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RESEARCH ARTICLE

Evaluation of the effect of aminophylline on inflammatory parameters in COVID-19 patients with acute respiratory distress syndrome

Arina Dery Puspitasari[1,2], Erika Astanti[3], Novika Selvia Putri [3], Anna Surgean Veterini[2,4]

[1] Pharmacy Practice Departement, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[2] Universitas Airlangga Hospital, Surabaya, Indonesia
[3] Magister Programme Study of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[4] Anesthesiology and Intensive Care Departement, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

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Correspondence
Arina Dery Puspitasari
Pharmacy Practice Departement
Faculty of Pharmacy
Universitas Airlangga
Surabaya
Indonesia
arinadery@ff.unair.ac.id

Abstract

Background: In Acute respiratory distress syndrome (ARDS), invasion and activation of pro- and anti-inflammatory mediators and cytokines result in oxidative damage to the lung tissue. Aminophylline is a combination of theophylline and ethyl diamine, has anti-inflammatory, bronchodilator, ROS inhibitor effects, and stimulates surfactant release. Mortality of ARDS in COVID-19 patients is high; aminophylline is expected to reduce the incidence of mortality. Information regarding the use of aminophylline in COVID-19 patients with ARDS is still limited. **Objective:** To evaluate the efficacy of aminophylline in inflammatory parameters in COVID-19 patients with ARDS. **Methods:** It was a retrospective cohort observational study at the Universitas Airlangga Hospital. Samples were hospitalised COVID-19 patients with ARDS who received a loading dose of 240-480 mg and a maintenance dose of 720-960 mg aminophylline. The primary outcomes were improved C-reactive protein (CRP), IL-6, lymphocytes, neutrophils, and Neutrophil-lymphocyte ratio (NLR), which were measured before and after administration of aminophylline with a duration of therapy of 1-5 days. **Result:** A total of 50 patients with ARDS were enrolled in the study. Lymphocyte and CRP decreased (p = 0.002; p = 0.128). IL-6, neutrophil, and NLR increased (p = 0.255; p = 0.064; p = 0.005). **Conclusion:** It can be concluded that the administration of aminophylline has not improved inflammatory parameters.

Introduction

Within two years, the world has been busy with mysterious pneumonia infection cases from the most populated cities. By identifying genetic sequences, it was found that SARS-CoV-2 caused the infection (Budiarti *et al*., 2022). Since the first case was reported, COVID-19 has spread worldwide; in October 2020, reported cases reached 39 million worldwide. In Indonesia, COVID-19 first entered in March 2020 (Rahmawati *et al.,* 2022). The massive increase in disease in various world regions underlies the determination of the pandemic status in March 2021 by the WHO (Siordia, 2020).

SARS-CoV-2 infection causes a clinical spectrum ranging from asymptomatic, mild (fever, dry cough, fatigue, without pneumonia or with mild pneumonia) and moderate symptoms. It requires oxygenation therapy (tachypnea, decreased oxygen saturation, and signs of respiratory distress) and severe symptoms (multiple organ dysfunction) requiring hospitalisation, oxygen support, and mechanical ventilation. Some cases lead to death (Costa *et al*., 2021). However, patients with COVID-19 often present without fever, and many patients do not have abnormal radiology findings (Kusumawardani *et al*., 2023).

Several studies state that most patients infected with critical COVID-19 experience organ dysfunction, of

which 67% had Acute Respiratory Distress Syndrome (ARDS), 29% had liver dysfunction, 29% had Acute Kidney Injury (AKI), 23% had a cardiac injury, and 2% had a pneumothorax (Fatoni & Rakhmatullah, 2021).

The SARS-CoV-2 virus spreads through droplets that enter the body through mucous membranes. The spike protein (S) in the virus binds to the ACE-2 receptor. It increases its expression in type II alveolar cells, where the receptor is expressed in lung epithelial cells, and causes alveolar damage, thereby disrupting the diffusion of oxygen and carbon dioxide. In ARDS, damage to the vascular endothelium or alveolar epithelium causes increased capillary permeability, accumulating protein-rich fluid in the alveoli, and then diffuse alveolar damage occurs. Invasion and activation of immune cells (neutrophils or monocytes, or both) occurs, in which pro- and anti-inflammatory mediators and cytokines are released (Singh *et al*., 2020; Pfortmueller *et al*., 2021), for example, IL-1, IL-6, and Tumor necrosis factor (TNF) (Fatoni & Rakhmatullah, 2021).

