http:// ijp.mums.ac.ir
Letter to Editor (Pages: 15281-15284)

Methylene Blue for the Treatment of COVID-19 in Pediatrics

* Daryoush Hamidi Alamdari[1], Bharat Bhushan[2]

[1] Surgical Oncology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

[2] Covenant Medical Center and University Medical Center, Texas Tech University Health Science Center (TTUHSC) Lubbock, Texas, USA.

Abstract

Despite vaccination against SARS-CoV-2, the COVID-19 pandemic continues to expand worldwide. Early reports suggested that only a minor proportion of pediatric population is affected by COVID-19 in comparison to adult population. Three percent of pediatric population needed admission to intensive care units, and only a small number of deaths have been reported. Available literature suggests that infants (children under 1 year) seem to be more vulnerable to COVID-19 virus infection with a higher severity of illness compared with other pediatric ages. Requirement for neonatal mechanical ventilation is 20%–22.4% (vs. 4% in children) (1).

Key Words: COVID-19, Methylene Blue, Pediatrics, Treatment.

* Please cite this article as: Hamidi Alamdari D, Bhushan B. Methylene Blue for the Treatment of COVID-19 in Pediatrics. Int J Pediatr 2022; 10 (1):15281-15284. DOI: **10.22038/IJP.2021.59339.4625**

**** Corresponding Author:***

Daryoush Hamidi Alamdari, Surgical Oncology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Email: Hamidiad@mums.ac.ir

Received date: Jul.289,2021; Accepted date:Nov.12,2021

Dear Editor,

Despite vaccination against SARS-CoV-2, the COVID-19 pandemic continues to expand worldwide. Early reports suggested that only a minor proportion of the pediatric population is affected by COVID-19 in comparison to the adult population. Three percent of the pediatric population needed admission to intensive care units, and only a small number of deaths have been reported. Available literature suggests that infants (children under 1 year) seem to be more vulnerable to COVID-19 virus infection with a higher severity of illness compared to other pediatric ages. Requirement for neonatal mechanical ventilation is 20%–22.4% (vs. 4% in children) (1).

Physicians caring for children should be disquietude about subgroups of children who can be at an increased risk for being more significantly affected by the illness, as particularly the younger ages underlying pulmonary pathology and many immunocompromising conditions have been associated with grievous outcomes in regard to the other coronavirus infections in pediatric population (2).

Supportive care alone is applied for the treatment of patients with mild or moderate symptoms. However, therapies such as monoclonal antibodies, antiviral therapy, glucocorticoids, and immunosuppression may be needed. Also, antiplatelet and anticoagulation therapies should be considered to prevent thrombotic complications (3).

There is uncertainty about efficacy and safety of antiviral drugs for the treatment of COVID-19 and the ongoing clinical trials are trying to find an effective antiviral drug.

The results of our clinical trials have revealed that MB decreases the hospital stay and mortality of severe patients (4, 5, 6). Another study has shown that MB also saved the patients who failed to respond to Remdesivir, Interferon-β, and Favipiravir therapies (7).

In the treatment process, LMB can work through the following mechanisms: 1) Antiviral activity against the SARS-CoV-2 virus; 2) Anti-hypoxemia activity by converting iron from the ferric (Fe^{3+}) state to the ferrous (Fe^{2+}) state. Due to this property, MB is an approved medicine for methemoglobinemia; 3) Inhibitor of nitrite production (nitrite converts ferrous iron to ferric iron in hemoglobin) by inhibiting nitric oxide synthase and guanylate cyclase in activated macrophages; 4) Antimicrobial agent; 5) Inhibitor of reactive oxygen species (superoxide anion and hydrogen peroxide scavenger); 6) Inhibitor of xanthine oxidase (which produces superoxide anion); 7) Anti-platelet aggregation drug; 8) Antifungal agent; 9) Anti-inflammatory agent; and 10) Anti-respiratory distress activity. The authors observed this effect in patients and this may be attributed to bronchodilator properties of MB (4, 5, 6).

