


# Aminophylline as anti-hypoxic add-on therapy in the management of COVID-19 in Baghdad: An experience from single center report case study

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**ABSTRACT:** Coronavirus has affected people of all ages, gender, and various health status. Persons with chronic diseases or other health conditions may have severe illness from COVID-19. There is no specific drug targeting the coronavirus. Aminophylline is a phosphodiesterase enzyme inhibitor that stimulates the respiratory center and peripherally relaxes the bronchial smooth muscle, which explain its anti-hypoxic effect. This study aimed to show the effect of aminophylline as an anti-hypoxic agent as add-on therapy to the high flow rate oxygen in COVID-19 patients who presented with low blood oxygen. This case management study was carried out in the Army Force Hospital-Respiratory Centre from 10<sup>th</sup> April-20<sup>th</sup> August 2020. Thirty-one patients with severe COVID-19 illness were treated with aminophylline (250-500 mg, slow intravenous infusion, per day) after 2-5 days of respiratory distress. Aminophylline therapy is effective in relieving the hypoxia by elevating the blood saturation with oxygen in 100% (10 out of 10 patients) in COVID-19 patients without evidence of risk factors or concomitant diseases. The effectiveness of aminophylline declined to 81.9% in patients with concomitant diseases, and it was ineffective in 4 patients, three of them survived with artificial ventilation, and one of them was died despite using all supportive measures. In conclusion, Aminophylline as anti-hypoxic agent is associated with improved outcome in severe COVID-19. Its effect is extended to patients with risk factors or concomitant diseases.

**KEYWORDS:** COVID-19; aminophylline; antihypoxic; survival rate.

## 1. INTRODUCTION

Different pharmacological interventions are used in the management of coronavirus disease (COVID-19), and none of them showed a specific promising effect that terminates the illness within a short period and without adverse reactions [1]. Symptomatic treatment proved to be effective and can be considered as life-threatening measures, including oxygen supplementation, antipyretic agents, antitussives, antibacterial agents in case of secondary infections...and so on [2]. The efficacy of short-acting or long-acting beta-2 adrenoceptor agonists is not assessed precisely in the management of COVID-19 because bronchospasm is not a clinical feature of coronavirus infection [3,4]. However, salbutamol metered-dose inhaler is a suitable medicine in the management of COVID-19 with respiratory distress [5]. There is clinical evidence that long-acting beta-2 agonists can improve the diffusive lung property in chronic obstructive lung disease, which may be useful in COVID-19 as the gas diffusion capacity of the lung is impaired [6, 7]. Aminophylline is a bronchodilator that acts by inhibiting the phosphodiesterase enzyme inhibitor leading to an increase in the intracellular level of cyclic adenosine monophosphate which producing a dilatation of the bronchial tree. Several studies showed that aminophylline has pleiotropic effects, including anti-inflammatory [8], antioxidant [9], and anti-hypoxia [10]. It relieves the symptoms associated with hypoxia-like headache and effectively alleviates the hypoxia when it is concomitantly used with other medicine [10]. In addition, it improves the respiratory muscles, and thereby reduces the status of hypercapnia associated with hypoxia [11]. In one case study, including three neonates who presented with severe acute respiratory syndrome coronavirus infection, aminophylline as a symptomatic treatment improved the clinical features of COVID-19 [12]. The rationale of this study is to evaluate the efficacy of aminophylline in COVID-19 patients as an anti-

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hypoxic agent rather than as a bronchodilator. The aim of this case management study is to show the clinical effect of using aminophylline as anti-hypoxic on the clinical features of COVID-19 patients

