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Original Article (Pages: 18517-18529)

The Effect of Pentoxifylline on the Prevention of ARDS in PICU Patients: A Randomized Double-Blind Clinical Trial

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Abstract

Background: Inflammation has a remarkable role in Acute Respiratory Distress Syndrome (ARDS) pathophysiology. Pentoxifylline is a phosphodiesterase IV inhibitor with anti-inflammatory and anti-thrombotic properties, which has had positive results in rodents with ARDS. Due to the lack of human studies, we designed this clinical trial to evaluate the pentoxifylline effect on ARDS prevention in high-risk pediatric patients.

Methods: We included thirty-four children from Akbar hospital's pediatric intensive care unit (PICU). These patients were highly susceptible to ARDS progression. Using a randomized, double-blind method, 17 patients received pentoxifylline tablets three times a day for a week, while others received placebo tablets at the same interval for seven days. Lung Injury Prediction Score (LIPS), vital signs, pulse oximetry, PaO2, pH, and PaCO2 were measured at baseline and every day for a week period. CRP was assessed at baseline, then on the third and seventh days. Finally, we imported all the data to SPSS software to compare the treatment and placebo groups.

Results: Each placebo and treatment group had seventeen patients who had no statistically significant difference in baseline demographic information or lab data. The variations in LIPS score (P=0.475), CRP (P=0.053), pH (P=0.199), PO2 (P=0.077), PCO2 (P=0.528), Heart rate (P=0.086), Respiratory rate (P=0.512), Diastolic blood pressure (P=0.572), Systolic blood pressure (P=0.517), and SPO2 (P=0.260) were compared between the two groups; and no significant difference was observed.

Conclusion: The results of this clinical trial suggest that pentoxifylline had no prophylactic effect on pediatric ARDS, but for confirmation, further clinical trials with different designs and larger sample sizes are required.

Key Words: ARDS, Pediatric ICU, Pentoxifylline, RCT.

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Received date: May.20,2023; Accepted date: Jan.20,2024

* Please cite this article as: Nazemi SS, Khademi G, Rahsepar S, Hajzadeh G, Naseri M, Bahramizadeh M, Abedi F, Sezavar M, Mohammadpour MH. The Effect of Pentoxifylline on the Prevention of Ards in Picu Patients: A Randomized Double-Blind Clinical Trial. Int J Pediatr 2024; 12 (01):18517-18529. DOI: **10.22038/ijp.2024.72502.5274**

1- INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a sort of acute respiratory failure with a remarkable mortality rate (1). ARDS was first described in 1967 with a case report which addressed the clinical manifestations of patients suffering from acute hypoxemia, non-cardiac pulmonary edema, and hyperventilation. Furthermore, these patients received positive pressure ventilation and had other complications such as sepsis, trauma, pneumonia, and aspiration (2).

The most common reasons for ARDS are pneumonia and sepsis. Aspiration, trauma, pancreatitis, transfusion, and drug toxicity are other less common reasons for ARDS development (3, 4).

The key players in the pathophysiology of ARDS are leucocyte dysfunction, abnormal platelet aggregation, and coagulant/anticoagulant imbalance. As a result of these irregular processes, alveolar and epithelial permeability changes, and the coagulation cascade over-activates (1). Interstitial and alveolar edema are the main characteristics of the exudative phase of ARDS (5).

Infection, aspiration, and mechanical ventilation can directly affect the alveolar epithelium, while other reasons, including sepsis, trauma, blood transfusion, and pancreatitis, cause indirect damage. No matter the cause, alveolar epithelium damage results in fluid infiltration and pulmonary edema (6). This fluid contains hyaline membranes, different proteins (e.g., fibrin and albumin), immunoglobulins, and inflammatory cells, particularly neutrophils (7). Macrophages produce proinflammatory cytokines (IL10, TNFα, IL1, IL6, IL8), which increase leucocyte migration and neutrophil activation. Neutrophils produce several proteases, cytokines, Neutrophil Extracellular Traps (NETs), and Reactive Oxygen Spaces (ROS), causing vascular endothelium damage and blood coagulation (6). The accumulation of proteins and fibrin remnants in the alveolar fluid results in surfactant degradation, decreasing pulmonary compliance and residual functional capacity, increasing dead space, causing gas exchange defect, atelectasis, and hypoxia (6). Initially, ARDS was assumed to be a neutrophil-mediated disorder, but since some cases of ARDS had severe neutropenia, other theories came across (8). Studies suggest that during the course of ARDS, the balance between regulatory T cell (T reg) and T helper 17 (TH17) impairs, and the number of TH17 cells rises. These cells produce IL17 which directly increases alveolar epithelium permeability and pulmonary edema (1).

