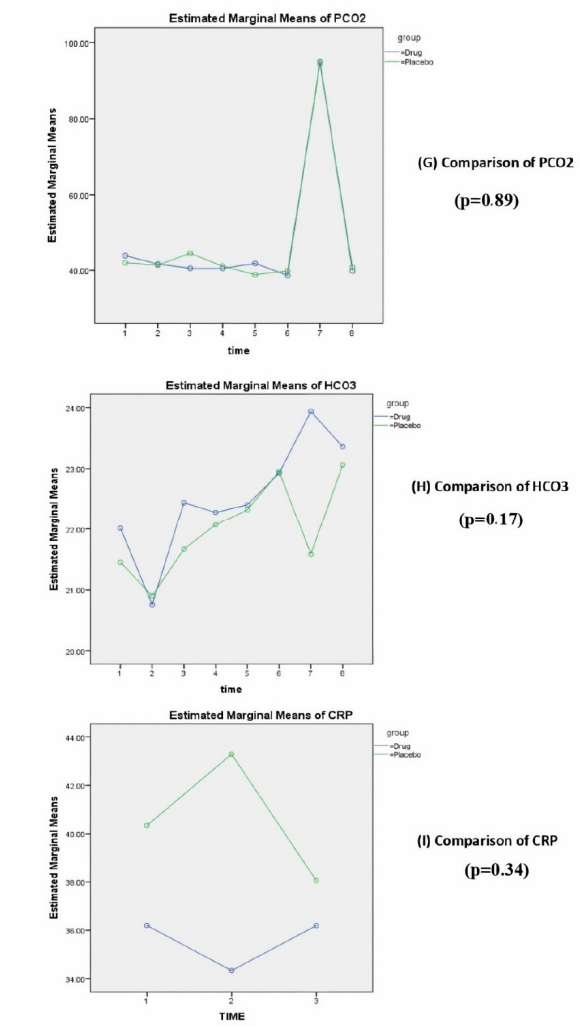

Figure 4. Comparison of (G) PCO_2, (H) HCO_3, (I) CRP in two case and control groups

increase in the number of patients with ARDS with moderate severity in the treatment group. We observed a 4-fold increase in patients with mild ARDS severity in the placebo group. Furthermore, no severe ARDS was observed in the treatment group on the seventh day.

Discussion

To lower the mortality rate of trauma patients, this study was designed to examine the preventive benefits of pentoxifylline in the development of ARDS. In our investigation, the heart rate of the treatment group (P = 0.036) was substantially lower than that of the placebo group. In addition, during the follow-up period, the PO_2 level in the treatment group was significantly higher than in the control group (P = 0.040). Breathing rate (P = 0.064), systolic blood pressure (P = 0.302), and CRP level (P = 0.341) were all lower in the treatment group than in the placebo group on most study days. However, these changes were not statistically significant. Moreover, the treatment group consistently had greater SPO_2 (P = 0.350) and HCO_3 (P = 0.172) than the placebo group, although this difference

Table 3. ARDS incidence and severity in treatment and placebo groups

Groupe		Day 1	Day 3	Day 7	*P* value
Pentoxifylline group	NO incidence (%)	19 (61.5)	21 (67.7)	25 (80.6)	
	Mild (%)	10 (32.5)	8 (25.8)	4 (12.9)	
	Moderate (%)	2 (6.5)	2 (6.5)	2 (6.5)	
	Severe (%)	0 (0)	0 (0)	0 (0)	
Placebo group	NO incidence (%)	21 (67.8)	20 (64.5)	22 (71)	
	Mild (%)	9 (29)	9 (29)	3 (9.6)	0.995
	Moderate (%)	1 (3.2)	2 (6.5)	4 (12.9)	
	Severe (%)	0 (0)	0 (0)	2 (6.5)	

†P Value Calculated by Generalized Estimating Equations Test

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was not statistically significant in any of the cases. Overall, our research demonstrated that pentoxifylline administration alters patients' clinical and laboratory symptoms up to a point.

