

Original Article

A CROSS-SECTIONAL OBSERVATIONAL STUDY TO EVALUATE THE EFFICACY OF METHYLENE BLUE IN THE TREATMENT OF HYPOXIC COVID-19 PATIENTS

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ABSTRACT

Objective: The primary objective of this study is to evaluate the effectiveness of Methylene Blue (MB) in reducing hypoxia in COVID-19 patients.

Methods: A retrospective cross-sectional observational record-based study was conducted at Sai Krishna Multi-Specialty Hospital, Karimnagar, Telangana, over four months with 100 case sheets. A paired equal variance T-test was used to compare the pre-and post-treatment levels of SpO₂ and respiratory rate among the hypoxic patients.

Results: Out of 100 case sheets examined, about 70 patients were between the age groups of 45 to 54 years, 58 were males and 42 were females. The mean SPO₂ before treatment was 71.47% compared with day 3 values of SPO₂, which is 77.76%, and there was a significant improvement in the mean saturation levels with a P value less than 0.0001. There was a significant improvement in the mean respiratory rate, which was 26.92±0.85 at baseline before treatment, 23.93±0.90 on Day 3, and 21.42±1.27 on Day 7 after treatment with methylene blue and the P value is less than 0.0001.

Conclusion: This study concludes that Methylene blue intervention in COVID-related acute respiratory distress syndrome avoids the devastating consequences and improves patients' condition by reducing hypoxemia and respiratory distress.

Keywords: Acute respiratory distress syndrome, Hypoxemia, Respiratory rate

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INTRODUCTION

Corona Virus is an RNA virus that causes severe acute respiratory distress syndrome characterized by multi-organ failure, respiratory distress, and excessive inflammation, including cytokine storm, brought on by the virus spreading through the blood [1, 2]. The strain of coronavirus responsible for the COVID-19 pandemic is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). 6.6 million people worldwide have died from this dreadful Covid-19 sickness as of November 2022 [3]. The cascade of events in the pathogenesis of SARS-CoV-2 infection is viral invasion and replication, a dysregulated immune response, multiple organ damage, and recovery [4]. The anti-viral drugs, immunotherapy, and cell therapy were effective only if they were administered before the initiation of the inflammatory cascade. Several drugs like chloroquine, hydroxychloroquine, azithromycin, lopinavir, ritonavir, ribavirin, tocilizumab, baricitinib, remdesivir, favipiravir, ruxolitinib, teicoplanin, ivermectin, doxycycline, corticosteroids, heparin and NSAIDS were used [5]. Several vaccines were also discovered to combat COVID-19 and these include Covishield, Covaxin, Sputnik V, Pfizer BioNtech, Moderna, Zydus, etc [6].

Despite the administration of a high percentage of Oxygen support by non-invasive and invasive ventilation in COVID patients, there was continued hypoxemia and increased respiratory distress [7]. This paved the way for the introduction of Methylene blue in the treatment of COVID-19 patients with disproportional hypoxemia and distress. Methylene blue (MB) has indeed been explored as a potential treatment for COVID-19, particularly for patients suffering from hypoxemia (low oxygen levels in the blood) and respiratory distress, including those who experience severe lung damage or acute respiratory distress syndrome (ARDS). Methylene blue is a phenothiazine dye that has a variety of medical applications due to its ability to act as a redox agent (helping in electron transfer), and its effects on mitochondrial function. Methylene blue occurs in two forms, which are oxidised and reduced forms. The reduced form is an anti-oxidant and alleviates oxidative stress, whereas the oxidized form is an oxidant and elevates oxidative stress. Therefore, reduced

methylene blue also known as Leucomethylene blue, is used for treating severely hospitalized COVID-19 patients [8]. Other established medical uses of Methylene Blue are antidote for cyanide poisoning, photodynamic therapy, Hepatitis C and HIV, hypotension in sepsis and vasoplegia, psoriasis, and diagnostic marker [8, 9].

The various effects of Methylene blue against the SARS-CoV-2 virus are as follows [10-12]:

- Methylene blue has been found to improve mitochondrial function and enhance cellular oxygen utilization. MB helps by improving the efficiency of oxygen usage at the cellular level. It can act on the cytochrome c oxidase in the electron transport chain of mitochondria, potentially improving oxygen consumption and reducing hypoxic conditions. This could theoretically assist in reversing the oxygen deficit in tissues affected by COVID-19.
- Methylene blue has antioxidant properties, meaning it can neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are produced in excess during infections like COVID-19, contributing to tissue damage and inflammation. By mitigating oxidative stress, MB might help reduce the inflammation that contributes to lung injury and other systemic effects of the virus. This could potentially help patients experiencing cytokine storms, a key feature of severe COVID-19, where excessive inflammation causes widespread tissue damage. Inhibits binding of spike protein to host receptor, impairs membrane fusion resulting in reduced viral entry. Reduces viral uncoating and protein translation by increasing lysosomal pH, and inhibits RNA-dependent RNA polymerase through zinc ionophores, resulting in reduced viral replication. Inhibits NLRP3, and reduces excess nitric oxide activity and reactive oxygen species activity, resulting in reduced hyperinflammation.
- MB has been used to treat hypotension (low blood pressure), particularly in conditions like sepsis or vasoplegia (a state of extreme blood vessel dilation). In severe COVID-19 cases where blood pressure drops and organ perfusion is compromised, MB may help improve hemodynamic stability and restore proper blood circulation.