An increased number of cases of mucormycosis (Black Fungus) is observed in the recent surge of COVID-19 in India (8). It is a fatal disease, especially if treatment is started late. The therapeutic options currently available are aggressive surgical debridement and the use of antifungal agents. The main effective drug is amphotericin B, while fluconazole, and voriconazole have no effect. Amphotericin B has acute side effects (proinflammatory cytokine production: nausea, vomiting, rigors, fever, hypertension or hypotension, and hypoxia) and chronic side effects (nephrotoxicity include renal insufficiency, hypokalemia, hypomagnesemia, metabolic academia, and polyuria due to nephrogenic diabetes insipidus) (9). MB can destroy the mitochondria of fungus at a concentration of 500 ppm without the mentioned side effects (10). Despite the reported severe toxicity, its high cost and shortages of

amphotericin B, MB may be very effective in the treatment of mucormycosis in COVID-19 patients.

MB is an FDA-approved drug, inexpensive, ubiquitously accessible, widely used as an antidote to paraquat poisoning, to treat ifosfamide encephalopathy, to maintain blood pressure in patients with septic shock, and to support orthotopic liver transplantation (11).

It is mentioned that for COVID-19 treatment in adults, the golden time for MB administration should be upon diagnosis and at least before the severe stage of the disease sets in, leading to multiorgan involvement and failure; this is to be considered for the pediatric population, as well. If the findings of our trials are verified by larger clinical trials and other research centers for both the pediatric and adult population, it can not only save COVID-19 patients from stressful respiratory distress, but can also reduce hospital stay and mortality.

FUNDING: The clinical trials were supported by grants from Mashhad University of Medical Sciences (Grant numbers: 990096, 990845).

COMPETING INTERESTS

None.

ETHICAL APPROVAL

These clinical trials were performed at Mashhad University of Medical Sciences after the ethics committee approval (ClinicalTrials.gov: NCT04370288; IRCT20191228045924N120).

REFERENCES

1. Trevisanuto D, Cavallin F, Cavicchiolo ME, Borellini M, Calgaro S, Baraldi E. Coronavirus infection in neonates: a systematic review. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2021 May 1; 106(3):330-5.

2. Omigi C., Englund J.A., Bradford M.C., Qin X., Boeckh M., Waghmare A. Characteristics, and outcomes of coronavirus infection in children: role of viral factors and an immunocompromised state. J Pediatr Infect Dis Soc. 2019; 8(1):21–28.

3. Christakis DA. Pediatrics and COVID-19. Jama. 2020 Sep 22; 324(12):1147-8.

4. Alamdari DH, Moghaddam AB, Amini S, Keramati MR, Zarmehri AM, Alamdari AH, et al. Application of methylene blue-vitamin C–N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial. European Journal of Pharmacology. 2020; 885:173494.

5. Hamidi-Alamdari D, Hafizi-Lotfabadi S, Bagheri-Moghaddam A, Safari H, Mozdourian M, Javidarabshahi Z, et al. Methylene Blue for Treatment of Hospitalized Covid-19 Patients: A Randomized, Controlled, Open-Label Clinical Trial, Phase 2. Rev Invest Clin. 2021; 73:190-198.

6. Alamdari DH, Lotfabadi SH, Darban BM, Agheli-Rad M, Saadatian S, Hashemi SH, et al. Methylene Blue for Treatment of Hospitalized COVID-19 Patients, Randomized, Controlled, Open-Label Clinical Trial, Phase 3. Aristotle Biomedical Journal. 2021 Mar 24; 3(2):12-8.

7. Lotfabadi SH, Moghaddam AB, Shamsi MS, Hoseini HB, Khaleghimanesh B, Saadatian S. Methylene Blue as Rescue Therapy for COVID-19 Patients who failed to Respond to other Therapies (Final Report). Am J Clin Case Rep. 2021; 2(5):1040.

8. Gandra S, Ram S, Levitz SM. The “Black Fungus” in India: The Emerging Syndemic of COVID-19–Associated Mucormycosis.

9. Laniado-Laborín R, Cabrales-Vargas MN. Amphotericin B: side effects and

toxicity. Revista iberoamericana de micología. 2009 Oct 1; 26(4):223-7.

10. Bragulat MR, Abarca ML, Bruguera MT, Caba es FJ. Dyes as fungal inhibitors: effect on colony diameter. Applied and environmental microbiology. 1991 Sep; 57(9):2777-80.

11. May JM, Qu ZC, Cobb CE. Reduction and uptake of methylene blue by human erythrocytes. American Journal of Physiology-Cell Physiology. 2004; 286:C1390-8.