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Evidence based Effective Management of COVID 19 Patients on An Outpatient Basis, In Semi Urban/Urban Area of Indian Sub-Continent, With Promising Outcome.

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Abstract

The pandemic of SARS Corona virus, since December 2019 has challenged the human race and the medical professionals through its multiple variant strains. Multiple modalities of treatment have been empirically formulated and implemented across the globe due to variability of viral strains in different countries. Till to the present date, throughout the first and second waves, the vaccinations (both virulent and avirulent) have been successful in fostering the acquired immunity to the host. Despite of the vaccinations, individuals were diagnosed positive through Rerverse transcriptase polymerized reaction (RT PCR) tests which shows the potency of genomic variation of the virus to thrive inside the host. Since multiple variants of strains were diagnosed with in a span of two years, no standard consensus or protocol has been set up by World Health Organization or any other body. The medical professionals were able to render only the symptomatic treatment to the infected people with available resources of drugs. Retero viral drugs like Remedisvir have been helpful in reducing the viral loads to some extent but were not a standard regimen of drugs. The survival of patients was purely dependent upon, immune status of the individual.

It is well known that the Corona virus has been an inhabitant of upper and lower respiratory tract with peculiar mode of spread through air, surface contact etc. However, some variants are confined to only the upper respiratory tract initially, later involving other systems.

In this article, we present our clinical experience in attending and managing the Corona positive patients who presented to us in the initial stage with positive symptoms as well as those patients who had additionally suffered the fungal sinusitis/osteomyelitis of the maxillofacial region and para nasal sinuses as a sequel of post COVID infection.

Key words: *COVID 19, Clarithromycin, Ivermectin, Fungal sinusitis/osteomyelitis.*

Introduction

Covid19 is has been the largest pandemic in the history of mankind with longer span of existence throughout the world. There have been various treatment and management regimens practiced empirically due to multiple variants of corona virus with varying symptoms since past 2 years. COVID - 19 pandemic has resulted varying symptoms in number of imminent deaths in spite of various treatment algorithms that were practiced.

Various treatment methodologies have been implemented in treating COVID-19, including the guidelines of the organizations such as World Health organization and Indian Council of Medical Research. Also clinical trials and Randomized control trials were carried out worldwide, significantly to contain the disease by using drugs like Remedesvir, Chloroquine, Corticosteroids, Ecosprin etc.

Countable number of Clinical trials and studies have been conducted in treating patients with mild to moderate COVID-19 symptoms by using drugs like Clarithromycin and Ivermectin by oral route with emphasis on each of them in separate studies.

The aim of bringing out this study is to bring out proven effective, yet cheaper treatment medication regimen with maximum safety to the common population of urban/ semi-urban areas of all the countries irrespective of gender and age. We were interested in bringing out the combination drug regimen of Tab. Clarithromycin 250 mg, Tab. Ivermectin 12mg in treating COVID- 19 with mild to moderate symptoms, to the public domain with the evidence-based study such that it could benefit the needed in containing the disease at mild to moderate level, instead leading to severe sequalae and complications.

Materials and Methods

Total number of patients treated: 322 (COVID infected patients 303, fungal sinusitis/osteomyelitis-19).

Duration of study: December 2019 to March 2021 at a private polyclinic and TelanganaVaidya vidhana parishad district hospital, Telangana state, India

Ethical review: The study was approved by ethics committee, Government district hospital, Khammam (Rc.No.Spl/ACI/MB/2020)

All patients were treated on outpatient basis and home quarantine till complete recovery from the disease. Selection criteria included patients who were suspicious of COVID19symptoms and with mild symptoms of cough, cold, fever, myalgia, running nose, loss of smell and taste, dyspnoea etc. Investigations included were routine blood investigations like complete blood picture, serum bilirubin, serum creatinine, blood urea, Reverse transcriptase polymerized chain reaction RT PCR, Chest X ray, High resolution Computerized Tomography (HRCT) scan for affordable patients. Patients with moderate to severe symptoms such as acute respiratory distress syndrome, intravascular thrombosis, embolism,

respiratory distress, co-morbidities, pregnant women, patients aged below 12 years were excluded from the study. The COVID infected patients and contact family members were given the combination of Tab. Clarithromycin 250 mg twice daily, Tab. Ivermectin 12 mg twice daily for a period of 5 days and were found to have no COVID symptoms till the end of 21 days.

