Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.42.006723

Treatment of Severe COVID-19 Outpatients by Methylene Blue (First Report)

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ARTICLE INFO

Received: February 21, 2022

Published: March 01, 2022

Citation: Saied Hafizi Lotfabadi, Daryoush Hamidi Alamdari, Behzad Mavaji Darban. Treatment of Severe COVID-19 Outpatients by Methylene Blue (First Report). Biomed J Sci & Tech Res 42(2)-2022. BJSTR. MS.ID.006723.

Abbreviations: MB: Methylene Blue; HTN: History of Hypertension; HT: Heart Disease; WBC: White Blood Cell; CRP: C-Reactive Protein; AST: Aspartate Amino Transferase; GGOs: Ground-Glass Opacities; HRCT: Lung High-Resolution Computed Tomography

ABSTRACT

Background: There is a debate about pharmacological treatment for COVID-19. In our clinical trials (phase1, 2, 3), we showed the efficacy of reduced Methylene Blue (MB) as an adjunct therapy along with standard care protocols in the treatment of severe COVID-19 patients. Also, we coined MB as an anti-hypoxemia and an anti-respiratory distress agent.

Objective: To verify the efficacy of MB as the last option for the treatment of severe COVID-19 outpatient who did not respond to Remdesivir, Interferon-β, and Favipiravir therapies.

Methods: Seven outpatients with confirmed cases of severe COVID-19 were recruited. Patients were received oral MB (the reduced form: 1mg/kg T.I.D. for 2-days, followed by 1mg/kg B.I.D. for the next 12 days) along with standard care.

Results: Outpatients recovered completely.

Conclusion: Considering all properties of MB such as anti-viral, antibiotic, anticoagulant, immunomodulatory, antioxidants, anti-hypoxemia, and anti-respiratory; it could be applied as an adjunct therapy along with standard care protocols in the clinical management of COVID-19 outpatients. MB is a cheap and FDA-approved drug for methemoglobinemia.

Keywords: COVID-19; Treatment; Methylene Blue; Outpatients

Introduction

There are no evidence-based treatments that are appropriate for the management of COVID-19 outpatients. The incubation period is 2 to 14 days. Symptoms that typically appear within five days of exposure, are fever, dry cough, shortness of breath, fatigue, and feeding difficulty. To date, the only dexamethasone has shown efficacy in hospitalized patients with COVID-19 [1]. Early initiation of antiviral therapy for COVID-19 could improve clinical outcomes by halting clinical progression, and also might shorten the duration of viral shedding, potentially reducing onward transmission [2]. In the clinical setting for the management of severe COVID-19 patients, anti-viral agents, antibiotics, anticoagulants, immunomodulatory drugs, antioxidants, fluid therapy, and oxygen support are applied for treatment [3,4]. The results of our clinical trials (phase 1, 2, 3) for treatment of COVID-19 patients showed that the use of oral Methylene Blue (MB) leads to a significant decrease in-hospital stay and about a 10 % decrease in mortality in the treated group. We suggested that the addition of MB to the treatment protocols for severe COVID-19 patients was associated with significant clinical

benefits [5-7]. MB has these properties such as anti-viral, antibiotic, anticoagulant, immunomodulatory, antioxidants, anti-hypoxemia, and anti-respiratory, which could be applied in the clinical management of COVID-19 outpatients as well [6-8]. Therefore, in this case series study, we used MB for the treatment of severe COVID-19 outpatients to evaluate its efficacy for these patients.

Material and Methods

This study was performed at Mashhad University of Medical Sciences, Mashhad, Iran, after ethics committee approval (IR.MUMS.REC.1399.122; ClinicalTrials.gov Identifier: NCT04370288; April 19, 2020) and taking written informed consent from patients. The clinical trial has been conducted according to the principles expressed in the Declaration of Helsinki. Methylene blue syrup (or powder) formulation: The compositions of the syrup were MB, vitamin C. The special formulation for MB (the reduced form) was patented (IR-139950140003002083) (on June 1, 2020, PCT). It should be noted that the current standard care protocols were applied according to WHO guidelines. In the current standard care protocols, outpatients receive supplemental oxygen, antibiotics, anticoagulants, corticosteroids, zinc, vitamin C, and vitamin D [3,4].

