

Clinical Effects and Outcomes of Methylene Blue in Treatment of Covid 19 Patients

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), a novel betacoronavirus and the most recent one of the seven coronaviruses (CoVs) known to infect humans, is responsible for COVID-19, which has been declared a pandemic by the World Health

Almost one year after the onset of COVID-19 pandemic in Wuhan, China and still no specific therapy has emerged, counting millions of dead worldwide.

Owing to the multiplicity of mechanisms involved in COVID-19 pathogenic expressions, such as severe hypoxia, excessive inflammatory reaction and impaired immune response, an emerging therapeutic paradigm is the searching for agents acting as multifunctional drugs.

Methylene blue (MB), the antique medication, seems to meet the above criterion

Additionally, M.B. has a strong antifibrotic action and is very fast acting.

this study describe the clinical outcomes of hypoxic coronavirus disease 2019 (covid-19) patients treated with intravenous methylene blue (mb) in a tertiary care hospital

MATERIALS AND METHODS

A total of 30 patients with severe acute respiratory distress were taken up for the study. data related to objectives of study was collected. methylene blue was given in intravenous and nebulised form in our hospital from June 08 to September 10 2020

RESULTS

1. our study showed that methylene blue helped in improving saturation of patient
2. reducing patient need for higher modes of ventilation
3. improvement in chest xray
4. also reduced in hospital mortality
5. prevented complications related to covid in future like fibrosis

CONCLUSION

we conclude that administration of methylene blue to covid 19 patients helped in improvement of patients oxygen saturation, in hospital mortality, reduced need for higher modes of ventilation and post covid complications like fibrosis.

KEYWORDS :- ACE2, antiviral, COVID-19, methylene blue, SARS-CoV-2, spike protein, Acute respiratory distress syndrome, Coronavirus disease 2019, Methylene blue, Rescue therapy

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I. Background

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome-coronavirus (SARS-CoV-2) has severely impacted healthcare systems all over the world. Though the exact pathogenesis of SARS-CoV-2 is unknown, various hypotheses have proposed cytokine storm or hyperinflammatory syndrome as probable causes for the rapid worsening of the disease.

Various drugs have been repurposed for treatment in the absence of definitive therapy with emphasis on the provision of supportive care including oxygenation, ventilator support, and other critical care life supports.

Methylene blue (MB) or Bis (dimethylamino) phenazathionium chloride trihydrate, an organic dye, has been used extensively in an array of clinical conditions for the past two centuries. Few clinical conditions where the role of MB has been documented include treatment of malaria, refractory septic shock, catecholamine refractory vasoplegia, methemoglobinemia, and therapeutic benefit in hypoxia caused due to pulmonary

vasodilation in patients of hepatopulmonary syndrome due to inhibition of guanylate cyclase and nitric oxide synthetase.

Various theories have been postulated highlighting the benefits of administering MB as a salvage therapy among COVID-19 patients for its antiviral, anti-inflammatory, and antioxidant properties and have been proposed as a rescue therapy for improving the refractory hypoxia in COVID-19 patients.

Till date, no clinical trials have been conducted evaluating the clinical effects of MB among COVID-19 patients

MB inhibits the viral attachment and entry of SARS-CoV-2 by blocking the protein–protein interaction (PPI) of its spike protein with ACE2 on the host cell which is the first critical step initiating the viral entry. They suggested that this antiviral activity could be useful in the prevention and treatment of COVID-19 either as an oral or inhaled medication.

methylene blue (mb) photochemical technology has been proven to inactivate lipid-enveloped viruses with high efficiency and safety. the present study aimed to investigate the sars-cov-2 inactivation effects of methylene blue in plasma

DATA SOURCE

Data were collected between June 08 to September 10, 2020, and the clinical outcomes were monitored till October 30, 2020. Demographics, clinical, and laboratory data on admission and the subsequent trends, mode of respiratory support (invasive mechanical ventilation, noninvasive mechanical ventilation, and oxygen mask), fraction of inspired oxygen (FiO₂), SpO₂/FiO₂ ratio and treatment administered were collected from the electronic medical records. The collected data were analyzed and interpreted by two independent intensivists. The clinical team provided clarification on missing or redundant data.