Patients who were economically backward and those who could not afford costly treatment options like injection Remedesvir, Tocilizumab including hospitalization care were focused with intent of benefit from this treatment regimen. Our medication regimen of treatment included Tab. Clarithromycin 250mg twice daily, Tab. Ivermectin 12 mg twice daily, Tab Paracetamol 650mg t.i d./s.o.s, Tab. Ecosprin 75 mg o.d, Tab. Monteleukadst twice daily to all COVID infected patients. Along with this drug regimen, the nebulisation with oxygen/ salbutamol respules to patients who developed signs like dyspnoea, right or left basal pneumonitis of lungs, bronchitis, oxygen saturation levels varying between 90% or less than 94% were given on s.o.s basis.

However, we kept all the patients for home quarantine for 21 days under observation through phone call/ video phone call and personal visit as and when required.

Those patients who suffered with COVID- 19, after subsiding of the COVID symptoms initially, presented with purulent discharge from the nostril, oral cavity, nasal obstruction and sinus head ache. Such patients were referred to dental evaluation and needful. All these patients were followed by maxillofacial surgeon and were found to have findings such as discharge of pus from oral cavity, oro-cutaneous fistula, necrotic exposed bone in the maxilla/mandible etc. Investigations such as contrast enhanced CT scan of para-nasal sinuses (CECT), maxilla and mandible, nasal swab for fungal culture, biopsy from maxilla/mandible was carried out, to establish the diagnosis of fungal sinusitis/osteomyelitis. RT PCR, routine blood investigations along with high resonance CT scan of thorax (HRCT) were advised for clearance to perform surgery under general anesthesia. Inj Amphotericin B, Inj Posaconazole were the antifungal drugs that were given to the patients pre and post operatively, to control the spread of fungal sinusitis/osteomyelitis (Rhino cerebral mucor mycosis/ black fungus)

Inj Liposomal Amphotericin B 50 mg 0.3-0.7mg per kg body weight tid/q.i.d intra venous infusion slowly for 1-2 hrs for one week pre operatively and b.d/t.i.d for 4-6 weeks post operatively was given in patients with normal cardio renal status after assessment. For patients whose serum creatinine levels, liver function tests were raised or when liposomal Amphotericin B was in scarcity, Inj. Posaconazole 300mg b.d on day 1, followed by b.d/t.i.d was given intravenously for one week pre and post operatively. After one week post operatively, these injections were converted to oral tablets with a dose of 100mg delayed release, per oral b.d on day one and 100mg/t.i.d. from second day onwards. Duration of therapy was based on invasiveness of disease, recovery from symptoms, neutropenia or immuno suppression with regards to the usage of both the drugs. The average duration of time for drug administration was between 6-10 weeks.

For patients diagnosed with fungal sinusitis and sound bone without necrosis Posaconazole was chosen with the intent of salavage therapy both in injection and tablet forms. Patients with signs of fungal sinusitis who showed mucosal thickening on CECT and sound bone clinically, were kept under close observation along with drug therapy and follow up. Nasal swab or culture, mucosal and bone biopsy by Caldwell-Luc procedure were done to confirm the diagnosis of fungal sinusitis/osteomyelitis.

Infrastructure maxillectomy (5 cases), sub- total maxillectomy (4 cases), total maxillectomy (4 cases, total maxillectomy + ethmoidectomy -2 cases), segmental and hemi mandiblectomy (4 cases) were performed under general anesthesia for patients who were diagnosed with fungal osteomyelitis.