An excessive increase in pro-inflammatory agents causes a cytokine storm, a key feature of ARDS (Pfortmueller *et al*., 2021). Neutrophils and other inflammatory cells produce oxidative damage to lung tissue (Aslan *et al*., 2021). ARDS parameters include hypoxemia ≤SpO_2 92%, RR ≥ 30 times/minute, and ≤PaO_2/FiO_2 300 mmHg even with oxygen administration, elevated marker values of inflammatory agents such as interleukins, TNF, C-reactive protein (CRP) (Fernando *et al*., 2021).

The current management of ARDS therapy is primarily to address oxygenation and ventilation in non-pharmacological patients in the prone position and NC, HFNC, ventilator, or ECMO breathing apparatus, while the provided pharmacological therapy is in the form of supporting therapy, namely corticosteroids, antiviral agents, anticoagulants, antibiotics. , IL-6 inhibitors, and vitamin D. Aminophylline is given as an adjunctive therapy to standard treatment (Ge *et al*., 2020; Fernando *et al*., 2021).

Aminophylline is a combination of theophylline and ethylenediamine with a ratio of 2: 1. Aminophylline has antihypoxia, anti-inflammatory, bronchodilator, vasodilator, ROS inhibitor effects, reduces oedema formation, stimulates surfactant release and can prevent virus replication (Mokra & Mokry, 2021; Montao *et al*., 2022).

There are studies examining the anti-inflammatory activity of nonselective Phosphodiesterase inhibitors (PDE inhibitors) in lung tissue and respiratory parameters in ARDS using animal models; the result is that aminophylline use showed significant anti-inflammatory activity, Tumour necrosis factor alfa (TNFα), IL-1β, -6, -8, -13, -18, receptor for advance glycation end product (RAGE), sphingosine-1-phospate (S1P), nitrite/nitrate, nitrite was decreased suggesting the potential of this drug to be a valuable component of ARDS therapy (Kosutova *et al*., 2023).

Aminophylline use can reduce the high mortality incidence of ARDS in COVID-19 patients. Information on the use of aminophylline in COVID-19 patients with ARDS is still limited; research regarding patterns and the effect of aminophylline is expected to provide meaningful information in the health sector.

Methods

Design

The research was conducted in a retrospective cohort observational study with a time-limited sampling research design. The researchers collected data through patient medical records at Universitas Airlangga Hospital (RSUA) in Surabaya from June to August 2021. The medical records met the inclusion and exclusion criteria and were screened, taken, and then recorded on a data collection sheet. Ethical permission for this study was obtained by requesting ethical approval from the RSUA ethics committee. The patient's identity is kept confidential, and the researcher bears all operational costs related to the research. The study population was all patients diagnosed with COVID-19 and confirmed through laboratory data with complications of ARDS who were treated in the ICU. Inclusion criteria for patients 18-65 years old, geriatric ≥ 65 years. Patients who have incomplete medical record data were excluded from this study. Fifty-one patients met the criteria, but one was excluded due to insufficient data. The sample criteria were patients with ARDS with RR ≥30 times/minute, hypoxemia SpO_2 < 92% and PaO_2/FiO_2 ≤ 300 mmHg. The independent variable is the administration of aminophylline therapy at a dose based on the patient's weight, and the dependent variable is laboratory data and clinical data before and after the administration of aminophylline.

Data analysis

Data analysis was carried out using descriptive analysis and hypothesis testing. Nominal-scaled data, such as gender and age, are frequency distributions, while ratio-scaled variables are expressed as means and standard deviations. Data analysis began with the normality test (Saphiro-Wilk) before and after administering aminophylline. The normality test results were not normally distributed; a nonparametric statistical test was performed.

