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Management of Covid -19 Positive Pregnant Women and General Population with Methylene Blue and Cefditoren-Pivoxil

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Abstract

COVID-19 season has seen multiple genomic variants of Corona virus with multiple regimens of treatment across the world. The virus has shown affect on respiratory system irrespective of variants. All age groups were affected including the pregnant women, except children below 12 years of age. Mild to moderate symptoms were confined to nose and nasopharynx and upper respiratory tract where as moderate to severe symptoms were reserved to upper respiratory tract and lungs. The recovery of the patient was subjective to individual immune state and age to a major extent. Existence of co-morbidities added a compromise in terms of recovery time period. In our experience, a total of 64 cases of COVID-19 patients were studied which included 32 pregnant women and 32 subjects of general population who presented with moderate symptoms.

Usage of methylene blue in treating methhemoglobinemia is well documented and the same was applied in treating COVID-19/mucor mycosis patients, as the pathophysiology mimics similar in both the disease entities. In our study, all the patients were treated with a combination of 1 ml of 0.1% methylene blue+ budesonamide nebulization in 0.9% normal saline/ distilled water, Tab Cefditoren Pivoxil (400mg), twice daily for 5 days. This combination of medication was effective in treating COVID-19 affected pregnant women as well as the general population safely, without any untoward sequalae.

Introduction

COVID-19 has been a challenge to the human race as well as to the medical fraternity. For the past 3 years human life has undergone detrimental changes especially in respiratory system and hitherto causing other organ failures where in leading to death of the patient. There were various regimens that were tried for COVID-19 treatment. But there is no specific treatment approved for COVID 19 positive pregnant ladies. Also, there is no safe standardized treatment for mild to moderate COVID 19 positive patients, at home quarantine with low cost and easily administered regimen available at home.

Methylene blue is a tricyclic phenothiazine compound dye which has been in use since 1891 and has been approved by the FDA, for the purpose of antibacterial, methemoglobinemia and malarial parasite, bladder tuberculosis, anti-fibrotic agent, for staining the pathological lesions before doing surgery, inactivation of viruses in blood products prior to transfusion when activated by light. It can be administered intravenous, sublingual and by nebulization. It inhibits SARS C0V-2/ ACE 2 protein- protein interaction, a mechanism that can contribute to its antiviral activity against COVID-19. The chief use of methylene blue in COVID-19 is nitric oxide mediated reduction in inflammatory cascades in addition to inhibiting canonical inflammasomes.[1,2,3,4]

Cefditoren is a third generation cephalosporin for oral administration which has a broad spectrum of activity and is particularly active against the bacterial pathogens involved in community respiratory tract infections. Cefditoren has been associated with a marked decrease in circulating levels of IL-6 and other pro-inflammatory cytokines and mediators of epithelial damage. The aim of introducing this drug is to show the effectiveness of this drug against the COVID -19 affected pregnant women and general population. Cefditoren has been assigned to pregnancy category B by FDA [5].

Corona virus, after affecting the respiratory alveolar system, mimics methemoglobinemea. In these cases usage of methylene blue inhibits hypoxia. We initiated treatment in COVID-19 affected pregnant women and general population using oral Cefditoren and methylene blue nebulization because of their low cost, ease of administration at home.

Materials and Methods

Our study was carried out as randomized trial, at an outpatient day care clinic and government district hospital. An ethical committee approval was obtained for the study (Rc. No MRD/279/2021). Patient' s age range was between 18-75 years with male and female genders inclusive comprising of COVID19 affected pregnant women and general population.

Both category patients commonly presented with moderate symptoms such as running nose, cough, loss of smell and taste, fever, myalgia; with breathlessness and generalized weakness being additional symptoms in general population group (middle and elderly aged). A total of 64 patients were included in the study who were diagnosed and treated for COVID 19 with oral Cefditoren 400mg twice daily for 5 days, inhalation with methylene blue of 0.1% dilution in 3.5ml normal saline, and budosenamide. Along

with these medications patients were supplemented with symptomatic medications such as oral paracetamol (650 mg), Vitamin C (500mg).

Patients were followed up on 5, 10, 15th day respectively. More than half of the patients irrespective of the above mentioned category, recovered from COVID 19 symptoms within first 10 days. RTPCR test was the confirmatory test which was done at the time of diagnosis and recovery period. Apart from that, routine blood investigations like CBP, CUE, platelet count, C-reactive protein, serum-urea, creatinine, electrolytes, liver function tests were also done.