Debridement of the surgical site with antiseptic solution (betadine and normal saline 0.9%, 10%H202 15 drops to 1ml spproxiamately as 20-30 ml solution) was done on every alternate day, along with antral pack dressing, till healing has taken place without any residual signs of infection.

All patients recovered uneventfully because of earliest diagnosis and in time treatment. Follow up of patients was done on fifteen postoperative day, and every 15 days thereafter for 6-10 weeks.

Results

The oral medication regimen was prescribed for 5 days initially, which was extended further for 10 and 15 days respectively depending upon the existence of symptoms. The average duration of recovery was noted to be 10-15 days irrespective of age and gender. Patients with mild symptoms of COVID-19, recovered within a span of 7-10 days on an average. Patients presented with oxygen saturation of 90%-92% on day 1, improved to 94% on day 5 and 94 and above on day 10 and 15 respectively. Patients with symptoms of cough, breathlessness, fever, and signs positive for rhonchi, crepitations, oxygen saturation of 90% with HRCT score of 8/25 and above had a slow recovery rate (day 15). These patients also showed signs of right and left basal pneumonitis on Chest X ray and HRCT scan. In patients with symptoms such as loss of smell, taste, myalgia, dry cough (oxygen saturation of 94%) the recovery time period was faster (day 7-10). The drug regimen was effective in all patients who presented with the above said symptoms which showed significant change in subsiding of symptoms and improvement of oxygen saturation levels progressively from day 5 to day 10 and 15 eventually. RT PCR test was done on day 1, day 10 and day 15 (for those who got positive on day 10).

In spite of low immunity status in 2 cancer patients (colorectal cancer (1), cervix cancer (1)), with COVID-19 positive symptoms, recovered well with our drug regimen without any co-morbidities. As per the demographic data of our study, the incidence of COVID 19 is significantly found to be more in the age group of 31-50 years (Table 1). A significant difference was observed between male and female Covid-19 patients with mean systolic blood pressure and diastolic blood pressure ($p<0.05$). The mean systolic and

diastolic blood pressure was higher in males than females. But no significant difference was observed with regards to mean pulse, temperature, respiratory rate (p>0.005) (Table 2).

A significant improvement in percentage of change in spO2 after day 5 is 3.31%, after day 10 is 5.61%, and after 15 days 5.68% respectively, which indicates the improvement of spO2 from day 1 to day 15(Table 4, Figure1).

Profile	No of COVID patients	% Of COVID patients
Gender		
Male	198	61.49
Female	124	38.51
Age groups		
<=30yrs	47	14.60
31-50yrs	162	50.31
51-70yrs	94	29.19
>=71yrs	19	5.90
Total	322	100.00
Mean age	46.80	
SD age	14.83	

Table1: Demographic profile of COVID patients

Parameters	Summery	Male	Female	Total	t-value	p-value
Pulse	Mean	91.46	91.77	91.58	-0.4952	0.6208
	SD	5.71	5.28	5.54		
SBP	Mean	118.08	114.96	116.88	3.6327	0.0003*
	SD	7.65	7.26	7.64		
DBP	Mean	77.30	74.83	76.35	3.5009	0.0005*
	SD	6.33	5.90	6.27		
Temp	Mean	100.38	100.26	100.34	1.5901	0.1128
	SD	0.74	0.56	0.67		
RR	Mean	20.88	20.37	20.68	0.9600	0.3378
	SD	5.82	1.12	4.62		

***p<0.05 indicates significant**

Table 2: Comparison of male and females with different parameters by independent t test

Resp systems	No of COVID patients	% of COVID patients
Normal	272	84.47
HECT	13	4.04
Rhonchi- unilateal	15	4.65
Left basal pneumobitis	5	1.55
Pneumonitis	5	1.55
Bronchitis	3	0.93
Crepitus	3	0.93
B/l rhonhi	2	0.62
Cxr-b/l	2	0.62
Bi-basal pneumonitis	1	0.31
Right basal pneumonitis	1	0.31
Total	322	100.00

Table 3: Status of respiratory system of COVID patients.