Results

Case 1

On December 10, 2020, a 60-year-old female, with a past medical history of Hypertension (HTN) and Ischemic Heart Disease (IHD), was admitted to the internal medicine department of the hospital due to headache, cough, myalgia, fever, reduced oxygen saturation (SpO2): 86%, and dyspnea which started 5 days before admission. Her RT- PCR was positive for SARS-CoV-2. Her blood work revealed White blood cell (WBC) counts: 6.4 $\times 10^3/\mu L$ with 83% neutrophils and 11% lymphocytes, platelet count: $129\times 10^3/\mu L$, lactate dehydrogenase (LDH): 870 IU/L, C-Reactive Protein (CRP): 120 mg/dL, total bilirubin: 1 mg/dL, aspartate aminotransferase (AST): 79 IU/L and Alanine Aminotransferase (ALT): 101 IU/L. Her lung High-Resolution Computed Tomography (HRCT) revealed diffuse bilateral Ground-Glass Opacities (GGOs) and consolidation in the peripheral lung regions. Both upper and lower lobes were involved. She was treated with Remdesivir (200 mg on the first day and 100 mg for 10 days), IFN-β (44 μg/sc daily for 4 doses), Meropenem 1 gr TDS, Ticoplanin (400mg/BID first day and then 200mg/BID), Azithromycin (500mg/day), and Dexamethasone (8 mg/day for 10 days).

After 8 days of treatment with her consent, the patient was discharged from the hospital with SpO2 (70%, on room air), and with the simple oxygen mask, SpO2 was 82-92%. She was treated as an outpatient in her home by oral MB powder as the last option (1mg/kg TID for 2-days, followed by 1mg/kg BID for the next days) along with standard care. There were no side effects or allergic reactions noted and just the color of urine became green. After 10 days of MB therapy, her SpO2 increased to 93-95% without oxygen therapy. The blood workup showed WBC counts: 7.8 $\times 10^3/\mu L$ with 79% neutrophils and 20% lymphocytes, platelet count: $197\times 10^3/\mu L$, LDH: 501 IU/L, CRP: 9.1 mg/dL, total bilirubin: 0.9 mg/dL, AST: 45 IU/L, and ALT: 64 IU/L.

Case 2

On January 20, 2021, a 58-year-old male without any past medical history presented with symptoms (cough, myalgia, fever, shivering, respiratory distress, and SpO2: 90%) which started 8 days before treatment. His RT- PCR was positive for SARS-CoV-2. His initial workup showed WBC count: 7.6 $\times 10^3/\mu L$ with 80% neutrophils and 17% lymphocytes, platelet count: $211\times 10^3/\mu L$, LDH: 744 IU/L, CRP: 54 mg/dL, total bilirubin: 1.1 mg/dL, AST: 39 U/L and ALT: 47 IU/L. His lung HRCT revealed diffuse GGOs and consolidation in the peripheral lung regions. Both upper and lower lobes were involved. He was treated only with MB (1 mg/kg every 8 hours for two days, followed by 1mg/kg every 12 hours for the next days). After 5 days of MB therapy, his SpO2 increased by 98% and respiratory distress showed marked improvement. The blood workup exhibited WBC count: 6.3 $\times 10^3/\mu L$ with 72% neutrophils and 23% lymphocytes, platelet count: $217\times 10^3/\mu L$, LDH: 231 IU/L, CRP: 9 mg/dL, total bilirubin: 1.1 mg/dL, AST: 31 IU/L and ALT: 39 IU/L.