Pregnant women/ general population, who presented with symptoms of loss of smell, maxillary/ pan sinusitis and those who were susceptible for the same, were advised the usage of the above medication for 7 days. Those patients who were diagnosed as having fungal osteomyelitis were prescribed the above regimen post operatively after surgical resection of the maxilla or mandible.

5 out of 32 among pregnant women were suspicious of mucormycosis in whom nasal swab test revealed fungal hyphae which were sent for culture and sensitivity. The reports were positive. 2 out of 32 patients under general category have shown the symptoms of mucosal thickening on CT scan of para nasal sinuses who were deemed susceptible for fungal sinusitis. However, incidence of mucormycosis was less in pregnant women as compared to general population.

Results

The study reveals that, with rise in the age factor, recovery period of COVID-19 was prolonged. Presence of breathlessness as a symptom, increased the time of recovery. The pregnant women recovered within or on the 10th day because of younger age, where as the recovery time for general population and higher age group ranged from 10th to 15th day, depending upon age, symptoms and co-morbidities. Low complications due to COVID-19 were noticed in pregnant women (except for 5 cases of positive fungal culture), and in general population. The results have been illustrated in the figures and tables below.

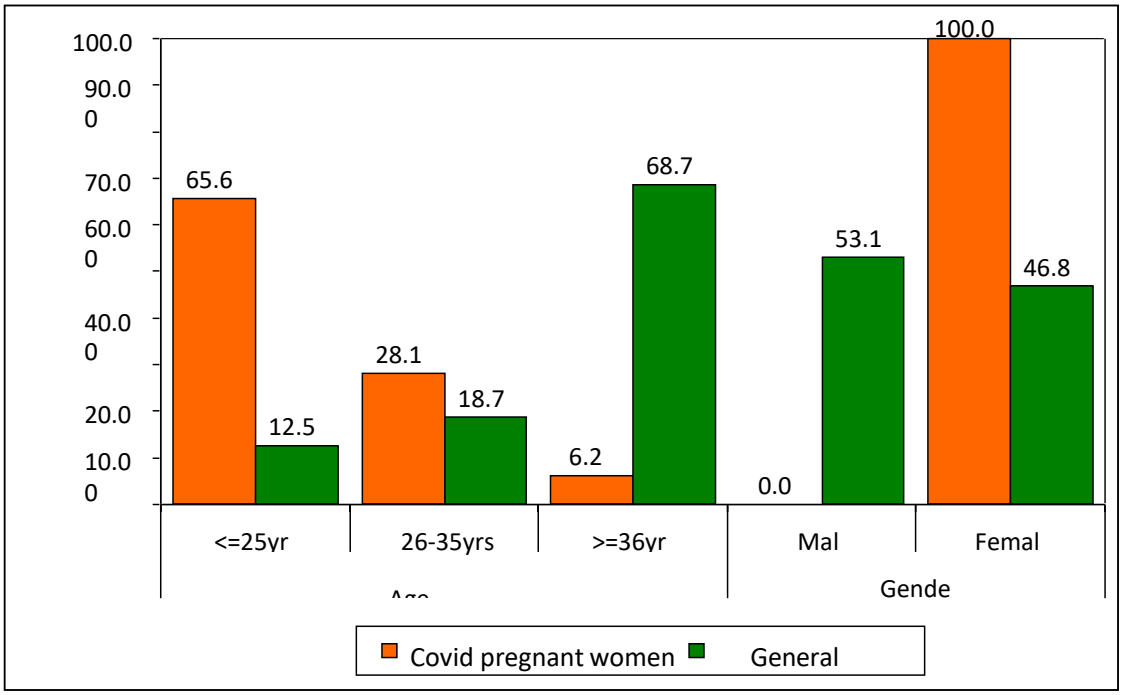

Figure 1: Comparison of pregnant women with covid and general population by demographic profile

Groups	Mean	SD	SE	t-value	P-value
Covid pregnant women	25.50	8.01	1.42	-6.9539	0.0001*
General population	47.81	16.29	2.88		

*p<0.05 indicates significant between two groups

Table1: Comparison of pregnant women with covid and general population with mean age by t test