Time points	Mean	SD	Mean Diff.	SD Diff.	% Of change	t-value	p-value
Day 1	90.43	2.85					
Day 5	93.42	2.07	-2.99	2.16	-3.31	-23.1225	0.0001*
Day 1	90.43	2.85					
Day 10	95.51	1.60	-5.08	2.88	-5.61	-29.3339	0.0001*
Day 1	90.43	2.85					
Day 15	95.57	1.65	-5.14	2.87	-5.68	-29.8864	0.0001*
Day 5	93.42	2.07					
Day 10	95.51	1.60	-2.09	1.99	-2.23	-17.5046	0.0001*
Day 5	93.42	2.07					
Day 15	95.57	1.65	-2.15	2.03	-2.30	-17.6270	0.0001*
Day 10	95.51	1.60					
Day 15	95.57	1.65	-0.06	0.51	-0.06	-2.0004	0.0464*

*p<0.05

Table 4: Comparison of spO2 scores at day 1, day 5, day 10 and day 15 by dependent t test

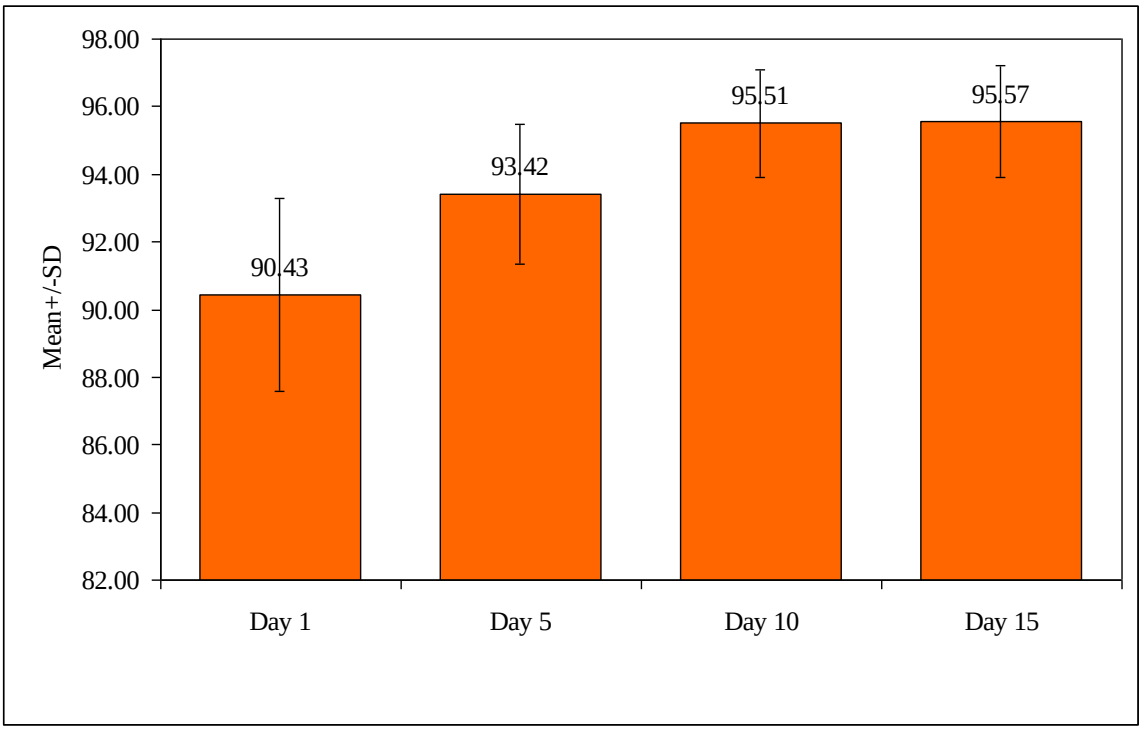


Figure 1: Comparison of spO2 scores at day 1, day 5, day 10 and day 15.