## 2. RESULTS

In this case management study, a thirty-one patient presented with COVID-19 and severe hypoxia ( $\text{SaO}_2 < 90\%$ ) were treated with intravenous infusion of aminophylline as an anti-hypoxic agent. The characteristics of patients showed the mean  $\pm$  SD of age was  $55.5 \pm 13.2$ , with a wide range (Table 1). The cardinal clinical features of COVID-19 were fever, cough, dyspnea, and headache (Table 1). Two patients complained from diarrhea and another two patients had disturbances of consciousness. The highest frequency of diseases that associated with COVID-19 are those related to cardiovascular diseases (e.g. hypertension, obesity, ischemic and valvular heart diseases, and smoking) (Table 1). Diseases linked to the respiratory system e.g. bronchial asthma, and chronic obstructive pulmonary disease uncommonly complicated by COVID-19 (Table 1). Twenty-seven out of 31 patients (87.1%) responded to aminophylline as add-on therapy to the high flow rate of oxygen; 10 of them were without risk factor or concomitant disease (Figure 1). Four out of 31 patients did not show response to aminophylline and high flow rate oxygen; two females and two males. Patients with poor outcomes despite administration of aminophylline, had risk factors and/or disease (Table 2). The mortality rate was 1 out of 31 (3.2%).

**Table 1.** Characteristics of the 31-patients with COVID-19.

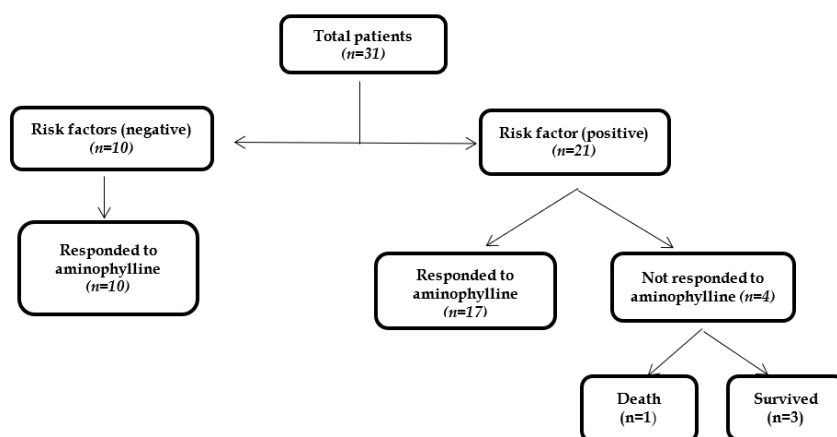
Variables	Results
Sex (male: female)	25:6
Age (year)	
Mean $\pm$ SD	55.5 $\pm$ 13.2
<b>Median (Inter-quarter)</b>	59 (50-64.5)
Clinical presentation	
Fever	31 (100)
Cough	27 (87.1)
Dyspnea	31 (100)
Headache	14 (45.2)
Diarrhea	2 (6.5)
Disturbances of consciousness	2 (6.5)
Risk factors	
Current smoking	8 (25.8)
Obesity	2 (6.5)
Hypertension	13 (41.9)
Diabetes Mellitus	14 (45.2)
Ischemic heart disease	4 (12.9)
Valvular Heart disease	1 (3.2)
Bronchial asthma	2 (6.5)
Chronic pulmonary obstructive lung disease	3 (9.7)
Rheumatoid arthritis	1 (3.2)

The results are expressed as number (percentage)

## 3. DISCUSSION

This case management study shows that the initiation of aminophylline intravenous infusion within 2-5 days of onset of severe hypoxia in patients with Covid-19 can accelerate the recovery of patients from the disease. The effectiveness of aminophylline in COVID-19 is reduced from 100% in patients without risk factor to 81% in patients with risk factors and/or concomitant diseases. Aminophylline is prescribed as an anti-hypoxic, not as a bronchodilator, to facilitate the action of a high flow rate of oxygen and elevates the blood saturation with oxygen. The dose of aminophylline (250-500mg, daily) that is used in this study is safe and it does not cause a significant adverse reaction [9]. In experimental animal studies, aminophylline infusion as add-on therapy improved the oxygenation in the experimental model of meconium syndrome [13]. Moreover, aminophylline has two important pharmacological actions (enhances the contraction of the diaphragm muscle, and stimulates the respiratory center) that play a role in improving blood oxygenation [14]. Recent studies reported that COVID-19 disease is an inflammatory disease associated with a significantly high level

