A Study on the Effect of Ivermectin on the Clinical Status in Patients with Moderate Covid-19 Diagnosis

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ABSRACT:OBJECTIVE: To evaluate the response of Ivermectin treatment on the clinical status during hospitalization in patients diagnosed with moderate Covid-19.

STUDY DESIGN AND METHOD: A comparative study of hospitalized patients with confirmed moderate COVID-19 positive patients were enrolled in our study from October 2020 to January 2021 at VivekanandhaMedical Care Hospital, Elayampalayam. Patients were divided into group A (Ivermectin plus Remdesivir) and group B (Remdesivir alone), and their changes in the lab parameters from base-line to end-point was comparedin both the groups. The statistical analysis was performed usinggraph pad instat 3.10.

RESULTS: 400 patients were enrolled;191 patients were included based on the exclusion and inclusion criteria. Out of these 112 patients received Ivermectin plus Remdesivir (58.63%) and79 patients received Remdesivir(41.36%) alone. In this study 114 (53.6%) were males and 51 (26.7%) were female patients. Age wise distribution in COVID-19 was found to be more prevalent between 51-60 years and about (26.17%) patients were enrolled. Common complaints on admission were found to be fever (20.91%) and cough (16.73%) are the most prevalent co-morbidity was DM (40.11%) and HTN (35.32%) followed by CAD, COPD, CKD and Thyroid. The mean difference of D-dimer, LDH, CRP were found to be statistically significant in both groups and the obtained p-value were 0.02, 0.04 and 0.04 respectively. Ivermectin+Remdesivir treated patients were seen to have a shorter hospital stay with a mean of 8.07±1.60, when compared to Remdesivir alone group with a mean 10.02±2.11.The p-value <0.01 was found to be statistically significant. The average days taken by the RT-PCR to become negative in Ivermectin+Remdesivirgroup was 7±7.3 and for Remdesivir alone group it was 9.7 ± 2.8 and the p-value was <0.04 was statistically significant.

CONCLUSION: As per the study, patients with moderate covid-19, those who received Ivermectin plus Remdesivir showed a significant improvement in their haemato- biochemical parameter, along with an achievement of negative RT-PCR in a shorter period of time and lower duration of hospitalization, when compared with the Remdesivirgroup.

KEYWORDS: Covid-19, Ivermectin, Haemato-biochemical parameters, Hospitalization, Recovery rate

I.   INTRODUCTION

A sudden outbreak causing severe respiratory illness in the Hubei Province of the Wuhan City in China, in the early December 2019 was identified. Later on 11th February 2020, the World Health Organization officially announced the novel contagious infection as Coronavirus disease of 2019 (COVID-19) and the causative agent was found to be severe acute respiratory syndrome coronavirus 2 (SARSCoV-2)[(1,2)]. This virus was found to be highly mutagenic and affected different people in different ways.The most common symptoms are found to be fever, dry cough, sore throat and tiredness. Some were also presented with symptoms of headache, diarrhoea, loss of taste or smell and rashes. In severe cases the patients were presented with pneumonia, chest pain and breathlessness [(3,4)].

The antiviral agents namely Remdesivir and Favipiravir, have shown some promising results in the treatment of COVID-19. However, these are very expensive and are mostly reserved

for severe cases only[5,6]. On the other hand, several national and international studies have reported encouraging results of Ivermectin in the treatment of mildly severe COVID-19 patients. Ivermectin is originally an FDA approved broad spectrum anti-parasitic drug used in the treatment of onchocerciasisand lymphatic filariasis since late 1970[7]. It stimulates gammaaminobutyric acid-controlled chloride channels, and leads to hyper polarisation and paralysis of the pathogenic organism. This drug also possesses a wide range of antiviral activities, against various RNA and DNA viruses [8,9]. Ivermectin has also proven its efficacy in the treatment of specific flaviviruses (dengue and encephalitis viruses) and the chikungunya virus in the in-vitro studies [10,11]. A study by Caly et al showed, SARS-CoV-2 infected Vero/Hslam cells when treated with Ivermectin resulted in a 5,000-fold reduction in the viral RNA 48 hours later and the possible mechanism was found to be the inhibition of importin α / β1 mediated transport of viral proteins both in and out of the nucleus[12]

Addition of Ivermectin along with a standard treatment regimen was also linked toa lower mortality rate inthe treatment of COVID-19 patients, especially in patients who required a ventilator support.[13] Wagstaff et al study indicated Ivermectin as a potent inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and a 99.8% reduction was observed in the viral RNA after 48 hours[14]. Till date the side effects reported on the usage of Ivermectin was also found to be minimal. The peak plasma concentration of Ivermectin is about 4 to 5 hours on oral ingestion and is almost 93% plasma protein bound. The drug was majorly metabolized by the hepatic CYP3A4 microsomal enzymes. The rare adverse effects reported include fever, pruritus, postural hypertension, tachycardia, oedema, headache lymphadenopathy, sore throat and cough. The usage of Ivermectin during pregnancy and in children below 5 years is however not recommended [15].This study was conducted to evaluate the response to Ivermectin in clinical status, during hospitalization in patients diagnosed with moderate COVID-19.