The pathophysiology and risk factors of ARDS in children are similar to those in adults, but the epidemiology is not quite the same (9, 10). As shown in a systematic review, the incidence of ARDS among children (2 weeks to 17 years) was 2.2-7.5 cases among 100000 patients. Besides, 3-3.2% of pediatric intensive care unit (PICU) cases are diagnosed with ARDS, with a mortality rate of 17-33% (9, 10). Compared to adults, the overall mortality is lower in children, but its negative impact on quality of life is higher due to younger age (10).

More than 60 percent of pediatric ARDS cases are secondary to pneumonia which has a lower fatality risk than sepsis or shock-induced ARDS (10, 11). Premature birth, cancer, and immunodeficiency are risk factors for higher mortality (12). According to clinical studies, the fatality rate in patients with severe ARDS ($PaO_2/FiO_2<100$) was three times higher

than that in patients with PaO_2/FiO_2 between 100-300; hence the degree of hypoxemia is a prognostic factor (10, 12).

According to American-European Consensus Conference, ARDS is defined as acute hypoxemia with $PaO_2/FiO_2 \leq 200$. In addition, the patient's radiography must also present a bilateral pulmonary infiltration (in the frontal section), and pulmonary artery wedge pressure must be ≤18 mmHg (13). ARDS diagnosis in children is somehow different. Based on the international Pediatric Acute Lung Injury Consensus Conference (PALICC), some conditions are required for pediatric ARDS diagnosis: (1) Cases with prenatal hypoxemia, premature pulmonary injuries, and other congenital disorders are excluded; (2) Pulmonary failure must not be associated with heart failure or fluid overload; (3) Acute hypoxemia and pulmonary infiltration must occur within seven days of the diagnosis of the underlying clinical disorder; (4) Imaging must present a new infiltration compatible with an acute pulmonary disease; (5) shown in **Table 1** (14).

Table-1: PALICC criteria for oxygenation impairment

	Noninvasive mechanical ventilation	Invasive mechanical ventilation		
	PARDS (regardless of staging)	mild	moderate	severe
Oxygenation	Full face-mask bi-level ventilation or CPAP * ≥5 mm H_2O $PaO_2/FiO_2 \leq 300$ Or $SpO_2/FiO_2 \leq 264$	4≤OI **<8 5≤OSI ***<7.5	8≤OI<16 7.5≤OSI<12.3	OI≥16 OSI≥12.3

* CPAP: Continuous Positive Airway Pressure
** Oxygenation Index (OI) = (FiO_2 × mean airway pressure × 100)/PaO_2
*** Oxygen Saturation Index (OSI) = (FiO_2 × mean airway pressure × 100)/SpO_2

Unfortunately, the treatment strategy for ARDS is limited to oxygen supplementation, fluid therapy, nutritional support, thrombosis prophylaxis, and antibiotics if needed (15, 16). The search for specific therapy has not been successful until now, and a few drugs, such as corticosteroids, were tested (17, 18). Pentoxifylline is a phosphodiesterase IV inhibitor, initially used for peripheral vascular disorders but may have a potential therapeutic effect on ARDS due to its anti-inflammatory and blood viscosity reducing mechanisms (19, 20). Pentoxifylline decreases natural killer cell activity, endothelial adhesion, and neutrophil degranulation, reducing inflammatory cytokines and lymphocyte activation (21, 22). On the other hand, pentoxifylline decreases thromboxane activity and elevates prostacyclin, plasmin, and antithrombin III synthesis. Therefore, it can inhibit platelet aggregation and reduce blood viscosity, resulting in better blood flow and tissue oxygenation (23). The most frequent side effects of pentoxifylline are gastrointestinal, including dyspepsia, nausea, and vomiting, while serious side effects like cardiovascular problems are rare (<1%) (24, 25).