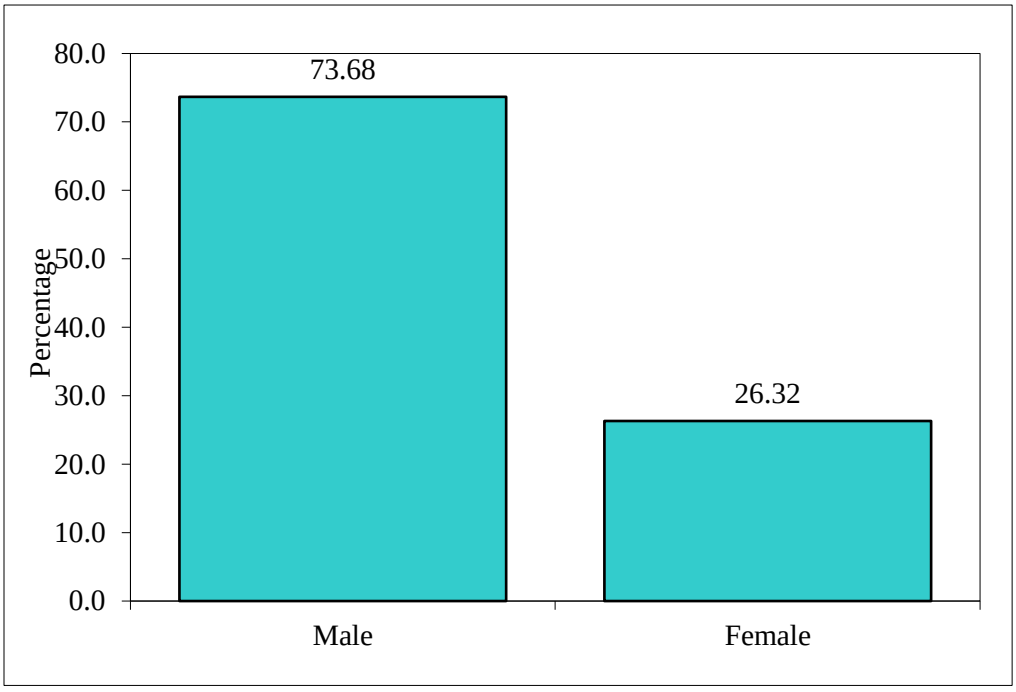


Fig 2: Gender wise distribution of COVID post fungal osteomyelitis patients

Time points	Mean	SD	Mean Diff.	SD Diff.	% of change	t-value	p-value
Day 1	94.16	1.71					
Day 5	94.95	1.03	-0.79	1.03	-0.84	-3.3356	0.0037*
Day 1	94.16	1.71					
Day 10	95.42	0.77	-1.26	1.41	-1.34	-3.9105	0.0010*
Day 1	94.16	1.71					
Day 15	95.79	1.03	-1.63	1.86	-1.73	-3.8191	0.0013*
Day 5	94.95	1.03					
Day 10	95.42	0.77	-0.47	0.61	-0.50	-3.3750	0.0034*
Day 5	94.95	1.03					
Day 15	95.79	1.03	-0.84	1.26	-0.89	-2.9158	0.0092*
Day 10	95.42	0.77					
Day 15	95.79	1.03	-0.37	1.01	-0.39	-1.5875	0.1298

Table 5: Comparison of spO2 scores of COVID post fungal osteomyelitis patients at day 1, day 5, day 10 and day 15 by dependent t test.