Case 3

On January 29, 2021, a 90-year-old female with a past medical history of HTN and IHD was treated by the administration of MB powder. She presented with fever, shivering, respiratory distress, and SpO2:60% which started 8 days before treatment. Her RT-PCR was positive for SARS-CoV-2. Her initial workup showed WBC count: $6.9\times 10^3/\mu L$ with 70% neutrophils and 25% lymphocytes, platelet count: $219\times 10^3/\mu L$, LDH: 841 IU/L, CRP: 64 mg/dL, total bilirubin: 1.4 mg/dL, AST: 57 U/L and ALT: 81 IU/L. Her lung HRCT revealed diffuse bilateral GGOs and consolidation in the peripheral lung regions. Both upper and especially lower lobes were involved. Her cardiologist advised her just take her medicine and oxygen support. She was treated only with MB (1 mg/kg every 8 hours for two days, followed by 1mg/kg every 12 hours for the next days). After 2 days of MB therapy, her respiratory distress showed marked improvement. After 10 days SpO2 reached 85% (on room air) and after 15 days reached 94%. The blood workup exhibited WBC count: 9.4 $\times 10^3/\mu L$ with 69% neutrophils and 31.2% lymphocytes, platelet count: $216\times 10^3/\mu L$, LDH: 401 IU/L, CRP: 8 mg/dL, total bilirubin: 1.2 mg/dL, AST: 47 IU/L and ALT: 57 IU/L.

Case 4

On October 11, 2020, a 72-year-old male with a past medical history of severe diabetes mellitus was treated by the administration of Azithromycin (500mg/day), Favipiravir (200 mg, 8 pills daily for 5 days), and Dexamethasone (8 mg/day for 10 days). His symptoms include cough, myalgia, fever, shivering, respiratory distress, and SpO2: 78% started 6 days before treatment. His RT- PCR was positive for SARS-CoV-2. His initial workup showed WBC count: 10.9 ×103/μL with 75% neutrophils and 21% lymphocytes, platelet count: 312×10^3/μL, LDH: 841 IU/L, CRP: 81 mg/dL, total bilirubin:1.9 mg/dL, AST: 67 U/L and ALT: 87 IU/L. His lung HRCT revealed diffuse bilateral GGOs and consolidation in the peripheral lung regions. There was no improvement after 10 days of treatment. He was advised to be hospitalized, but he refused it. On October 25, 2020, He was treated only with MB (1 mg/kg every 8 hours for two days, followed by 1mg/kg every 12 hours for the next days). After 7 days of MB therapy, his SpO2 increased by 93% and respiratory distress showed marked improvement. The blood workup exhibited WBC count: 8.7 ×10^3/μL with 71% neutrophils and 25% lymphocytes, platelet count: 245×10^3/μL, LDH: 200 IU/L, CRP: 12 mg/dL, total bilirubin: 1.5 mg/dL, AST: 41 IU/L and ALT: 50 IU/L.

Case 5

On December 24, 2020, a 74-year-old female without past medical was treated by the administration of Azithromycin (500mg/day), Remdesivir (200 mg on the first day and 100 mg for 4 days), Ceftriaxone 1 gr BID, Vancomycin 1 gr BID, and Dexamethasone (8 mg/day for 10 days). Her symptoms manifested as fever, shivering, respiratory distress, myalgia, and SpO2:86% started 2 days before treatment. Her RT- PCR was positive for SARS-CoV-2. Her lung HRCT revealed diffuse bilateral GGOs. Her initial workup showed WBC count: 14.2×10^3/μL with 75% neutrophils and 21% lymphocytes, platelet count: 301×10^3/μL, LDH: 901 IU/L, CRP: 87 mg/dL, total bilirubin: 2.4 mg/dL, AST: 76 U/L and ALT: 87 IU/L. There was a drop of SpO2 to 75% (on room air) after 7 days of treatment and an increase in respiratory rate. On December 24, 2020, she was treated only with MB (1 mg/kg every 8 hours for two days, followed by 1mg/kg every 12 hours for the next days). After 2 days of MB therapy, her respiratory distress showed marked improvement and SpO2 reached 93%. The blood workup exhibited WBC count: 5.9 ×10^3/μL with 72% neutrophils and 23.2% lymphocytes, platelet count: 219×10^3/μL, LDH: 207 IU/L, CRP: 9 mg/dL, total bilirubin: 1.7 mg/dL, AST: 51 IU/L and ALT: 59 IU/L.