In-vivo studies on mice have indicated that prophylactic administration of pentoxifylline significantly reduced inflammatory cytokines (IL2, IL6, IL10, IL17, and TGF-ß) and mortality rate in cecal ligation and puncture (CLP)-induced ARDS models. In addition, CLP-exposed mice had elevated Th17 population, which

impairs Treg/TH17 balance. Meanwhile, in Pentoxifylline-treated mice, the number of Treg and TH17 did not increase, and Treg/TH17 balance was also preserved (1).

In another in-vivo study, rats were exposed to hydrochloric acid to induce ARDS. According to the results, the sample group which received prophylactic pentoxifylline prior to hydrochloric acid exposure had significantly higher PaO_2 and lower cytokine and neutrophil load in their lungs (26).

Considering the importance of ARDS and its high mortality and morbidity risk, the use of a relatively safe medication like pentoxifylline seems rational. The potential therapeutic mechanisms of pentoxifylline and the results of in-vivo studies can also back up this rationale. Hence, we designed a clinical study to examine the prophylactic effect of pentoxifylline in pediatric ARDS for the first time.

2- METHODS

2-1. Design and Population

This randomized, double-blind clinical trial was conducted from September 2020 to January 2022, at Akbar Children's Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. The patients were admitted to PICU and had a high risk of ARDS development, according to the Lung Injury Prediction Score (LIPS). Patients were diagnosed by a critical care specialist and randomly received pentoxifylline or placebo tablets as a prophylactic approach.

2-1.1. Inclusion and exclusion criteria

We included PICU-admitted pediatric patients who had a LIPS score ≥4. These patients had a high risk of developing ARDS but did not fully complete the ARDS diagnostic criteria. Informed consent was acquired from all patients' legal guardians. Patients with prenatal hypoxemia, premature lung diseases (such as Meconium aspiration syndrome), adrenal insufficiency, vasculitis, lethal diseases, and methylxanthine or pentoxifylline intolerance were not included in this study. If patients developed any dangerous or intolerable side effects during the study, they would be excluded. Overall, 34 patients were eligible for the study.

2-2. Procedure

Thirty-four patients who entered the study were randomized into two groups: Sample and Placebo, with seventeen patients each. Pentoxifylline tablets (400 mg) were manufactured by Hakim pharmaceutical company, and placebo tablets were produced from Avicel and lactulose in the pharmaceutical laboratory of Pharmacy school, Mashhad University of medical sciences.

We performed block randomization using the www.randomization.com website, and random allocation was conducted using the same envelopes with random codes. The researcher and examiner were both blind to the allocation process. The sample group received 20 mg/kg/day of pentoxifylline (divided into three doses) for a week of trial. And the placebo group received the placebo tablet with the same dose, interval, and duration. The pentoxifylline and placebo tablets were similar, and patients were blind to the allocation. Chest Xray, CBC diff, VBG, LIPS score, pulse oximetry, and CRP were examined at baseline for all the patients. Furthermore, VBG, vital signs, and LIPS score were examined daily throughout the 7-day treatment period. CRP was evaluated on days 3 and 7, in addition to baseline. We considered the change of LIPS score as the primary endpoint, while the changes of CRP, VBG, lab data, and vital signs were the secondary endpoints.

2-3. Data analysis and Sample size

All the data and parameters obtained from patients were imported in SPSS software

version 20, and appropriate tests, such as Chi-square and independent T-test, were performed for each step.

To the best of our knowledge, this experiment is the first clinical trial to examine the preventive effect of pentoxifylline on pediatric ARDS. Hence, there was no previous guide on determining the sample size. We used LIPS score variation as the primary endpoint to calculate the sample size. Assuming equal variances, the reduction of LIPS score should be at least 50% to be considered a clinically significant outcome (27). Type 1 error (a) was considered to be 5%, and type 2 error (ß) 80%. Accordingly, the sample size of this study was calculated to be twenty using PASS software.

