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Evaluation of the efficacy of Methylene Blue administration in SARS-CoV-2- affected patients: a proof-of-concept phase 2, randomized, placebo- controlled, single blind clinical trial

Barda B [1], Di Mari B [1], Baserga A [1], Robatto A [1], Magenta L [1], Forlenza R [1], Messina P [1], Cerny A [1]

[1] Fondazione Epatocentro Ticino

Introduction The SARS-CoV-2 pandemic has revolutionized the scientific and medical world in the last two years. Methylene blue (MB) is a well-known molecule. *In vitro* studies have recently demonstrated its efficacy against SARS-CoV-2.

The aim of our study was to assess the efficacy of MB against early phase SARS-CoV-2 infections.

Methods All patients with a positive swab for SARS-CoV-2 were eligible for the trial. They were enrolled within the first 72 hours from the swab and randomized either in the MB arm or the placebo one. The intervention was a starting dose of 200 mg MB or placebo in the morning and 100 mg in the evening on the first day and afterwards the standard daily dose of 200 mg. Patients were followed up for safety and efficacy until day 84.

Results

The trial was conducted in Ticino, from the 3rd of December 2020 until 20th May 2021. It was stopped after the ad interim analysis. We evaluated 29 patients of those 8 were found SARS-CoV-2 negative. We analysed 21 patients, of which twelve in the MB group and nine in the placebo one.

After 5 days of treatments 2 (17%) of the patients had an undetectable virus RNA in the MB arm and 1 (11%) in the placebo arm. In the MB group one patient had undetectable RNA from day 3 and none in the placebo group, 75% and 44% of subjects were virus free by day 15 in the MB and placebo arm, respectively. None of the patients experienced serious adverse events.

Percentage of patients clearing SARS-CoV-2

Time point	Methylene blue, N = 12 N (%)	Placebo, N = 9 N (%)
Day 3	1 (8.3%)	0 (0%)
Day 6	2 (17%)	1 (11%)
Day 9	5 (42%)	4 (44%)
Day 12	6 (50%)	4 (44%)
Day 15	9 (75%)	4 (44%)
Day 21	10 (83%)	6 (67%)

Conclusions

MB has proved to be a safe and well tolerated drug. We did not find superiority of efficacy or viral clearance of MB compared to placebo. Nonetheless, the MB had undetectable virus starting from day three which is earlier than the placebo group, and the vast majority (75%) of subject of the MB had undetectable virus at day 15. The limitations of the study were that the trial started 72 hours after the positive swab and the decrease of the pandemic curve. Given the good *in vitro* efficacy, larger studies are needed to assess MB efficacy against COVID-19 *in vivo*.

Contact: Beatrice.Barda@hin.ch