Results

A total of 50 patients participated in the study between June until August 2021 (Table I). All were Universitas Airlangga Hospital (RSUA) patients with a mean age of 53.1 years (27-77 years); 32 patients (64%) were male and 18 patients (36%) were female. The proportion of patients >65 years is 10% and 18-65 years 45%. Patients with normal BMI is 52%, pre-obese 36%, and class I obesity is 12%. The length of stay of 11 patients (22%) 1-7 days, 19 patients (38%) 8-14 days, and 20 patients (40%) >14 days were treated. Thirty-four patients (68%) died and nine (18%) recovered. Twenty-six patients (52%) had diabetes mellitus, 23 patients (46%) had hypertension, two patients (4%) had asthma, three patients (6%) had cardiovascular disorders, three patients (6%) had AKI, four patients (8%) had Chronic kidney disease (CKD) and one patient (2%) had Chronic Obstructive Pulmonary Disease (COPD) is shown Table I.

The administration pattern of aminophylline in this study can be seen in that most patients received a loading dose of 240 mg and a maintenance dose of 720 mg. The route of drug administration for most patients with IV (intravenous) use and one route of the patient by oral administration, with a maximum duration of administration of 5 days with a range (of 1-18 days).

To determine the effect before and after aminophylline use in COVID-19 patients with ARDS shown in Table II, data were collected after aminophylline was administered and after aminophylline was discontinued (Table II). For the parameter of the P/F ratio, there was an increase in the mean value before aminophylline use of 118, with a range of 41-337, and after is 128, with a range of 26-450 (*p*-value 0.607). Clinical data on temperature experienced an initial average increase of 36.75 °C with a range of 34-41 and a final temperature of 38 °C with a range of 34-41(*p*-value 0.231). The average initial SpO_2 value was 91.88, and the final average was 90.94 (*p*-value 0.699). The initial average RR value was 32.3 times/minute, and the absolute standard was 26.5 times/minute (*p*-value 0.001).

Table I: Baseline characteristics of the patients (n = 50)

Variables	Result (%)
Gender	
Male	32 (64.0)
Female	18 (36.0)
Age range	
18-65 years of age	45 (90.0)
>65 year of age	5 (10.0)
Weight (Kg)	
Mean ±SD	71.20 ± 10.490003
Range	50 – 90
IBW	
Normal	26 (52.0)
Pre-obesity	18 (36.0)
Class I obesity	6 (12.0)
Length of stay	
1-7 days	11 (22.0)
8-14 days	19 (38.0)
>14 days	20 (40.0)
Outcome	
Referred to another hospital	1 (2.0)
Self isolation	6 (12.0)
Death	34 (68.0)
Recovery	9 (18.0)
Comorbidity	
Diabetes mellitus	26 (52.0)
Hypertension	23 (46.0)
Asthma	2 (4.0)
Heart disease	3 (6.0)
Acute kidney injury	3 (6.0)
Chronic kidney disease	4 (8.0)
COPD	1 (2.0)

*COPD: Chronic Obstruction Pulmonary Disease

Table II: Parameter changes before and after aminophylline administration

Characteristic	Before (Mean ± SD) (*n* = 50)	After (Mean ± SD) (*n* = 50)	*p*-value
P/F ratio	118.92 ± 64.39	128.00 ± 81.88	0.607
SpO_2	91.88 ± 11.47	90.94 ± 12.82	0.699
Temperature	36.75 ± 0.99	38.228 ± 8.29	0.231
Respiration rate	32.32 ± 10.21	26.53 ± 6.09	0.001
Neutrophil	80.31 ± 16.00	102.41 ± 118.59	0.064
Lymphocyte	11.53 ± 6.43	7.50 ± 5.17	0.002
Interleukin-6	229.94 ± 737.39	989.0 ± 3709.12	0.255
NLR	10.60 ± 10.48	19.7902 ± 19.79	0.005
CRP	103.56 ± 84.71	83.35 ± 78.68	0.128

In the inflammation parameter, the average CRP value decreased from 103 to 83 (*p*-value 0.128). On the interleukin data's average value increased from 229.9 to 989 (*p*-value 0.255), and the average value increased from 80.3 to 102.4 (*p*-value 0.064). In the lymphocyte parameter, the mean value decreased from 11.53 to 7.5 (*p*-value 0.002). An increase in the average neutrophil value and a decrease in the lymphocyte value, so the average neutrophil-versus-lymphocyte ratio increased from 10.6 to 19.79 (*p*-value 0.005).