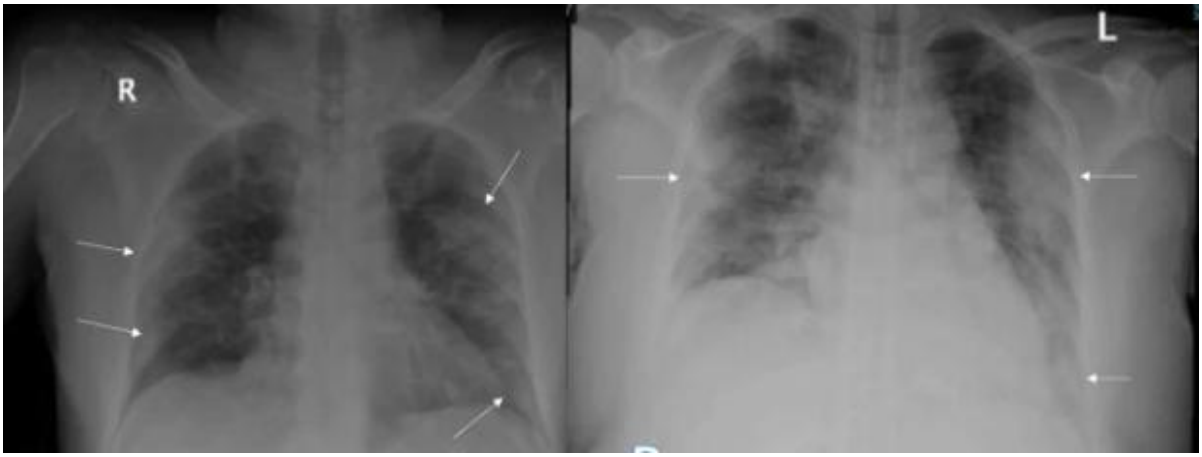


Fig 3: Chest X-ray showing changes from bilateral basal pneumonitis to pneumonic consolidation.

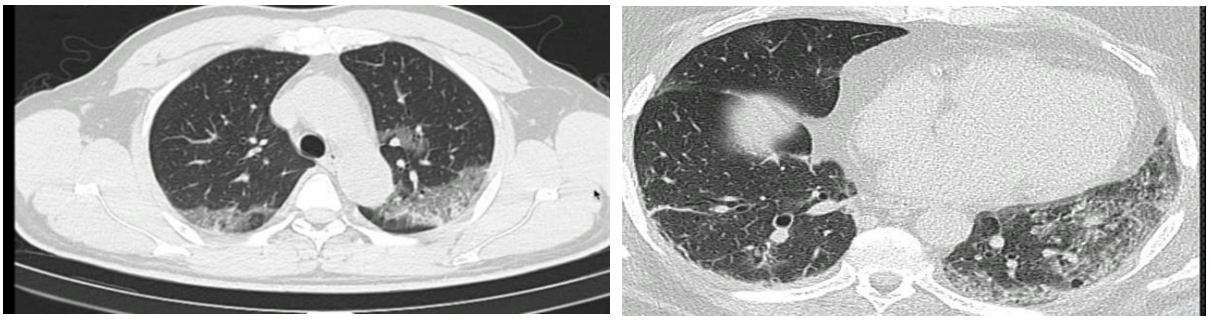
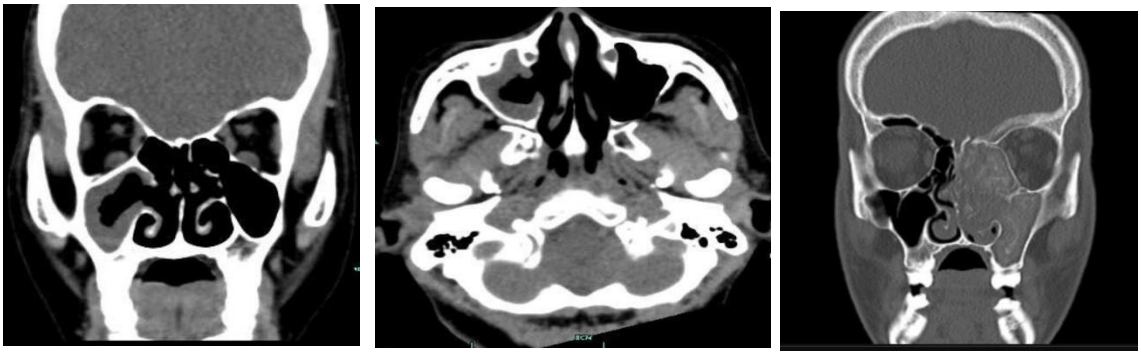


Fig: 4: HRCT scan of chest (cross section) showing ground glass appearance, in concomitance with COVID infection.