II. Materials And Methods

A total of 30 patients with severe acute respiratory distress were taken up for the study. data related to objectives of study was collected .methylene blue was given in intravenous and nebulised form in our hospital from june 08 to september 10 2020

. intravenous mb was administered as rescue therapy in dosage of 1 mg/kg body weight, with a maximum of five doses, to patients with high oxygen requirements (spo₂/fio₂ <200) apart from the standard of care after obtaining g6pd levels. data were abstracted from multiple electronic data sources or patient charts to provide information on patient characteristics, clinical and laboratory variables and outcomes

standard of care, such as antivirals, steroids, and anticoagulants, was administered apart from oxygen supplementation by nasal cannula, nonrebreather mask (nrbm), high flow nasal cannula (hfnc), or noninvasive ventilation (niv) as per the hospital protocol and discretion of the treating physician.

invasive mechanical ventilation was initiated based on the clinical assessment and spo₂/ fio₂ of the patients.

The study was conducted by the Department of emergency Medicine in a tertiary care hospital located in SSIMS Davangere India.

CRITERIA

Inclusion criteria are:

- signed informed consent
- age ≥ 18 years
- microbiologically confirmed SARS-CoV-2 infection
- negative pregnancy test in women of child-bearing age

EXCLUSION CRITERIA

- documented refusal to participate in the study
- known G-6-Phosphatase deficiency
- treatment with a serotonergic drug
- Pregnancy and breastfeeding
- History of G6PD deficiency
- Severe renal insufficiency
- deranged liver function test or Chronic liver disease