Neutrophil, lL-6, and NLR are increased but not statistically significant. The improved parameter in this study is the P/F ratio; the higher value means that the partial pressure of arterial oxygen in the body is high, and the respiration rate and CRP are decreased but not statically significant. The inflammatory parameter lymphocyte shows a statistically significant decrease. At the beginning of aminophylline use, five patients used invasive ventilators and an increase in the number of 29 patients when aminophylline was discontinued.

Discussion

In severe cases of COVID-19, SARS-CoV-2 infection affects the lower respiratory tract and infects type I and especially type II pneumocytes, where type II pneumocytes produce surfactant in the lungs. Viral infection causes a decrease in surfactant production and low surfactant levels cause alveolar collapse, altering oxygen and carbon dioxide in the lungs, eventually causes fatal pneumonia (Patria & Sabirin, 2021). Individuals exposed to infection with the same virus with mild symptoms have an effective immune system, compared to individuals with severe symptoms that can result in dysfunction of the immune reaction, which eventually exacerbates uncontrolled viral replication/expansion (Pfortmueller *et al*., 2021).

SARS-CoV-2 is a large single-stranded RNA virus with a genome encoding about ten proteins (including the nucleocapsid/replica/envelope/spike protein). The "S" spike protein is an important particle that mediates cell binding to the ACE receptor 2. Followed by coactivation of transmembrane protease serine subtype 2 (TMPRSS2) in nasal cavity cells, airway epithelial cells, or both, with increased expression of ACE-2 in type II alveolar cells. Followed by viral cell entry and replication of SARS-CoV-2, damage to endothelial tissue and epithelial structures occurs, resulting in increased permeability and alveolar and interstitial accumulation (oedema) of fluid rich in protein (Pfortmueller *et al*., 2021).

ARDS can be caused by pneumonia (30-50%) and sepsis (25-30%) (Fernando *et al*., 2021). In the early exudative phase, surfactant inactivation, fibrin deposition and formation of hyaline membranes, tissue inflammation, and disturbances of cell homeostasis were observed, including apoptosis and necrosis (i.e. type II pneumocytes), often resulting in Diffuse alveolar damage (DAD). Furthermore, proliferation will worsen fibroblasts and myofibroblast proliferation, eventually leading to pneumonia. Pulmonary fibrosis is formed with irreversible damage to the pulmonary circuit, probably triggered by the movement of cytokines, namely by Transforming-growth factor-beta (TGF-β) and Interleukin (IL)-1 β (Pfortmueller *et al*., 2021).

The therapeutic treatment of ARDS is mainly supportive therapy, which depends on the patient's condition, so there is no specific therapy. Aminophylline is an adjunct therapy in ARDS due to several beneficial effects of aminophylline, namely phrenic nerve and diaphragm activation; aminophylline is a xanthine alkaloid derivative that has a mild stimulant and bronchodilator effect, immunomodulator with an inhibitory effect on T lymphocytes in the respiratory tract, including neutrophil apoptosis and suppression of inflammatory genes at low doses, theophylline also has an anti-inflammatory effect with Histone deacetylase-2 (HDAC2) activity, which increases the response to steroid therapy, ROS inhibitors, reduces oedema formation, stimulates surfactant release in the lungs (Mokra & Mokry, 2021).

The dose administered is individualised based on theophylline serum concentration and the patient's response to achieve maximum benefit from aminophylline with minimal side effects. A 5-6 mg/kg BW loading dose should be given as a bolus to achieve initial plasma theophylline concentrations of 10-15 mcg/ml for 20-30 minutes. Administration of IV bolus is recommended from much of the literature for at least 30 minutes. An aminophylline infusion of 500 mcg / KgBW/hour is given to healthy adults who do not smoke for 24 hours. The rate of administration of aminophylline by IV injection or infusion should not exceed 1 ml or 25 mg/min because rapid administration can cause cardiac arrhythmias (Gahart *et al*., 2019).