The study aimed to determine the effectiveness of Methylene Blue in hypoxic COVID-19 patients by comparing the peripheral capillary oxygen saturation (SpO₂) and respiratory rate at baseline with those values after treatment with Methylene Blue.

MATERIALS AND METHODS

The study was a retrospective cross-sectional observational record-based study. Case sheets of patients diagnosed with COVID-19 and hospitalized due to severe hypoxemia and respiratory distress were used to perform the analysis. It was conducted at Sai Krishna multi-specialty hospital, Karimnagar, Telangana, and lasted four months, from May 2021 to August 2021. The consent to conduct the study was taken from the head of the Department of Pulmonology, Sai Krishna Hospital, Karimnagar, Telangana. SpO₂ and respiratory rate were analyzed based on convenience sampling using Case sheets of COVID-19 patients treated with methylene blue to reduce hypoxemia and respiratory distress.

Peripheral capillary oxygen saturation (SpO₂) is commonly measured by pulse oximetry, which provides an indirect measurement of arterial oxygenation (SaO₂) based on the differential absorption of light by oxygenated and deoxygenated blood during pulsatile blood flow [13]. Normal oxygen saturation at sea level ranges between 96% and 100% [14]. In clinical settings, respiratory rate is frequently used as a screening tool to detect respiratory tract infections. According to standards, tachypnea is a respiratory rate (RR) of more than 20 respirations per minute (rpm) [15]. The severity of respiratory distress was assessed clinically based on hypoxemia (SPO₂) and tachypnoea (RR).

Study subjects

Case sheets of 100 patients diagnosed with COVID-19 and with a history of severe hypoxemia (SPO₂ of 70%) and respiratory distress admitted at Sai Krishna multi-specialty hospital were evaluated to assess the effect of methylene blue in the treatment of COVID-19 patients.

Inclusion criteria

Case sheets of men and women aged 18 years and above diagnosed with COVID-19 through RTPCR and hospitalized due to severe hypoxemia and respiratory distress with baseline characteristics of acute onset, diffuse infiltrations, SPO₂<75% and RR>26 rpm were included in this study.

Exclusion criteria

Case sheets of pregnant and lactating women, prior administration of methylene blue 30 days before hospitalization, patients with known hypersensitivity to methylene blue, those on other standard treatment, and patients whose death is inevitable within 24 h of admission based on clinical assessment.

Methods

A retrospective cross-sectional observational study was conducted. A total of 100 case sheets were included in the study. Those patients were treated with 100 mg of Methylene blue (SAM-MB) in 500 ml NS through IV route thrice daily. No other standard treatment was given. Baseline parameters such as SPO₂ and respiratory rate were studied and compared with the values on the third and seventh day of admission. The collected data was tabulated and analyzed using MS Excel and SPSS software version 26.

Statistical analysis

The data collected was entered in Microsoft Excel and the analysis was performed using the software package for the social sciences (SPSS) version 26. The level of significance was taken as 0.05; therefore, the p-values of <0.05 were considered significant. Initially, the baseline characteristics were analyzed and then compared with post-treatment parameters to evaluate the treatment effects. Paired Equal Variance Two-tailed T-test was used for the analysis of continuous variables.

Primary outcome measures

Recovery from hypoxemia and tachypnoea based on pre-and post-treatment SPO₂, RR. Recovery from hypoxemia is defined as the duration of air-breathing after an acute hypoxic exposure that raised and normalized peripheral blood SpO₂ to >96%. Recovery from tachypnoea is defined as the reduction in respiratory rate to a normal range of 12-20 breaths per minute.