II. METHODOLOGY

This was a prospective observational study to compare the effect of Ivermectin + Remdesivir and Remdesivir alone in patients with mild and moderate COVID-19 infection. The study was conducted for a period of 4 months from Oct 2020 to Jan 2021 and was approved by the ethical committee of Vivekanandha Medical Care Hospital, Tiruchengodeand informed consent was obtained from all the patients.

In this study we have reviewedthe laboratory confirmed infection with SARS-COV- 2 of hospitalized patients during their admission. Thisstudy enrolled a total of 400 consecutive patients with SARS- COV-2 infection confirmed by RT- PCR, CT-SCORE (8-16) and SpO2 < 92%. Out of these the present study included 191 COVID-19 patients in which 112 received Ivermectin plus Remdesivir, while 79 received only Remdesivir. Remaining 209 study populationwere eliminated based on exclusion criteria like patientsunder 20 years, pregnant and lactating women, severe covid 19 patients and partial hospital stay. The two groups were compared in terms of their demographics, lab parameters, RT-PCR and duration of hospital stay.Patient demographics and clinical outcomes are represented as percentage, mean and standard deviation. Student t test were used to analyzethe statistical differences. All the calculations were performed by using graphpad instat 3.10.

III. RESULTS AND DISCUSSION

Sharun k et al 2020 literature study indicates that Ivermectin might be helpful in the treatment of covid-19[23]. In this study, patients prescribed with Ivermectin plus Remdesivir had better clinical status. Total population of 112 (58.63%) was administered with Ivermectin plus Remdesivir and 79 (41.36 %) were administered with Remdesivir alone. Among the 191 patients, the male proportion were 140 (73.29%) and females were 51(26.7%) as shown in the Table no: 1. The respective results obtained here coincided with the study conducted by Bai P [16].

Table no 1: Gender Wise Distribution

Gender	Percentage (%)
Male	140 (73)
Female	51(26)

With the increase in age the risk of associated complication with covid-19 also increases. Here the age distribution shows that the patients between 51-60 years (26.27%) and 61-70 years (25.13 %) was mostly affected as per table no 2. Our study was relevant to the study conducted by Yanez, N.D [17].

Table no 2: Age wise distribution

Age Distribution (Years)	Percentage (%)
21 – 30	4 (2.09)
31 – 40	25 (13.08)
41 – 50	33 (17.27)
51 – 60	50(26.17)
61 – 70	48 (25.13)
71 – 80	26(13.61)
81 – 90	5(2.61)

In our study 112 patients were administered with Ivermectin + Remdesivirand 79 patients were administered with Remdesivir alone as given in table no 3.

Table no 3: Percentage distribution of patients taking Ivermectin + Remdesivir and Remdesivir alone

Study Groups	Percentage (%)
Ivermectin + Remdesivir (Group A)	112 (58)
Remdesivir (Group B)	79 (41)

In this study, at the time of admission the major complaints were fever (20.91%), cough (16.73%), myalgia (13.09%) and breathing difficulty (9.17%) as per table 4. Perotte, R et al conducted a study based on the common initial complaints in covid-19 patients on admission and concluded that fever and shortness of breath were the chief ones [18].

Table 4: Complaints on admission

Complaints	Percentage (%)
Fever	42 (20.91)
Sore Throat	16 (8.23)
Cough	32 (16.73)
Breathing Difficulty	17 (9.17)
Chest Pain	3 (1.34)
Runny Nose	1 (0.8)
Head Ache	17 (9.17)
Myalgia	25 (13.09)
Anosmia	9 (4.85)
Dysgeusia	9 (4.85)
Diarrhoea	7 (3.64)
Vomiting	4 (2.29)
Tiredness	9 (4.85)

In this study the most prevalent comorbidity was found to be like diabetes mellites (40.11%) followed by hypertension (35.32%), CAD (7.78%), COPD (6.58%), CKD (5.38%) and Thyroid (4.79%) as given in table no 5. De

Almeida-Pitittoet al. 2020 studies showed that diabetes, hypertension especially cardiovascular disease is important risk factors for increasing mortality in COVID-19 patients [19].