3. RESULTS

3-1. Participants

In the beginning, 50 cases were examined, of which nine patients did not complete the inclusion criteria. Unfortunately, seven patients passed away early and did not complete the trial. Overall, 34 children were included in this study. Thirty-four eligible patients began the study and were divided into placebo and treatment groups (**Fig. 1**).

We gathered the demographic information and lab data for each patient, as displayed in **Table 2**. There was no significant difference between the pentoxifylline and placebo groups at baseline, except for the weight (P=0.0451).

3-2. Comparison of LIPS score between the groups

LIPS score was assessed at baseline and then daily during the 7-day trial for both placebo and treatment groups. According to the repeated measure ANOVA test, LIPS score alteration was not significantly different between placebo and treatment groups (P value=0.475) (**Fig. 2**).

3-3. CRP comparison (quantitative)

CRP was assessed for all patients at baseline, day 3, and day 7. The repeated measure ANOVA test showed that CRP variation was not significantly different between the groups on days 0, 3, and 7 (P=0.053) (**Fig. 3**).

3-4. VBG comparison

We measured pH in both placebo and treatment groups at baseline, then daily for seven days. However, pH was not different between the two groups using the repeated measure ANOVA test (P=0.199). PO_2 was measured and compared between placebo and treatment group at baseline and daily for seven days. The repeated measure ANOVA test showed no difference between the two groups (P=0.077). We measured and compared PCO_2 for both groups on days 0-7. Using repeated measure ANOVA test, PCO_2 was not significantly different among placebo and treatment groups, whether at baseline or follow-ups (P=0.528). SPO_2 was also assessed for every patient at baseline and then daily for seven days. The repeated measure ANOVA test showed no significant difference in SPO_2 among placebo and treatment groups (P=0.260) (**Fig. 4**).

3-5.Vital signs comparison

Respiratory rate, heart rate, diastolic blood pressure, and systolic blood pressure were examined for all patients at baseline and then daily for a 7-day trial. According to the repeated measure ANOVA test results, the p-values were 0.512, 0.086, 0.572, and 0.517, respectively (**Fig. 5**). So, there was no significant difference in vital signs between placebo and drug groups.

4. DISCUSSION

This clinical trial investigates the prophylactic effect of pentoxifylline in pediatric patients who were very likely to develop ARDS. ARDS has a high mortality and morbidity risk, but our

therapeutic options are limited to supportive care and symptom therapy (1, 16). Hence, the search for new therapeutic options can be pretty helpful. Pentoxifylline has potential anti-inflammatory mechanisms and has shown positive effects on preventing ARDS in rodents (1, 26). As a result, we arranged this study to evaluate pentoxifylline usage in pediatric ARDS prevention. Our results showed no significant difference in vital signs, VBG, CRP, and LIPS scores between the placebo and pentoxifylline groups, whether at baseline or follow-up assessments within the 7-day trial. We may conclude that pentoxifylline does not prevent ARDS in high-risk pediatric patients. However, for a clear conclusion, further clinical trials should be conducted.