III. Results

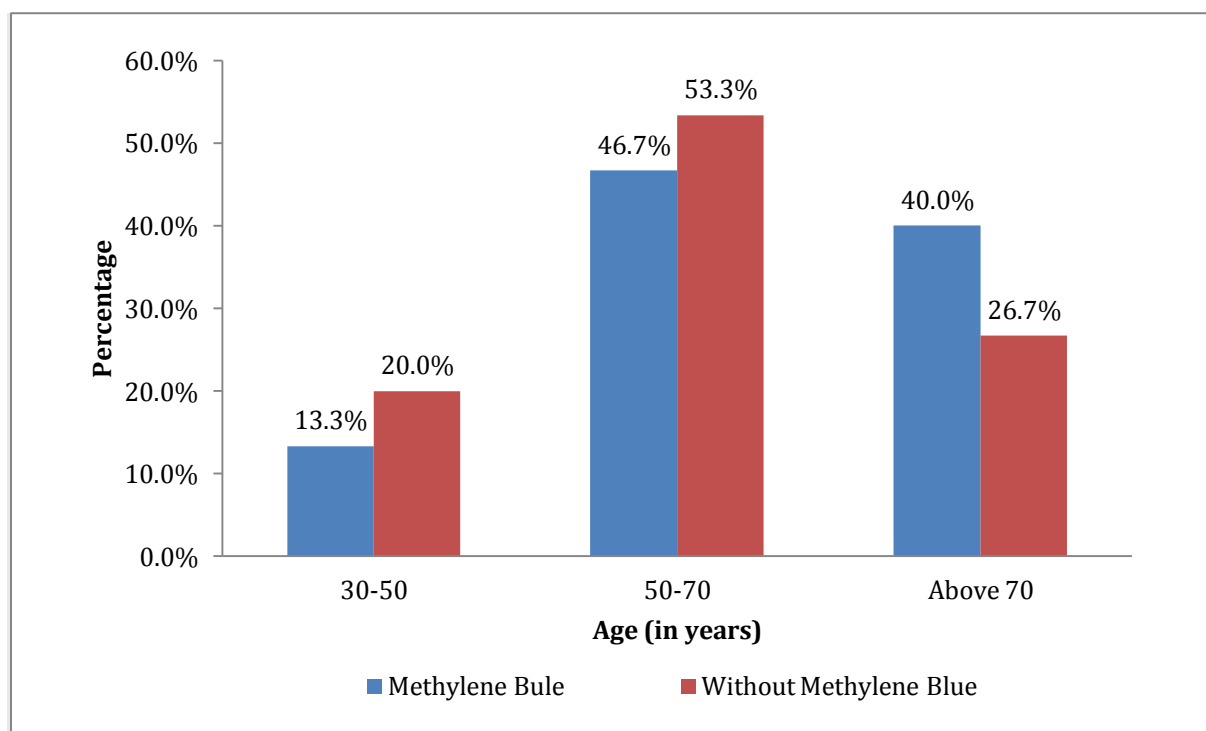
INTERPRETATION

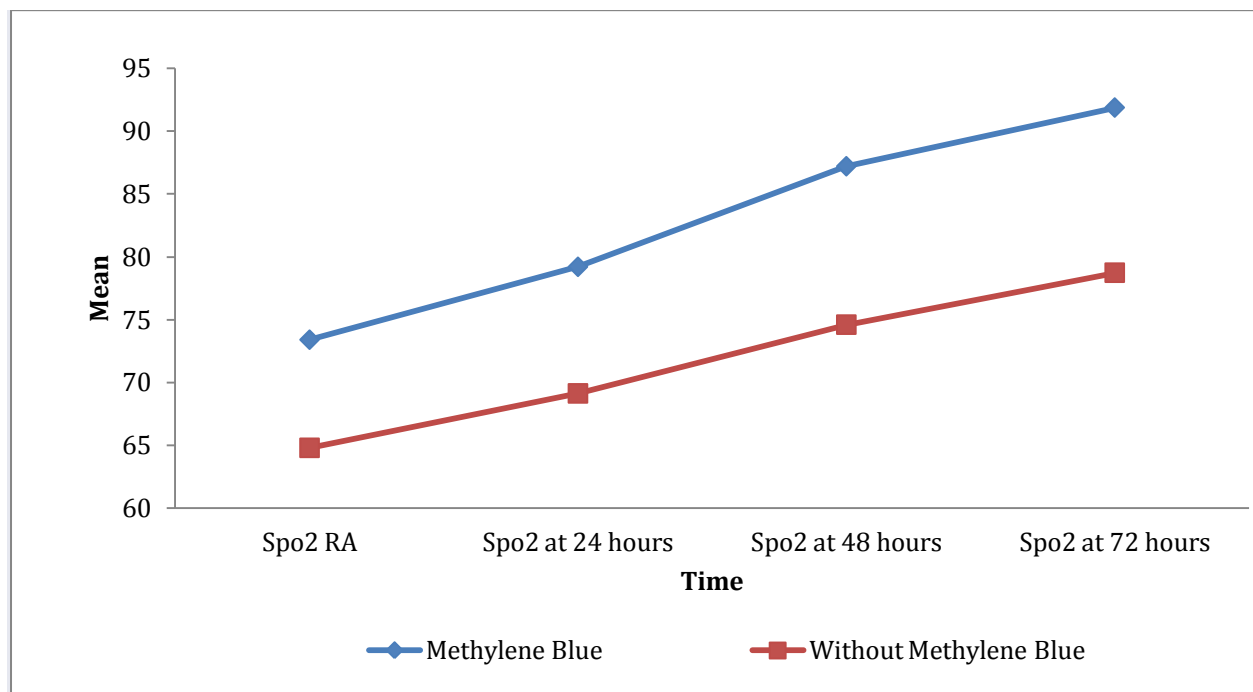
Our study showed that methylene blue helped in reducing patient need for higher modes of ventilation and also prevented in hospital mortality and complications related to covid in future like fibrosis .