Based on studies, loading doses of aminophylline have been performed and administered by IV bolus for 30 minutes, namely 240-480 mg, with the most widely administered dose being 240 mg. The maintenance dose by slow infusion is 720-960 mg/24 hours, with the highest dose being 720 mg/24 hours. The routes of administration of aminophylline are mainly IV, IV, and orally, as well as single oral because there is no IV supply. The longest duration of administration of aminophylline was five days.

Neutrophil, monocyte, or both immune cell invasion and activation occur, releasing inflammatory

mediators, cytokines, or both. Atelectasis, impaired pulmonary blood flow, pulmonary vascular obstruction, and increased ventilation-perfusion cause hypoxemia. IL-6, pleitropic on pro- and anti-inflammatory cytokines increases. Rapid replication of the virus can trigger a very strong immune response with excessive production of cytokines and chemokines, which eventually results in a cytokine storm (Fatoni & Rakhmatullah, 2021). Massive recruitment of neutrophils in cytokine storm through activation and chemotaxis determined a significant reduction lymphocyte count in circulation caused by depletion, consumption, and negative counterregulation (Regolo *et al*., 2022).

One feature of the pathophysiology of ARDS is the presence of a hyaline membrane, a fibrin-rich exudate that is formed due to activation of coagulation and inhibition of fibrinolysis (Pfortmueller *et al*., 2021). In patients with COVID-19, there is often an increase in D-dimer levels, which are protein fragments resulting from fibrin degradation, which indicates a coagulopathy disorder and increases the severity (Fatoni & Rakhmatullah, 2021). Several factors can be used to evaluate inflammation status in COVID-19. Inflammatory biomarkers are frequently used to predict COVID-19 severity, such as CRP, Procalcitonin (PCT), IL-6, NLR, and platelet to lymphocyte ratio (PLR) (Regolo *et al*., 2022).

In this study, inflammatory biomarkers NLR, IL-6, lymphocyte, and neutrophil are worsened while CRP is improved but not statistically significant. There is research related to NLR and CRP using receiver operating characteristic (ROC) curve and hazard ratio (HR). ROC curve built for NLR expressed as a continous variable showed an acceptable predictive power intra – hospital mortality, comparing NLR, PLR, and CRP. NLR had the largest area under the curve followed by CRP and PLR. The primary markers NLR and CRP hazard ratio obtained in the study used two cox regression models. An increase 1 unit in the standard deviation (SD) of NLR increases mortality by 45% to 60%, and an increase of 1 unit in the SD of CRP increases mortality by 4%. Non – linearity between NLR and CRP could emphasise that CRP and NLR are both increased at the beginning of COVID-19, but NLR is further elevated later, particularly in patients with fallen CRP. This could mean the NLR provides information on prolonged inflammation in COVID-19, particularly in worse prognosis (Regolo *et al*., 2022).

In this study, RR is statistically significant improved, but SpO_2 is not statistically significant. Other research showed that pulse oximetry and respiration rate are not statistically significant related; patients with low oxygen saturation do not usually exhibit increased RR, and increased RR does not reflect desaturation. RR is unrelated to cardiopulmonary function and gas exchange, while SpO_2 reflects oxygen saturation information and provides a direct screen for cardiopulmonary disease and gas exchange abnormalities (Mower *et al*., 1996).

The result of this study is that aminophylline did not improve inflammatory parameters in COVID-19 patients with ARDS. Unlike previous studies, nonselective Phosphodiesterase inhibitors (PDE inhibitors) in animal models showed positive improvement in inflammatory markers. Patients with concomitant morbidity are less responsive to aminophylline used; another study found that the severity of COVID-19 increased in patients with diabetes mellitus (Khalaf *et al*., 2020).

To the authors' knowledge, this study is the first research on aminophylline used in COVID-19 patients with ARDS. This study has strengths: it demonstrates that the NLR ratio is an effective biomarker in COVID-19 severity and is more cost-effective than CRP. It also has limitations: It is a retrospective study with homogenous clinical characteristics and demographics. Further studies using prospective multicentric is needed.

Conclusion

Aminophylline used in COVID-19 patients has not improved ARDS condition, as shown by inflammatory parameters is not improved. It might be caused by the high patient load when the pandemic and the patient got late treatment.

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Conflict of interest

The authors state no conflict of interest in this study and the article.

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