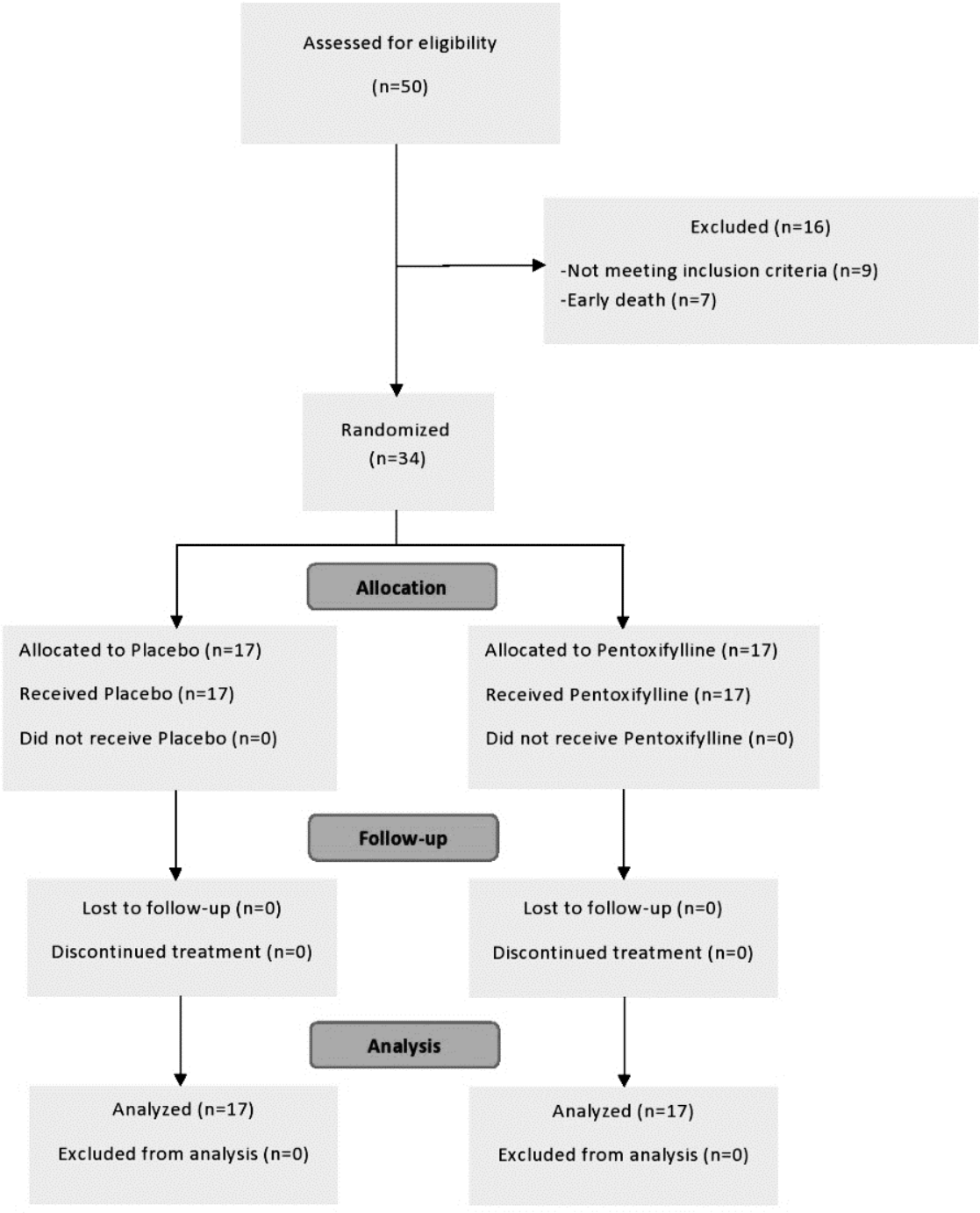

Fig. 1: Patient selection flowchart

Table-2: Patients' characteristics and Lab data

Variable	Mean ± SD		P Value
	Treatment	Placebo	
Gender	0.33	0.37	*0.525
Weight	13±8.733	15.8±12.19	**0.045
Height	83.13±24.70	82.57±36.76	**0.973
Age (year)	3.16±3.93	3.86±3.79	**0.603
Pulse rate	135±20	131±26	**0.599
Respiratory rate	36.35±13.72	40.13±16.66	**0.482

Systolic blood pressure (mmHg)	94.59±17.52	89.18±23.07	**0.447
Diastolic blood pressure (mmHg)	59.82±16.49	53.88±17.36	**0.314
RBC count (10^3 Cu/mm)	5.85±6.74	10.08±22.96	**0.314
WBC count (10^3 Cu/mm)	11.78±6.23	22.14±31.53	**0.193
Platelet count (10^3 Cu/mm)	220±122	252±140	**0.483
Hemoglobin (g/dL)	11.24±2.34	11.59±2.52	**0.676
Hematocrit	31.60±9.61	33.66±7.66	**0.502
Neutrophil (10^3 Cu/mm)	66.95±24.69	46.47±24.80	**0.862
Lymphocyte (10^3 Cu/mm)	25.33±19.38	23.44±17.10	**0.765
Eosinophil (10^3 Cu/mm)	0.02±0.05	0.45±0.79	**0.033
Basophil (10^3 Cu/mm)	0.02±0.05	0.07±0.15	**0.272
Monocyte (10^3 Cu/mm)	6.82±5.06	6.82±4.31	**0.999
Blast (10^3 Cu/mm)	0.00±0.00	3.82±15.76	**0.325
SpO_2	92.89±4.34	93.75±3.62	**0.626
pH	7.33±0.11	7.30±0.13	**0.465
PO_2	51.08±24.74	60.81±29.33	**0.304
PCO_2	39.45±11.52	40.08±15.90	**0.896
CRP	76.55±56.41	55.98±52.18	**0.278
LIPS	8.44±2.08	8.03±2.12	**0.572