(A) (B) (C)

Fig: 5 Post COVID CECT scan of paranasal sinuses (coronal &axial) showing mucosal thickening of right maxillary sinus (A&B); fungal sinusitis leading to of left maxillary and ethmoidal sinuses.

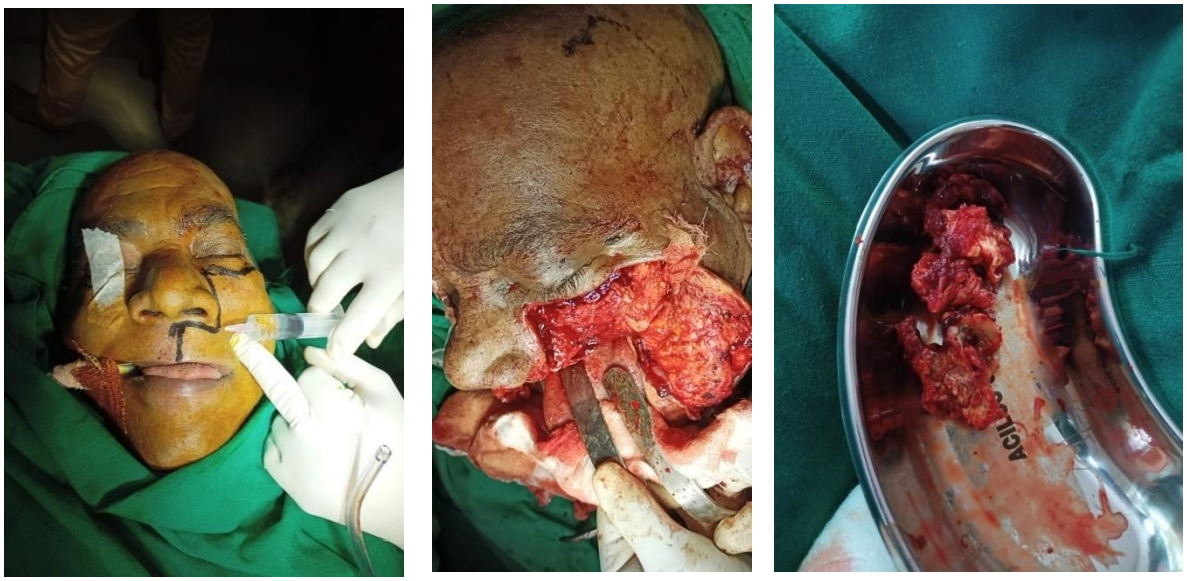


Fig 6: Sub-total maxillectomy with Weber-Fergusson incision

Discussion

Since December 2019, Corona virus has shown its lethal effects all over the world, different treatment regimens were practiced across various health care centers which were cost effective and varying with each other. There was no standard treatment protocol available to control or eradicate the pandemic because of the genomic variants produced by the Corona virus, which was even recognized by the World Health Organization.

The World Health Organisation advised that, Tab Ivermectin12 mg be used to treat COVID 19 only within clinical trials. It has not recommended the use of Clarythromycin in clinical trials and guidelines of COVID-19 treatment. The Indian Council of medical research has not mentioned the usage of Clarithromycin in its COVID-19 treatment guidelines. [1,2] Therefore many drugs including Inj Remedesvir, Tocilizumab, corticosteroids, Chloroquine etc were vigorously used on an empirical basis, with varying outcome results including deaths.

Kajuko Yamamoto et al, in a multi-centric randomized control trial aimed at evaluating effect of Clarithromycin in patients with mild COVID pneumonia who don't require oxygen administration. They conducted study in three groups over 60 patients. Group A had administration of Clarithromycin 800 mg/day. Group B had administration of Clarithromycin 400mg/day and group B had placebo therapy without Clarithromycin [3].