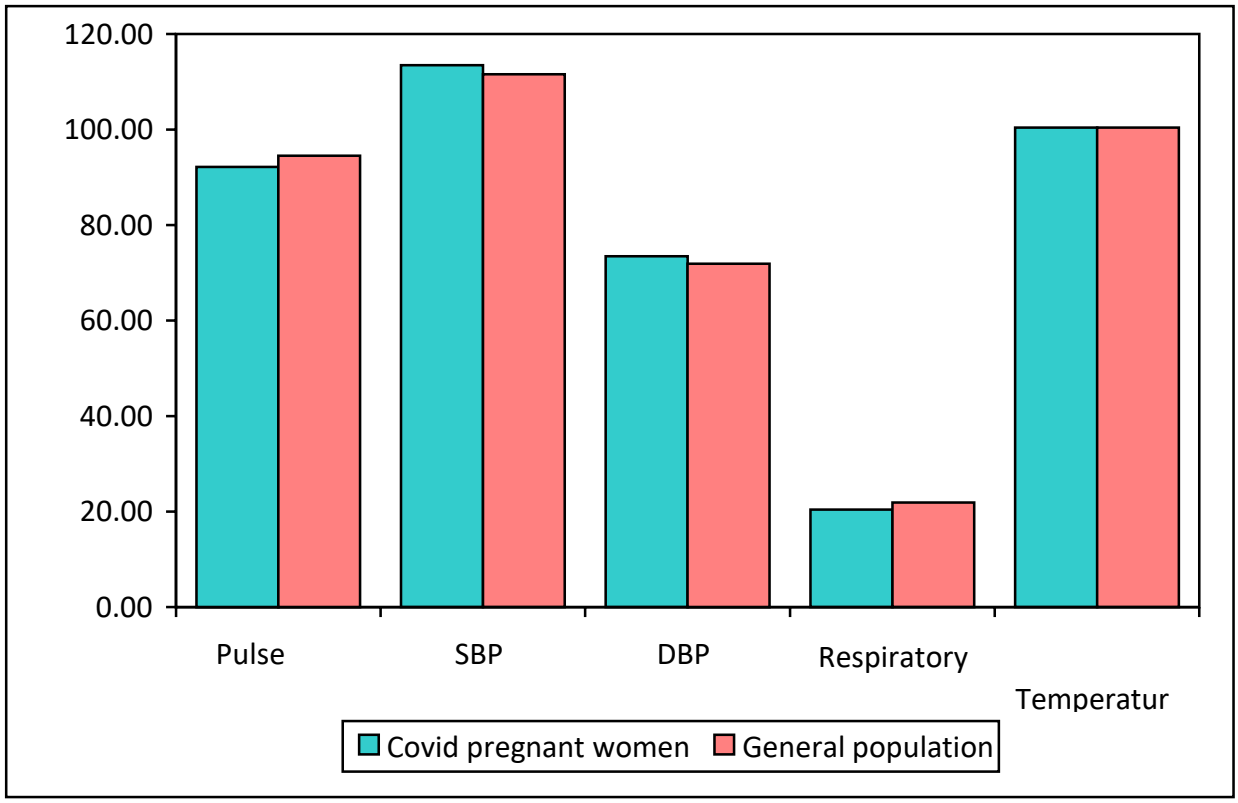

Figure 2: Comparison of pregnant women with covid and general population with clinical parameters

Clinical parameters	Covid pregnant women		General population		t-value	p-value
	Mean	Std.Dev.	Mean	Std.Dev.		
Pulse rate	92.19	3.88	94.50	4.31	-2.2554	0.0276*
SBP	113.44	5.45	111.56	3.69	1.6110	0.1123
DBP	73.44	5.45	71.88	4.71	1.2267	0.2246
Respiratory rate	20.38	0.79	21.88	2.21	-3.6128	0.0006*
Temperature	100.41	0.98	100.41	0.76	0.0000	1.0000

*p<0.05 indicates significant between two groups

Table: 2 Comparison of pregnant women with covid and general population with clinical parameters by independent t test

Groups	Mean	SD	SE	t-value	P-value
Covid pregnant women	10.13	0.49	0.09	-4.7044	0.0001*
General population	11.91	2.08	0.37		

*p<0.05 indicates significant between two groups

Table 3: Comparison of pregnant women with covid and general population with mean recovery period by t test