Age (in years)	Groups		Total	p value
	Methylene Blue	Without Methylene Blue		
30-50	2	3	5	0.717
	13.3%	20.0%	16.7%	
50-70	7	8	15	
	46.7%	53.3%	50.0%	
Above 70	6	4	10	
	40.0%	26.7%	33.3%	
Total	15	15	30	
	100.0%	100.0%	100.0%	

Parameters	Methylene Blue		Without Methylene Blue		t value	p value
	Mean	SD	Mean	SD		
Day of illness	6.33	2.23	8.27	3.49	-1.81	0.083
HRCT Score	11.60	6.50	9.93	6.32	0.71	0.482
No of Ventilator Days	1.13	1.55	5.93	6.77	-2.68	0.017
Total No of Hospital Days	4.73	1.44	14.33	9.79	-3.76	0.002

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KEYWORDS :-ace2, antiviral, covid-19, methylene blue, , sars-cov-2, spike protein, acute respiratory distress syndrome, coronavirus disease 2019, methylene blue, rescue therapy

IV. Discussion

This case series would be to our knowledge the first study in india that presents data of hypoxic covid-19 patients treated with intravenous mb. the rapid surge in the number of patients infected with covid and the high caseload on the hospitals have led medical researchers to identify new drugs that could help treat patients with covid- 19.

various drugs with known safety profiles, easy availability, and effectiveness in managing complications have been studied. mb an organic dye has been used extensively in an array of clinical conditions for the past two centuries and has been proposed as a rescue therapy for improving the refractory hypoxia in covid-19 patients.

various theories have been postulated highlighting the benefits of administering mb as a salvage therapy among covid- 19 patients including antiviral, anti-inflammatory, and antioxidant properties. mb in presence of light has broad-spectrum virucidal activity and has been used to inactivate viruses in blood products prior to transfusions.

bojadzic et al. proposed that mb inhibits the viral attachment and entry of sars-cov-2 by blocking the ppi of its spike protein with ace2 on the host cell which is the first critical step initiating the viral entry.

they suggested that this antiviral activity could be useful in the prevention and treatment of covid-19 either as an oral or inhaled medication. gendrot et al.²¹ demonstrated that nonphoto-activated mb showed high in vitro antiviral effective activity against sarscov-2 with an inhibitory concentration (ic) ic50 (0.3 μm) and ic90 (0.75 μm) compatible with oral uptake and iv administration. this in vitro activity was higher than those obtained with drugs such as hydroxychloroquine (1.5 μm), azithromycin (20.1 μm), remdesivir (23 μm), lopinavir (26.6 μm), or ritonavir (>100 μm).

barber et al. and vardhana et al. reported that mb by blocking the downstream cosignaling ppis of the cytotoxic t lymphocytes, restores their cytotoxicity, activation, proliferation, and cytokine secreting activity thereby restoring t cell homeostasis and function, which in turn improves viral clearance.

henry et al. proposed that mb could be of considerable help in the management of covid-19 based on a survey of 2,500 french patients treated with a combination of α -lipoic acid, hydroxycitrate, and mb as part of cancer care in whom nil infections of the virus were reported. they proposed that upon absorption, mb undergoes one-electron reduction and becomes a neutral lipophilic mb radical. this radical acts as a weak base (pka ~9) which could cause transient alkalization of cytosolic spaces.

V. Conclusions

our study proved that use of methylene blue in patients helped in reducing their oxygen requirement ,length of hospital stay was reduced,improvement in chest xray was seen

mb due to its polypharmacological action against sars-cov-2, an inexpensive and widely available drug with minimal side effects, has a significant potential in the treatment of covid-19.

further metaanalysis needed to know further use of methylene blue in covid and refractory hypoxic patients

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