

Methylene Blue for Treatment of COVID-19 and Mucormycosis



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The efficacy and safety of antiviral drugs for the treatment of COVID-19 are still unclear, and the ongoing clinical trials are trying to find an effective antiviral drug. Our clinical trials (phases 1,2,3) showed the safety and efficacy of methylene blue (MB) therapy in decreasing the hospital stay and mortality of severe patients [1-3]. Also, we demonstrated that MB could save patients who did not respond to Remdesivir, Interferon- β , and Favipiravir therapies [4]. MB encapsulates many of the required mechanisms for COVID-19 treatment: 1) Anti-viral activity against the SARS-CoV-2 virus, 2) Anti-hypoxemia activity by converting the ferric (Fe^{3+}) state to the ferrous (Fe^{2+}) state. Due to this property, MB is an FDA approved medicine for methemoglobinemia, 3) Anti-respiratory distress activity, 4) Inhibiting nitric oxide synthase in activated macrophages, 5) Antimicrobial agent, 6) Inhibitor of reactive oxygen species (superoxide anion and hydrogen peroxide scavenger), 7) Inhibitor of xanthine oxidase (which produces superoxide anion), 8) Anti-platelet aggregation drug, 9) Anti-inflammatory agent, 10) Bronchodilator property, 11) Antifungal agent (1,2,3).

The recent dramatic surge of COVID-19 in India is accompanied by the increased number of cases of mucormycosis (Black Fungus) [5]. Mucormycosis is an uncommon and fatal disease, especially if medical treatment is started late. The intracranial involvement of mucormycosis rises the fatality rate to as high as 90%. For treatment, aggressive surgical debridement is performed along with the use of antifungal agents. In COVID-19 patients, mucormycosis is a serious threat and the main drug for the treatment is amphotericin B; and other drugs such as

fluconazole and voriconazole have no effect. Amphotericin B has acute and chronic side effects because of proinflammatory cytokine production; acute side effects are nausea, vomiting, rigors, fever, hypertension or hypotension, and hypoxia and the chronic side effects are nephrotoxicity include renal insufficiency, hypokalemia, hypomagnesemia, metabolic acidemia, and polyuria due to nephrogenic diabetes insipidus. These side effects sometimes lead to discontinuation of therapy despite a life-threatening systemic fungal infection [6]. Therefore, it is necessary to take all measures to overcome this problem by using other effective drugs. It is proved that MB can destroy the mitochondria of fungus at a concentration of 500 ppm without mentioned side effects. Considering the reported shortages of amphotericin B, its high cost, severe toxicity, and effectiveness of MB in covid-19 patient treatment, MB also could be the drug of choice for the mucormycosis treatment in these patients.

MB is an FDA-approved drug, inexpensive and ubiquitously accessible. MB is a "Magic Bullet" for COVID-19 treatment by considering the mechanisms of drug. We recommend that the golden time of MB administration should be upon diagnosis and at least before the severe stage of the disease sets in leading to multi-organ involvement and failure. If the findings of these trials are verified by larger clinical trials and other research centers, it could not only save COVID-19 patients from stressful respiratory distress but can also reduce hospital stay and mortality.

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