A cytokine storm refers to a sharp increase in the production of proinflammatory molecules in response to infection or other external stimuli (19). As a consequence, there is an exceptionally high concentration of cytokines in the inflammatory areas, which ultimately leads in organ damage and also causes the immune cells' protective feedback system to be lost. As previously discussed, cytokine storms are one of the primary mechanisms underlying ARDS. Pentoxifylline has been demonstrated in previous studies to have anti-inflammatory properties, and as a result, it may be utilized to prevent ARDS. Pentoxifylline appears to lower PDE-4 levels and enhance cAMP levels. The amount of degraded cAMP is reduced when PDE-4 is inhibited, which raises the level of cAMP inside the cells (20, 21). The regulation of NF-κB reduces the interaction between leukocytes and platelets and lowers the generation of proinflammatory cytokines and reactive oxygen species. Another mechanism by which pentoxifylline inhibits inflammatory processes is NF-κB regulation (22). Another mechanism underlying the effects of pentoxifylline has recently been suggested. Adenylate cyclase activity is increased by adenosine A2A receptors, which increase the level of cAMP in various cells—including neutrophils, macrophages, T cells, natural killer cells, endothelial cells, and platelets (23, 24). The inactivation of 2 key inflammatory pathways—the NF-B and JAK/STAT pathways—is the main reason for the capacity of A2A adenosine receptors to control inflammatory responses. In addition, increased cAMP levels reduced the release of oxidants and cytokines (24). Pentoxifylline can enhance the sensitivity of adenosine A2A receptors to extracellular adenosine, thereby contributing to the anti-inflammatory properties of these receptors. It has been demonstrated that pentoxifylline can reduce lung inflammation and neutrophil activity when administered concurrently with fluid resuscitation in hemorrhagic shock in rats (23). Pentoxifylline has also been shown to minimize lung damage and death in ARDS-infected rats. This effect appears to be mediated by increasing cAMP levels, balancing the Treg/Th17 ratio, and reducing the release of interleukins 2, 6, 10, and 17 (25). In addition, when rats received preventive pentoxifylline, the results showed a significant reduction in both cytokine and protein content measured by bronchoalveolar lavage and a significant increase in arterial blood oxygen pressure (PaO_2) in the pentoxifylline-treated rats. Moreover, there was a significant decrease in neutrophils and macrophages in the lungs, whereas the pentoxifylline-treated group showed no significant alternation (26). Recently, another study evaluated the efficacy and safety of pentoxifylline in hospitalized patients with COVID-19. In this study, 72 eligible patients received 400 mg pentoxifylline 3 times a day for 10 days, along with the national regimen. Although they reported no clinical benefit with pentoxifylline treatment, they observed a significant change in the mean serum levels of interleukin-6 (IL-6) and glutathione after 5 days in the pentoxifylline group (27). Pentoxifylline is, therefore, anticipated to facilitate the clinical course of ARDS or delay its onset by lowering inflammation in accordance with the mechanism above. Similarly, many other anti-inflammatory agents have been examined to investigate their effects on preventing ARDS. For instance, Weigelt et al demonstrated that administering methylprednisolone to patients at high risk of ARDS had no appreciable impact on the risk factors for ARDS, patients' ventilatory demands, or duration of hospitalization in the intensive care unit. Consequently, they did not suggest methylprednisolone administration for ARDS (28). In another study, Schein et al evaluated the effects of methylprednisolone and dexamethasone in patients with septic shock who were prone to the development of ARDS. The findings of this study revealed that neither methylprednisolone nor dexamethasone could prevent ARDS (29). In a related study, Bone et al found that methylprednisolone therapy increased the risk of ARDS recurrence and increased mortality rates in addition to not delaying the development of ARDS in patients experiencing septic shock (30). Statins, which inhibit HMG-coenzyme A reductase, have been investigated for the treatment of ARDS because of their anti-inflammatory properties. Statins did not influence the recovery rate, mortality reduction, or requirement for mechanical ventilation caused by ARDS. Statins have also been demonstrated to not affect preventing the development of ARDS (31). Hemang et al examined the impact of statins prescription before high-risk procedures on preventing ARDS after surgery and indicated that administering statins does not affect preventing ARDS in patients experiencing high-risk surgeries (32). Festik et al demonstrated that administering budesonide-formoterol inhalation to patients at risk for ARDS increased oxygen delivery and SPO2/FIO2 ratio (33). Another study investigated the effect of nebulized heparin in patients with or at risk for ARDS. The results revealed that nebulized heparin did not affect these patients' well-being but caused less lung damage and reduced hospitalization (34). However, there are conflicting findings regarding the efficacy of anti-inflammatory medications in patients with ARDS. Meanwhile, our study demonstrated that patients receiving pentoxifylline progressed better than those in the control group in terms of clinical and laboratory markers. These differences were significant in some cases (PO_2 level and heart rate) and insignificant in others (CRP, respiratory rate, systolic blood pressure, HCO_3, and SPO_2). To the best of our knowledge, no human study has investigated the effect of preventive pentoxifylline administration on the incidence of ARDS in traumatic patients. However, this study had some limitations. First, only a few patients met the inclusion criteria, resulting in a small sample size. Second, the follow-up duration of the study seemed short; a longer study period would demonstrate higher efficacy. Third, because we had fewer patients, the age range of our patients was restricted to those between the ages of 20 and 40 years. Also, we recommend examining inflammatory markers such as CRP, IL6, and TNFα in future studies. Longer clinical trials are strongly advised because we were unable to continue monitoring the patients after 1

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week of observation.

Conclusion

The results of this randomized, triple-blind, placebo-controlled clinical trial revealed that pentoxifylline administration in trauma patients had no beneficial effects on ARDS. Still, they improved some vital signs and laboratory variations. However, additional randomized clinical trials with larger sample sizes, longer durations, and different doses are required for a more accurate assessment of the effectiveness of pentoxifylline.

Authorship Contribution Statement

Sepehr Shirzadeh performed the experiments. Vahid Jomehzadeh supervised the study. Navid Omidkhoda wrote the paper draft. Amir Hooshang Mohammadpour and Reza Mannani corrected the draft.

Acknowledgment

The authors extend their gratitude to all of the participants in the study—patients, families, and staff members from every unit.

Ethical Consideration

This clinical trial was evaluated and approved by the local Ethics Committee of Mashhad University of Medical Sciences (code: IR.MUMS.MEDICAL.REC.1400.141) and registered in the Iranian Registry of Clinical Trials (IRCT20210711051839N1). Consent forms were obtained from all patients.

Conflict of Interests

The authors declare that they have no competing interests.

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