Groups	Mean	SD	SE	t-value	P-value
Covid pregnant women	94.19	1.26	0.22	3.2051	0.0021*
General population	93.25	1.08	0.19		

*p<0.05 indicates significant between two groups

Table 4: Comparison of pregnant women with covid and general population with mean Spo2 by t test

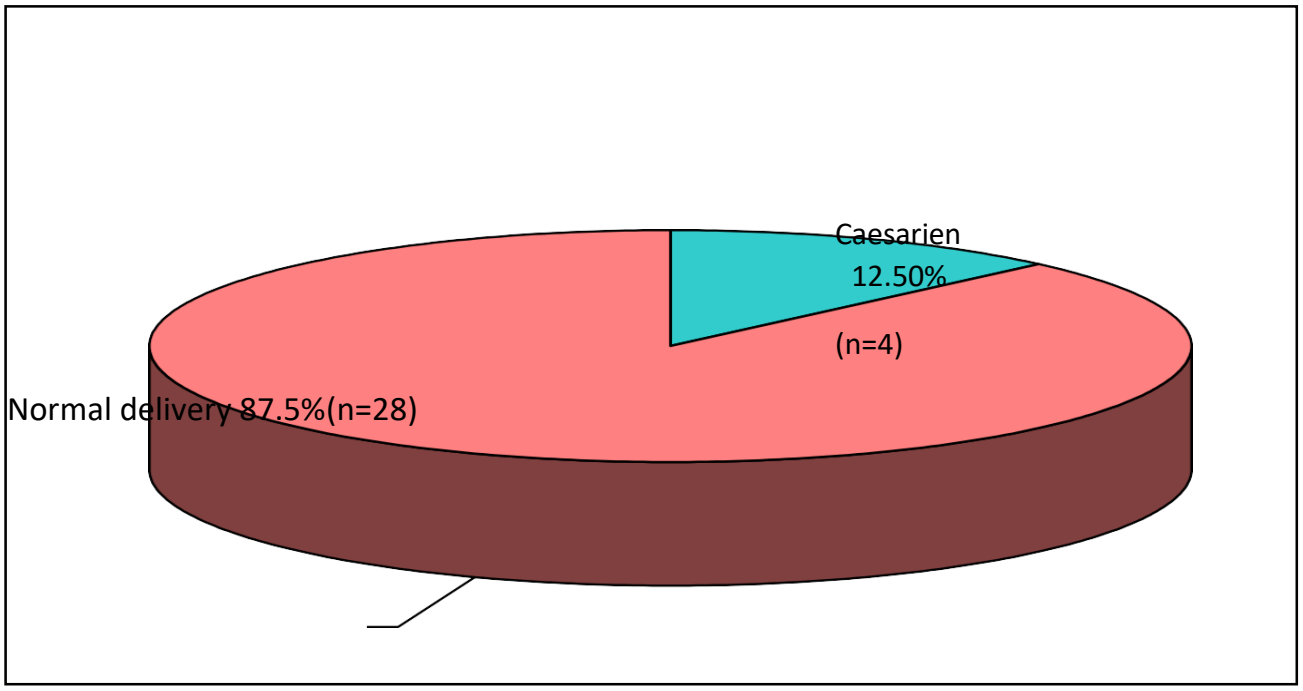

Figure 3: Delivery status in pregnant women with covid

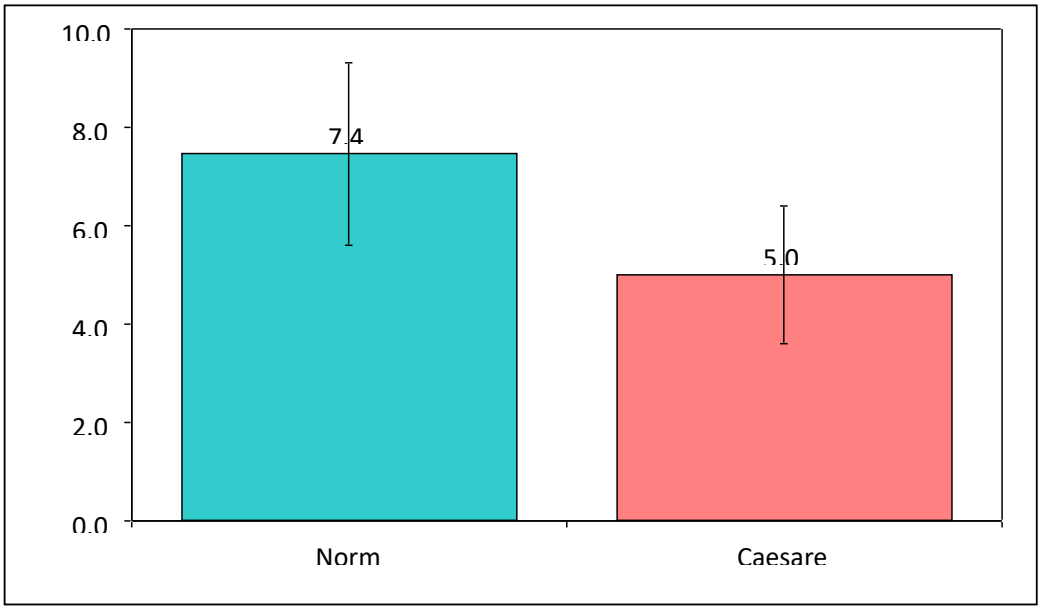

Figure 4: Comparison of type of delivery in pregnant women with covid with mean duration of pregnant (in months)

Discussion

Methylene blue application as medicine in COVID-19 patients has been an effective method in managing the progression and control of cytokine storm. Primarily, methylene blue is used in treatment of methhemoglobinemia. Methylene blue was selected in treatment of COVID-19 patients since the COVID-19 symptoms mimic methhemoglobinemia on respiratory system in terms of Interleukin -6, C-reactive protein, Interfron production to reverse the pathological respiratory status. Methylene blue was also used in tuberculosis of lung, urinary bladder and was successfully treated for the same. In our study, we have not noticed any immediate or late side effects regarding treatment with methylene blue.[1,2,3]

In our study we have used 10 ml of 10% methylene blue in 90ml of distilled water/ 0.9% normal saline to titrate into 0.1% methylene blue saturation solution. We used 1 ml of methylene blue along with budesonamide respule plus 3.5ml distilled water in nebulization form(3 times/day for 5 days) for both category of patients(pregnant women and general population) with moderate COVID symptoms. In case of positive mucormycosis patients, we administered the above drug combination 6 hourly for 7 days.

Methylene blue was tried for containing the mucormycosis (black fungus) affecting the nasopharyngeal airway, paranasal sinuses and respiratory system. It was observed that antifungal activity of methylene blue was not only seen against the species of Candida albicans but also for non albicans species of Candida. It was proposed that methylene blue acts through disfunctioning