Bryant, Andew et al, stated that re-proposed medicines may have a role against SARS COVID -2 virus. The antiparasitic Ivermectin with anti-viral and anti-inflammatory properties has now been tested in numerous clinical trials. They also stated that meta-analysis of 15 clinical trials found that Ivermectin reduced risk of death, when compared with treatment with no Ivermectin.

Moderate certainity evidence finds that large reduction in COVID-19 deaths is possible using Ivermectin early in the clinical course. This may reduce the number progressing to severe disease. This is a low-cost treatment.

Since Corona virus is a RNA virus, Tab. Clarithromycin (250mg), Tab. Ivermectin 12mg were effective against all variants of corona virus in containing the disease as per our observations in this study. Both these drugs have ani-inflammatory action. Clarithromycin is an immune modulator and suppresses cytokine storm. Its use was associated with decrease in circulating C reactive protein, tumor necrosis factor alfa, Interleukin (IL 6), by increase of production of Interferon- gamma, and decrease of production of IL6 by mono nuclear cells and by suppression of SARS COVID 19 viral load. Tab Ivermectin acts on corona virus by preventing viral proteins from entering the host cell nucleus (Caly et al., 2020) [4, 5, 6].

This combination of Clarithromycin and Ivermectin as oral medication regimen was successful at par with other medications that were used in addressing mild to moderate COVID-19 patients, both in treatment results and cost-effectiveness and minimizing co-morbidities.

The side effects were very minimal (nausea) used with the above regimen as compared to drugs used in other studies in treating COVID 19. This medication regime could be used by patients with mild COVID symptoms involving both upper and lower respiratory tract with greater effectiveness. Patients were followed up at intervals of day 5, 7, 10, 15 respectively from the onset of the disease. From day 5 onwards, symptoms gradually subsided and improved to the normal asymptomatic level by the end of 10/15 days.

In order to provide cheaper medication that are available commonly at the urban/ semi-urban levels for easy availability to the common population which can be consumed orally under medical supervision, even at home quarantine by storing at local temperature, this medication regimen was implemented with consistent results and satisfactory recovery rate.

The incidence rate of fungal sinusitis/osteomyelitis globally varies from 0.0005 to 1.7 per million population. In India, prevalence of fungal osteomyelitis/sinusitis is estimated as 140 per million population, which is about 80 times higher than the prevalence in developed countries [1, 7].

Occurrence of fungal sinusitis in post COVID patients is probably due to decreased immunity status and flaring of fungus which is a commensal in the upper airway tract, secondary to Corona virus infection. In our observation, the complete recovery of to normalcy with improved general health status was observed to be between 3-6 months. The fatal incidences reported due to fungal sinusitis were rare as observed in our study, due to in time surgical treatment with effective action of Liposomal Amphotericin –B and Posaconazole in controlling and eradicating the disease spread.

In our experience, we observed that, avoidance of corticosteroids/other immune modulating drugs and prescribing the two-drug regimen of Clarithromycin and Ivermectin for mild to moderate COVID -19 patients, also helped in controlling and preventing the occurrence of fungal sinusitis/osteomyelitis.

Conclusion

The purpose of this study appears fulfilled overall, with the results showing significant fast recovery (day 10) in patients with mild symptoms and slow recovery (day 15) in cases of low oxygen saturation with moderate symptoms like cough with breathlessness in relation with HRCT values.

Although various treatment algorithms were suggested and implemented in treatment of COVID- 19, reportedly there are no studies mentioned in the literature so far with this combination of drug regimen.

In comparison with WHO treatment protocol and medication, our drug regimen showed significant improvement with regards to patients' symptoms and co-morbidities.

Declaration of interest: The authors declare that there are no known competing financial interests or personal relationships that could have appeared to influence the work described in this article.

Conflict of interest: The authors have no conflicts of interests to declare.

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