RESULTS

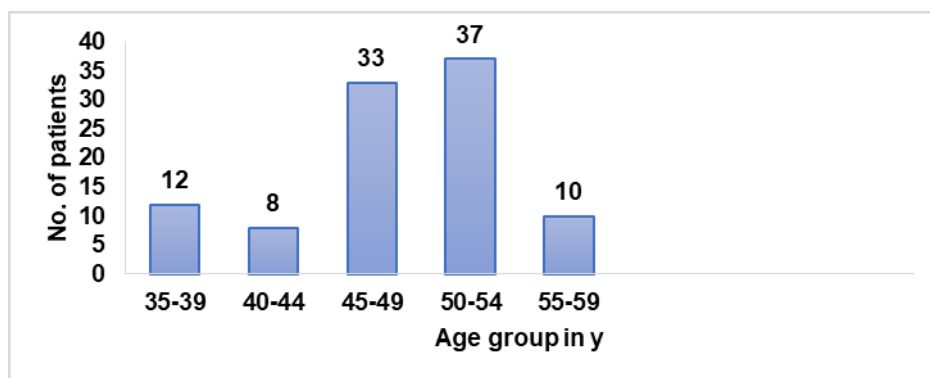
Secondary outcome measures

Clinical response and overall therapeutic response based on general cure or treatment failure. Clinical response is the reduction in clinical symptoms (hypoxemia and tachypnoea) and overall therapeutic response is the total improvement in response to treatment with methylene blue.

Table 1: Age-wise distribution of patients

Age group in years	No. of patients	Mean+SD
35-39	12	37.08+1.62
40-44	8	43.37+1.40
45-49	33	46.87+1.38
50-54	37	52.05+1.41
55-59	10	57+1.49

Using Microsoft Excel and SPSS software, the mean age and standard deviation of the patients were calculated.

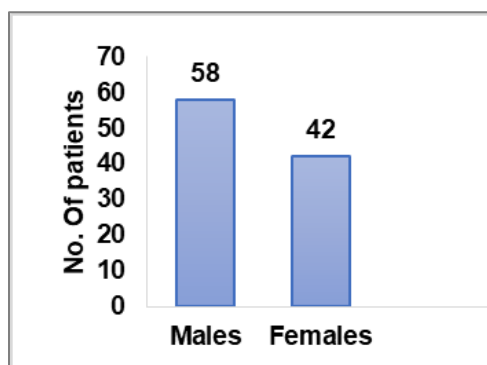


Graph 1: Age-wise distribution of patients

Table 2: Gender-wise distribution of patients

Gender	No. of patients	Percentage
Males	58	58%
Females	42	42%
Total	100	100%

Using Microsoft Excel, the percentage of male and female patients was calculated.



Graph 2: Gender-wise distribution of patients

Table 3: Comparison of baseline, Day 3 and Day 7 SPO₂

Parameter	Mean+SD	P value
Baseline SPO ₂	71.47+1.22	*P<0.00001
Day 3 SPO ₂	77.76+1.80	
Day 7 SPO ₂	89.92+1.43	

*Paired equal variance two-tailed t-test showing a significant improvement in post-treatment SPO₂ levels.

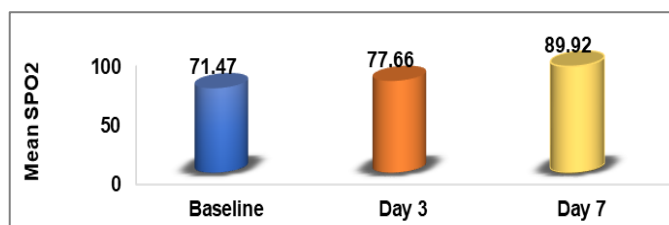
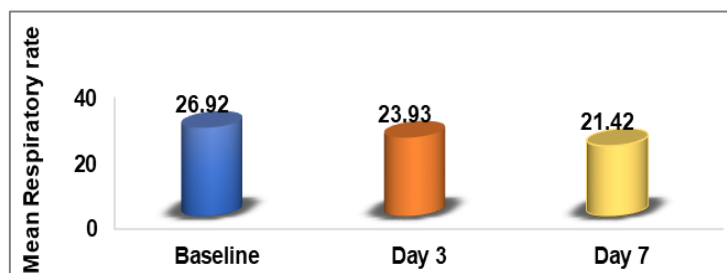
Graph 3: Comparison of baseline and day 3 and day 7 SPO₂

Table 4: Comparison of baseline, Day 3, and day 7 RR

Parameter	Mean+SD	P value
Baseline RR	26.92+0.85	P<0.00001
Day 3 RR	23.93+0.90	
Day 7 RR	21.42+1.27	

*Paired Equal Variance Two-tailed T-test showing a significant improvement in post-treatment reduction of respiratory rate.