of mitochondria, altering redox status and disruption of membrane integrity to deplete the ergosterol level. Further, it was also confirmed that methylene blue inhibits yeast to hyphal transition which is essential for survival and for virulence in the host body [4]. Fortunately, after completion of above course of medication in mucor mycosis positive cases, nasal swab test for mucor mycosis came negative after 15 days.

In our study, methylene blue nebulization was given to COVID-19 + susceptible fungal sinusitis cases with mucosal thickening of the nasal cavity and paranasal sinuses as well as for diagnosed cases of fungal osteomyelitis of maxilla/mandible and paranasal sinuses. Patients who underwent surgical resection of the maxilla/ mandible as well as patients who received sinus lavage in mucosal thickening cases were prescribed this regimen of methylene blue nebulization prophylactically. This improved not only the patient's recovery from symptoms of COVID-19 and fungal sinusitis/osteomyelitis but also enhanced better healing in patients who got operated for mucormycosis.

Cefditoren 400mg, twice daily for 5 days decreases IL-6 levels in the body, thereby aids in the control of progression of COVID-19 disease.5 No relevant side effects were noticed with regards to the usage of this medication in COVID-19 affected pregnant women. As related to our study, the disease status of COVID-19 in pregnant ladies decreased probably because of better immune status. That is why the average duration of the disease has been decreased in pregnant ladies when compared with general population. Also, no untoward incidents have been noticed in new born babies as well. Therefore, through the experience of our study, we recommend the combination of methylene blue+ Cefditoren in COVID-19 affected pregnant ladies.

Conclusion

Methylene blue is an easily accessible medication for all category of COVID-19 positive patients above 18 years for curing the ailment of COVID. Cefditoren benefits pregnant ladies from recovery of COVID-19 ailments.

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