Case 6

On December 1, 2020, a 67-year-old male without any past medical history was treated by the administration of Azithromycin (500mg/day), Remdesivir (200 mg on the first day and 100 mg for 4 days), Ceftriaxone 1 gr BID, Vancomycin 1 gr BID, and Dexamethasone (8 mg/day for 10 days), as he presented with fever, shivering, respiratory distress, myalgia, and SpO2:76% which started 5 days before treatment. His RT- PCR was positive for SARS-CoV-2. His initial workup showed WBC count: 11.1×10^3/μL with 76% neutrophils and 20% lymphocytes, platelet count: 211×10^3/μL, LDH: 821 IU/L, CRP: 77 mg/dL, total bilirubin: 1.6 mg/dL, AST: 57 U/L and ALT: 78 IU/L. His lung HRCT revealed diffuse bilateral GGOs. After 22 days of treatment with his consent, the patient was discharged from the hospital with SpO2 (82%, on room air), and with the simple oxygen mask, SpO2 was 91%. He was treated only with MB (1 mg/kg every 8 hours for two days, followed by 1mg/kg every 12 hours for the next days). After 7 days of MB therapy, his respiratory distress showed marked improvement and SpO2 reached 93%. The blood workup exhibited WBC count: 5.7 ×10^3/μL with 71% neutrophils and 24.2% lymphocytes, platelet count: 251×10^3/μL, LDH: 289 IU/L, CRP: 8.9 mg/dL, total bilirubin: 1.7 mg/dL, AST: 47 IU/L and ALT: 57 IU/L.

Case 7

On December 1, 2020, a 60-year-old male without any past medical history was treated by the administration of Azithromycin (500mg/day), Remdesivir (200 mg on the first day and 100 mg for 4 days), Ceftriaxone 1 gr BID, Vancomycin 1 gr BID, and Dexamethasone (8 mg/day for 10 days). He was noted to have a fever, shivering, respiratory distress, myalgia, and SpO2: 78% started 8 days before treatment. His RT- PCR was positive for SARS-CoV-2. His lung HRCT was noted to have diffuse bilateral GGOs and consolidation in the peripheral lung regions. Both upper and especially lower lobes were involved. His initial workup showed WBC count: 15.4×10^3/μL with 81% neutrophils and 15% lymphocytes, platelet count: 365×10^3/μL, LDH: 748 IU/L, CRP: 95 mg/dL, total bilirubin: 2.8 mg/dL, AST: 87 U/L and ALT: 97 IU/L. After 25 days of treatment with his consent, the patient was discharged from the hospital with SpO2 (84%) on room air, and with the simple oxygen mask, SpO2 was 93%. He was treated only with MB (1 mg/kg every 8 hours for two days, followed by 1mg/kg every 12 hours for the next days). After 8 days of MB therapy, his respiratory distress showed marked improvement and SpO2 reached 93%. The blood workup exhibited WBC count: 8.7 ×10^3/μL with 74% neutrophils and 26.3% lymphocytes, platelet count: 314×10^3/μL, LDH: 215 IU/L, CRP: 2.5 mg/dL, total bilirubin: 1.5 mg/dL, AST: 51 IU/L and ALT: 59 IU/L.