* Chi-square test
** Independent T-test

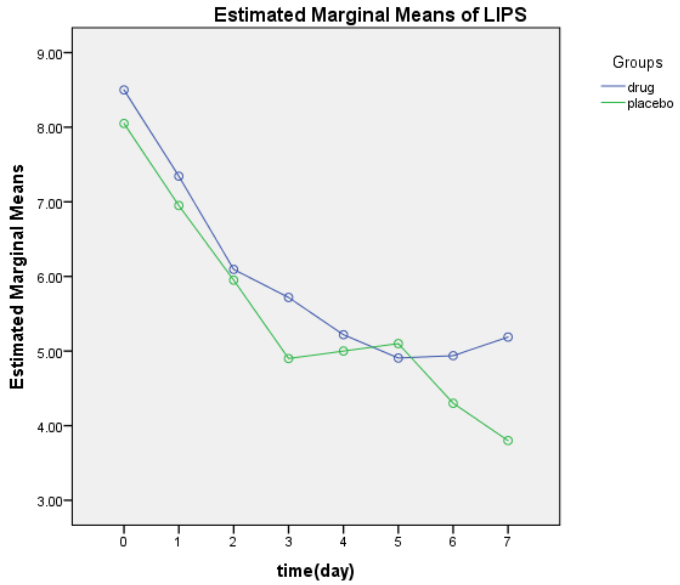

Fig. 2: LIPS score alterations in placebo and drug groups

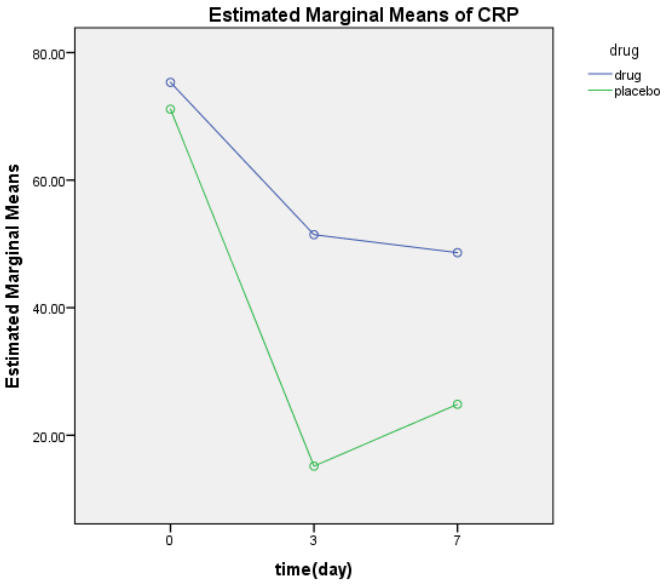

Fig. 3: CRP variations in placebo and drug groups

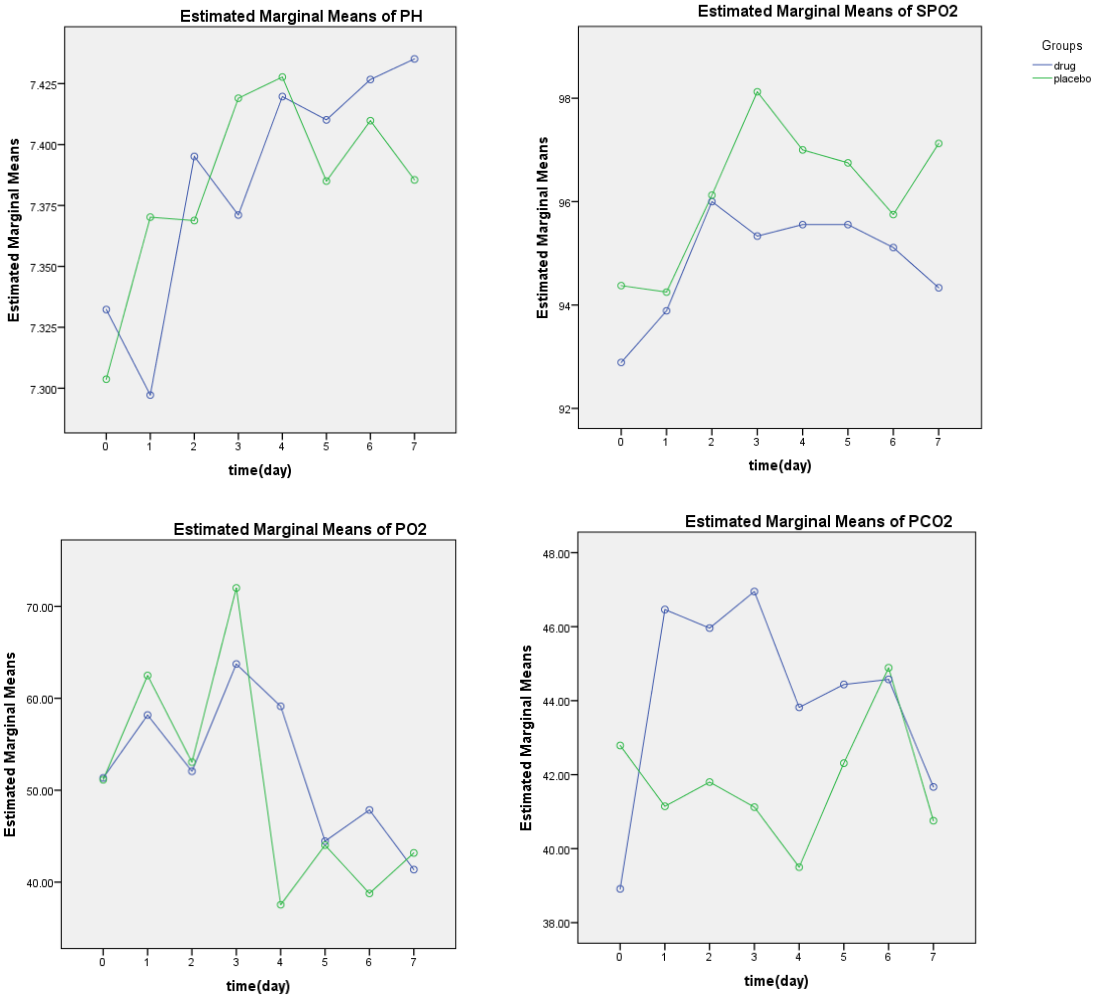

Fig. 4: VBG variations in placebo and drug groups

The rationale for conducting this study was the potential therapeutic mechanisms of pentoxifylline and previous in-vivo studies. Cytokine storm is a remarkable elevation of proinflammatory mediators in response to infections or other triggers. Cytokine storm can cause organ damage and is one of the main mechanisms of ARDS development (28). Previously, phosphodiesterase IV inhibitors positively affected respiratory disorders such as asthma, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis (29).

As explained earlier, pentoxifylline is a phosphodiesterase IV inhibitor that increases cAMP concentration; hence it can suppress inflammatory cytokines and oxidant agents and present anti-inflammatory effects (28, 30). In addition, pentoxifylline can inhibit nuclear factor kappa-B (NF-κB), a critical inflammation pathway, which reduces leucocyte/platelet interaction and decreases proinflammatory cytokines and ROS (31). Also, pentoxifylline can enhance the response of the A2A adenosine receptor to extracellular adenosine, which elevates cAMP in inflammatory cells and inhibits the inflammatory process (30, 32). An in-vivo study showed that pentoxifylline administration with fluid therapy could suppress pulmonary inflammation and neutrophil activity in rodents with hemorrhagic shock (33). Another study on mice demonstrated that pentoxifylline elevates cAMP, reduces interleukin production, and preserves Treg/TH17 balance. As a result, pentoxifylline reduced pulmonary injury, ARDS, and mortality in mice (1).