Graph 4: Comparison of baseline and day 3 and day 7 RR

Demographic factors

- **Age distribution:** The study found that patients between the ages of 45 and 49 were most affected by COVID-19, as indicated in table 1 and Graph 1.
- **Gender distribution:** Males were found to be more affected than females, as shown in table 2 and Graph 2. Specifically, males aged 45-54 seemed to be the most impacted group, suggesting a gender and age-based vulnerability to COVID-19.
- **Clinical observations and methylene blue treatment**
- **Oxygen saturation (SpO₂) levels:** The mean SpO₂ before treatment was compared with values on Day 3 and Day 7. A significant improvement in oxygen saturation was noted, with $P < 0.05$, indicating that Methylene blue significantly improved hypoxemia. Table 3 and Graph 3 show the progression of mean SpO₂ levels from baseline to Day 3 and Day 7, demonstrating the positive effects of Methylene blue on oxygenation in COVID-19 patients.
- **Respiratory rates:** Respiratory rates were recorded at baseline, Day 3, and Day 7. A significant reduction in tachypnea (rapid breathing) was observed, with $P < 0.0001$ indicating a strong correlation between MB treatment and improved respiratory function. The findings in table 4 and Graph 4 highlight that Methylene blue helped reduce abnormal breathing patterns, a common complication in severe COVID-19 cases.
- **Symptom relief and recovery:** After treatment with Methylene blue, there was a notable reduction in several symptoms such as fatigue, dry cough, headache, fever, and loss of smell, which are frequently observed in COVID-19 patients. The duration of hospital stay was also reduced, indicating a faster recovery with Methylene blue treatment. All patients treated with Methylene blue fully recovered within 1 to 2 mo, suggesting its effectiveness in promoting recovery and improving the overall health condition of COVID-19 patients.

Methylene blue's effectiveness: Treatment with Methylene blue demonstrated:

Significant improvement in oxygen saturation levels and respiratory rates, with results showing statistical significance ($P < 0.05$ and $P < 0.0001$). Reduction in symptoms like fatigue, cough, fever, and loss of smell. Shorter hospital stays and complete recovery in 1-2 mo. This suggests that Methylene blue has therapeutic potential in mitigating hypoxemia, reducing tachypnea, and improving recovery times in COVID-19 patients, making it a valuable adjunct to traditional COVID-19 treatments. However, these findings would benefit from further clinical validation and larger-scale studies to establish the full scope of its effectiveness in a broader patient population.

DISCUSSION

Methylene blue is a tricyclic phenothiazine dye used to treat COVID-19 patients with severe hypoxemia and respiratory distress [11]. It was evident that the lungs were the most affected organs in patients with COVID-19 due to the invasion of the virus and damage to the respiratory endothelium resulting in inflammation leading to hypoxemia and respiratory distress [16]. Studies have shown that the addition of Methylene blue in the COVID-19 treatment protocol enhanced the oxygen saturation levels and reduced respiratory distress, shortened hospital stay, and reduced mortality of patients [17]. Therefore, in the present study, the efficacy of methylene blue in hypoxic COVID-19 patients was evaluated.

In this study, the common age group of affected patients ranged from 44 to 55 years and the median age was 49 years, consistent with a similar study conducted by Chaolin Huang *et al.* [18]. Males were more affected than females and the results were consistent with a similar study conducted by Meng Y *et al.* [19]. This might be due to higher expression of ACE-2, lifestyle behavior such as smoking and drinking, and immunological differences driven by sex hormones and X chromosomes [20]. There was a significant improvement in SPO₂ and respiratory rate after treatment of

patients with methylene blue. A similar study conducted by D. Hamidi-Alamdari *et al.* concluded that an addition of MB to the treatment protocols significantly improved SpO₂ and respiratory distress in COVID-19 patients, which resulted in decreased hospital stay and mortality [17]. Sanei ZS *et al.* conducted a study and observed that the oral administration of Methylene blue demonstrated positive effects on improving SpO₂ levels and reducing inflammatory markers in COVID-19-related ARDS patients [21]. Methylene blue is also effective in the treatment of bovine Coronavirus *in vitro* [22]. Methylene blue served as a life-saving drug in the treatment of hypoxemia and respiratory distress in hospitalized COVID-19 patients [23].

LIMITATIONS OF THE STUDY

The results of the study cannot be generalized as the study was a cross-sectional observational study conducted in a single hospital. The duration of the study is also small and conducted over a small group of patients. The efficacy would have been better evaluated if it was a large multi-centric study conducted among a large group of patients for a longer duration.

CONCLUSION

In hospitalized patients with COVID-19, the major symptoms were hypoxemia and respiratory distress. As these symptoms may aggravate and result in the death of the patient, it is important to choose a drug that improves oxygen saturation and reduces respiratory distress. In this hospital Inj. Methylene blue was used to combat the ARDS symptoms. This study conducted using Case sheets of treated patients concludes that Methylene blue intervention in COVID-related ARDS avoids the devastating consequences and improves patients' condition.

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AUTHORS CONTRIBUTIONS

Dr. Narender Sayini has planned, designed the concept of the manuscript, and drafted the manuscript, Dr. Padma Racharla has supported in drafting and collecting the reference articles.

CONFLICTS OF INTERESTS

Declared none

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