of interleukin-6 [15, 16]. Tamburro et al reported that aminophylline significantly reduced the serum IL-6 in critically ill children admitted in the intensive care unit, and the anti-inflammatory effect of aminophylline is associated with clinical improvement [17]. Patients with concomitant morbidity are less likely to respond to aminophylline, and this finding agreed with other studies that found the severity of COVID-19 is increased in diabetic patients compared with those without diabetes [18]. *In silico* study from Saudi Arabia showed that, molecular docking of the coronavirus proteins are interacted with theophylline, remdesivir, and lopinavir, indicating that theophylline has a specific anti-coronavirus effect [19]. Other *in silico* study found that theophylline has the ability to bind to the RNA binding region on the N protein of coronavirus, suggesting that theophylline has a direct antiviral effect besides its effects on the respiratory system [20]. Therefore, the findings of this clinical study confirmed the current *in silico* computational studies. One of the most important limitations of the study is this study is uncontrolled, which is impossible to carry a placebo-controlled study on COVID-19 in a single center in the Middle East countries.



**Figure 1.** Schematic diagram showed the outcome of using aminophylline as antihypoxic in the management of COVID-19 patients with low oxygen blood saturation.

**Table 2.** Characteristic features of four patients with poor outcomes despite aminophylline therapy.

Variables	Results
Sex (male: female)	2:2
Age (year)	
Clinical presentation	
Fever	4
Cough	4
Dyspnea	4
Headache	3
Diarrhea	0
Disturbances of consciousness	1
Risk factors	
Current smoking	0
Obesity	1
Hypertension	2
Diabetes Mellitus	2
Ischemic heart disease	1
Valvular Heart disease	1
Bronchial asthma	0
Chronic pulmonary obstructive lung disease	0
Rheumatoid arthritis	1

The results represented as number

#### 4. CONCLUSION

Aminophylline as add on therapy to high rate oxygen flow accelerates the recovery of patients from COVID-19 by having an anti-hypoxic effect. This study confirmed current studies that phosphodiesterase enzyme inhibitors are useful in the management of viral diseases including coronavirus.

## 5. MATERIALS AND METHODS

This case management study was performed in the Army Force Hospital-Respiratory Centre in Baghdad from 10<sup>th</sup> April-20<sup>th</sup> August 2020. This study was approved by the Ethical committee at the Army Force Hospital (No.270, dated 01-04-2020). Patients who presented with clinical signs and symptoms suggestive of COVID-19, and confirmed by polymerase chain reaction, and radiological examination, including chest X-ray and computerized tomography of the lung. The patients were allocated randomly using randomized tables. The inclusion criteria were patients with COVID-19 and presented with severe hypoxia (Hypoxia was defined as the blood oxygen saturation of <93%), and radiological features indicating respiratory distress syndrome. The percentage of blood oxygenation was determined by Plus Oximeter. A total number of 31 patients (25 males and 6 females) were included in this case management study. Each patient according to his/her clinical conditions was treated with a slowly intravenous aminophylline infusion (250-500 mg, daily). Aminophylline was added to a pint of a glucose-saline solution, and a drip was running at a rate of 4ml per minutes. All the patients were treated with antiviral (Favipiravir, 800 mg twice daily for 5 days) anticoagulant (Enoxaparin, 6000 IU/day, Dexamethasone 6mg/day), antimicrobials whenever there was evidence of bacterial infection, symptomatic treatment for headache, fever, and cough. The high flow rate of oxygen (10-15L/min), and aminophylline was used as add-on-therapy after 2-5 days of deterioration of the general health and severe dyspnea (saturated oxygen <90%). The characteristic data including, the clinical features, risk factors, presence of concomitant illnesses were recorded. All the patients were monitored, and patients who did not respond to aminophylline or whose saturated blood oxygen dropped to <90% were admitted into the intensive care unit, where they were managed with mechanical ventilator. Excel 2010 software program was used for analyzing the data. The results are expressed as frequencies, percentages, and whenever possible as mean ± SD.

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**Conflict of interest statement:** The authors declare no conflict of interest in the manuscript.

**Ethics Committee Approval:** All procedures conducted in this study were approved by Ethical Committee of the Army Force Hospital in Baghdad, Iraq with the approval number of 270/01-04-2020.

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