Table 5: Prevalence of comorbidities

Comorbidity	Percentage(%)
Hypertension	67 (35.32)
Diabetes mellitus	77 (40.11)
COPD	12 (6.58)
CAD	15 (7.78)
CKD	10 (5.38)
Thyroid	8 (4.79)

Yang X and Tan C et al 2020 conducted a study which showed thatat the baseline there were not many differences in inflammatory markers between the groups. The seriousness of the infection has been related with lyphopenia, neutrophilia, raised ALT, AST, LDH, CRP and ferritin levels [20,21]and the duration of hospital stay in covid 19 patients. [22]

In this study, a mean difference 17.52 ± 19.64 and 13.62 ± 31.56 was obtained in group A and group B respectively when the baseline and endpoint D-Dimer levels were evaluated. Mean reduction in LDH was 29.25 ± 30.66 and 21.44 ± 21.15 in group A and group B. CRP levels also

reduced in both the groups with a mean difference of 0.25 ± 0.67 and 0.24 ± 0.76 respectively.The obtained P-values were 0.02, 0.04 and 0.04 respectively and found to be statistically significant as given in table no 6, 7, 8.. Thus, those patients administered with Ivermectin+ Remdesivir showed a substantial improvement in D-Dimer, CRP, LDH, RT-PCR. the hospital stay was also found to be significantly reduced in this group when compared to the group that was administered with Remdesivir alone. The mean difference of D-dimer, LDH, CRP were found to be statistically significant in both groups.

Table 6: Mean Differences in D-dimer levels

Study Groups	Base – Line	End - Points	Mean Difference (D-Dimer levels)
Ivermectin + Remdesivir (Group A)	163.38 ± 27.37	145.85 ± 30.11	17.52 ± 19.64
Remdesivir (Group B)	161.53 ±32.54	147.91± 33.34	13.62±31.56

Table 7: Mean Differences in the level of LDH in both the groups

Study Groups	Base – Line	End – Point	Mean Difference (LDH levels)
Ivermectin + Remdesivir (Group A)	303.36 ± 35.86	274.11 ± 41.77	29.25 ± 30.66
Remdesivir (Group B)	320.22 ± 35.45	298.77 ± 37.26	21.44 ± 21.15

Table 8: Mean Differences in serum CRP levels in the study population.

Study Groups	Base - Line	End - Point	Mean Difference (CRP levels)
Ivermectin + Remdesivir (Group A)	6.69 ± 0.70	6.43 ± 0.95	0.25 ± 0.67
Remdesivir (Group B)	6.46 ± 0.93	6.21 ± 1.05	0.24 ± 0.76

In this study Ivermectin+Remdesivir treated patients were seen to have a shorter hospital stay with a mean of 8.07±1.60, when compared to Remdesivir alone group with a mean 10.02±2.11 as per table no 9. The p-value obtained showed a<0.0001 significance statistically. Khan et al 2020 published a scientific letter which showed that there was an early discharge in patients who were treated with Ivermectin as adjuvant therapy [24].

Table 9: Mean Differences on duration of hospital stay.

Study Groups	Mean Difference (Hospital Stay)
Ivermectin + Remdesivir (Group A)	8.07±1.60
Remdesivir (Group B)	10.02±2.11

The average days taken for a negative RT-PCR result in Ivermectin+Remdesivir group showed a mean of7.85 ±7.3 and for Remdesivir alone group it was 9.7 ± 2.8 in our study and the p-value was <0.04 and was statistically significant as mention in table no 10. Dominican Republic's clinical trial found that 99% of the patients recovered with a significant reduction of recovery time when treated with Ivermectin [25].

Table 10: Mean Differences on average days taken for a negative RT-PCR report in both the groups.

Study Groups	Mean Difference (RT-PCRReport)
Ivermectin + Remdesivir (Group A)	7.85±7.3
Remdesivir (Group B)	9.72± 2.8

Rajter et al 2021conducted a study in which patients with COVID-19 received Ivermectin and rest witha usual care and it was concluded that a lower mortality was observed in the Ivermectin group[21]. Many physicians now are recommending the usage of Ivermectin in many countries,[26] and have stated that patient's viral replication levels declined very quickly after the administration of Ivermectin. Physicians' also noticed that single dosage of Ivermectin could improve patient's condition significantly. Rajter et al.in his study showed astatistically significant improvement in the mortality rate among the COVID-19 patients administrated with Ivermectin [1].In our study Ivermectin was found to be very effective in treating the corona virus infection when compared to the Remdesivir group.

IV. CONCLUSION

Among the patients with moderate COVID-19, those treated with Ivermectin plus Remdesivir showed a statistically significant reduction in the clinical status. The addition of Ivermectin plus Remdesivir was very effective in the treatment of COVID-19 patients with significant reduction in inflammatory markers, recovery time and hospital staywhen compared to Remdesivirtreatment only. Appropriate rapid reduction of the viral DNAis essential to control disease progression, therefore a need to manage the COVID-19 patients with safe, cheap, widely available treatment is very important. Our present study showed that Ivermectin+Remdesivirwould help to prevent severe complications and transmission of covid-19 to the society. Early use of Ivermectin+Remdesivir is very useful for controlling the COVID 19 infection

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