No previous study investigated the effect of pentoxifylline on ARDS prevention in children. Hence, considering the anti-inflammatory effects of pentoxifylline, here we address the studies that evaluated the use of anti-inflammatory medications on ARDS prevention. Corticosteroids were one of the therapeutic candidates. Weigelt et al. showed that methylprednisolone administration in ARDS susceptible patients did not significantly improve ventilation need and hospitalization period (34). In another study, Rolan M H Schein et al. concluded that methylprednisolone and dexamethasone did not prevent ARDS in septic patients (35). In addition, Roger C Bone et al. showed that methylprednisolone elevated ARDS progression and mortality in patients with sepsis (36). Bajwa et al. used statins for patients with a high risk of ARDS and concluded that statins did not reduce ARDS progression and mortality (37). Yadav et al. used statins to prevent ARDS before high-risk surgeries but did not observe any positive effects (38).

Anti-inflammatory inhalations were also used in clinical trials. ford et al. used treprostinil inhalation for ARDS prevention which had no positive effect (39). On the other hand, Festic et al. showed that formoterol/budesonide inhalation significantly improved oxygenation and SpO_2/FiO_2 ratio in patients with risk of ARDS progression (40). Besides anti-inflammatory properties, pentoxifylline shows antithrombotic effects and lowers blood viscosity.(23) Since no other studies investigated the use of pentoxifylline for ADRS in humans, we focused on the studies that used antithrombotic medications for ARDS. Dixon et al. administrated nebulized heparin for patients with or at risk of ARDS. They reported that heparin does not improve patients ‘daily function but reduces pulmonary injury and hospitalization period (41). Kor et al. showed that aspirin prophylaxis for seven days does not prevent ARDS in high-risk patients (42). These studies have conflicting outcomes, but a majority of them indicate that anti-inflammatory and anti-thrombotic treatments do not prevent

pediatric ARDS, which is compatible with our results.

4-1. Limitations and strengths of the study

Based on this clinical trial, pentoxifylline had no significant effect on primary or secondary outcomes. However, several limitations may have affected the outcomes. Our weak points were the small sample size and the use of oral pharmaceuticals. The calculated sample size was 20, but 17 patients were allocated to each placebo and treatment group at the end. Nevertheless, patient selection was difficult due to the small number of eligible patients who could fulfill the inclusion criteria. In some cases, parents did not agree with the study terms, which decreased the sample size.

Our patients were admitted to PICU. This stressful condition can alter gastrointestinal absorption and decrease the bioavailability of oral drugs, which is why intravenous administration is more desirable in ICU patients. Studies suggest that delayed gastric emptying is prevalent among critically ill patients, which affects drug absorption. Besides, in patients who experience shock states, blood flow is shunted away from non-vital organs like intestines towards the vital ones, decreasing gastrointestinal perfusion and enteric absorption (43-45). The use of oral pentoxifylline in this study might have decreased its efficacy. Also, we had a 7-day treatment period which may not be enough time to fully evaluate the preventive effect of pentoxifylline.

This trial has some strengths too. The current study is the first clinical trial to assess the effect of pentoxifylline on ADRS prevention. Therefore, it can be used as a reference to design further clinical trials. Besides, we used randomization methods with a double-blind design which decreases the risk of bias and enhances the reliability of the results. All of the patients completed the follow-up period, reducing the possible errors.

We recommend that more clinical trials with larger sample sizes, longer treatment periods, and different dosages should be designed to achieve a better understanding of the use of pentoxifylline in ARDS prevention. In addition, combination therapy of pentoxifylline with other anti-inflammatory drugs can be a good idea for future clinical trials.

5- CONCLUSION

The treatment and placebo groups had no significant difference in LIPS score, VBG, and CRP parameters, whether at baseline or daily follow-ups. Considering our small sample size, we recommend conducting more clinical trials with larger sample sizes, different dosages, and more extended administration periods to get better results.

6- ETHICAL CONSIDERATIONS

We acquired written informed consent from all Patients' legal guardians. This study protocol was authorized by the Ethical Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.REC.1399.317); and it was registered at the Iranian Registry of Clinical Trials (IRCT2090522043672N).

7- CONFLICT OF INTERESTS

None.

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