Discussion

In this study, MB has been used as the last option for the treatment of severe COVID-19 outpatient who did not respond to Remdesivir, Interferon-β, and Favipiravir therapies. Seven patients recovered completely. Considering the properties of MB, the results of these case series study, and the results of the clinical trial phase

1, 2, 3 [5-7]; MB as an adjunct therapy, could be applied for the treatment of COVID-19 patients along with standard care protocol, which has a very high clinical benefit for recovery. Also in our another study, as the last option of treatment and rescue therapy, MB was administered to 83 patients who failed to respond to antiviral drugs; 72 patients recovered completely, and 11 patients died [9]. In a case-control study during the 2009 H1N1 influenza pandemic in Canada, early antiviral treatment is an established protocol to manage severe disease progression [10]. In general, it is recommended to start antiviral therapy as soon as possible for patients to prevent the viral disease progression [11,12]. This early intervention might be considered critically important to effectively reduce the SARS-CoV-2 viral load and clinical outcomes improvement by halting clinical progression [13]. This might be shortening the duration of viral shedding, which potentially reducing onward transmission. It is reported that approximately 35% of people with COVID-19 have not returned to their previous level of health 14 to 21 days after diagnosis [14]. These "long haulers" have a syndrome referred to as long COVID. Therefore, an early effective antiviral treatment by primary care physicians could reduce this event. It is reported that patients with a higher viral load on day 7 had a higher rate of hospitalization than those with a better clearance of viral RNA on day 7 [15]. On the other hand, there is currently no consensus on the specific antiviral drug for the treatment of COVID-19 patients. Considering the approved mechanism of antiviral effect of MB against the SARS-CoV-2 virus [16-18], along with other important properties such as anti-hypoxemia activity, anti-respiratory distress activity, an inhibitor of nitrite production, antimicrobial agent, an inhibitor of reactive oxygen species, an inhibitor of xanthine oxidase, anti-platelet aggregation, antifungal agent, anti-inflammatory agent; MB could be considered as the drug of choice for early treatment in outpatients along with other supportive cares [5-7]. MB is in two forms: the oxidized form (oxidant: dark blue) and the reduced form (antioxidant, colorless). In plasma, MB is reduced to LMB which is excreted primarily in the urine. [19] MB has been widely used for more than 200 hundred years for the treatment of malaria (15 mg/kg), bipolar disorder (2-5 mg/Kg), vasoplegic syndrome (2 mg/kg), sepsis (1-2 mg/Kg) and methemoglobinemia (1-2 mg/Kg) [20]. Reduced MB, as an anti-hypoxemia drug, converts Fe^{3+} in methemoglobin to Fe^{2+} so that the oxygen is bound to Fe^{2+} and can be transported. Also, MB is used as an antidote to paraquat poisoning, to treat ifosamide encephalopathy, to maintain blood pressure in patients with septic shock, and to support orthotopic liver transplantation [21]. In our study, we showed higher oxidative stress in COVID-19 patients [5]. The reduced form of MB on the other hand, as an antioxidant, quenches oxidative stress and decreases hypoxemia.

Conclusion

Since MB appears to encapsulate many of the required mechanisms for the treatment of COVID-19 patients and is an FDA-approved drug for methemoglobinemia, is inexpensive and ubiquitously accessible; these mark MB as an excellent treatment option for COVID-19 patients along with other standard cares. MB may help to avoid the overwhelming of healthcare systems. Larger, multi-centered studies are required to substantiate the efficacy of MB for treatment.

Ethical Approval

IR.MUMS.REC.1399.122; Clinical Trials.gov Identifier: NCT04370288; April 19, 2020.

Research Data

Data is available on request through the authors and permission of the ethical committee of the University.

Funding Information

This work was supported by a grant from Mashhad University of Medical Sciences (Grant number: 990096).

Credit Authorship Contribution Statement

Daryoush Hamidi Alamdari, Saied Hafizi Lotfabadi, (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing); Behzad Mavaji Darban (Conceptualization, Data curation, Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing).

Declaration of Competing Interest

There are no conflicts of interest in all authors.

Acknowledgment

The authors gratefully acknowledge Mr. Hasan Masoudzadeh and Dr. Ahmad Reza Tavassoli in Imam Reza Hospital for their excellent cooperation.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.42.006723

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