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EFFICACY OF MONTELUKAST IN TREATING COVID-19 A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY

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Abstract:

Background and Objectives: The corona virus disease 2019 (COVID-19) pandemic continues to affect the global. The goal of the current study is to evaluate how montelukast affects both the length of hospital stay and progression of the disease.

Methods: It was a Randomized Controlled Study with placebo, conducted for a period of 6 months in a tertiary care hospital. The study was double blind. All patients above the age of 16 years, both males and females, admitted with a diagnosis of mild or moderate COVID-19 based on RT-PCR report during the study period were included in the study. Patients with a known allergy to OR adverse drug reaction with montelukast, unwilling to participate in the study, patients included in any other ongoing studies & pregnant and lactating females were excluded from the study. A total of 80 patients were calculated as the sample size considering the recovery rate of 40%, with 5% precision and 80% power. The patients were equally divided between both the groups.

Results: At the time of admission; among those treated with montelukast, 68% were mild cases and 30% moderate & with placebo, 82% were mild cases and 17% were moderate. Regarding the other prescribed medications, heparin, corticosteroid and azithromycin were commonly given in both the groups & it did not show any statistically significant difference. ($p>0.05$). Progression to severe disease was the primary outcome which was higher in montelukast group (20.22%) compared to placebo group (15.78%), but it was not statistically significant. Among the secondary outcomes, ICU admission was higher in placebo group, but discharge rate by 10^{th} day of admission was nearly similar in both the groups (52%).

Conclusion: There was no difference in primary or secondary outcomes with the use of montelukast compared to placebo.

Keywords: COVID-19, Montelukast, placebo, Randomized Controlled Study, double blind, health status.

INTRODUCTION

Since its initial report in November 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has spread to every part of the globe. It was discovered a few months later that symptom of a few patients lasted longer than four weeks. The term "Long-term COVID or Extended-COVID" refers to the extension of the disease. 10% of COVID-19 patients are

thought to be affected by extended-COVID, according to certain studies. Male sex, advanced age, and comorbidities are some of the risk variables linked to a bad prognosis, although they do not appear to be related to the likelihood of developing long-term COVID.[1,2]

The pandemic, which began with the novel corona virus 2019 (COVID-19), has not yet been contained despite significant global efforts and attempts to manage and cure the illness. There is not yet a specific therapy for COVID-19 infection currently available. A broad spectrum of symptoms, such as cough, headache, arthralgia, fever, abdominal pain, asthenia, brain fog, and skin manifestations are indicative of long-term COVID-19 infection. Dyspnea is one of the most common symptoms, in addition to the challenges like completing everyday tasks like social and self-care activities.[3,4]

With the use of the receptor angiotensin converting enzyme 2 (ACE2) present in lungs, SARS-CoV-2 enters human cells. In addition to the lung, ACE2 is also expressed in the kidney, heart, gut, vascular endothelium, and other organs.[5] The entire immune response as well as processes generated at the pulmonary and extra pulmonary levels have been recognized as key players in the pathophysiology of COVID-19.[6]

Antinuclear antibodies and other autoimmune indicators are very prevalent in COVID-19 patients, suggesting the potential benefit of certain therapies. Respiratory symptoms resulting from systemic inflammation in long-term COVID-19 may be related to leukotrienes, the pro-inflammatory mediators that take role in immune response control.[7]

A class of medications known as “Leukotriene Receptor Antagonists” (LTRAs) are used to treat the symptoms of allergic rhinitis and asthma. Both respiratory function and airway hyper-responsiveness are improved by their bronchodilator effect and suppression of airway inflammation. LTRAs reduce inflammation and bronchoconstriction by reducing the effects of leukotrienes C4, D4, and E4 when they bind to CysLT1 receptors in the lungs and bronchi.[8]

Strongly suppressing oxidative stress, montelukast is a cysteinyl leukotriene (cysLT) receptor antagonist with anti-inflammatory properties. CysLTs may also have an impact on cytokine production. Recent research has demonstrated that montelukast medication lowers the levels of TNF-α, IL-6, and IL-1b among other cytokines.[9]

The use of montelukast during the acute phase of COVID-19 has been suggested by recent research because of its potential antiviral and anti-inflammatory properties. Because of its affinity for the ACE2 receptor, montelukast has the ability to block the entry of SARS-CoV-2 into the cell, hence reducing both the duration and severity of the illness.[10] Furthermore, montelukast has been proposed to potentially shorten the replication cycle of the virus. The goal of the current study is to evaluate how montelukast affects both the length of hospital stay and progression of the disease.

MATERIALS AND METHODS

It was a Randomized Controlled Study with placebo conducted for a period of 6 months in a tertiary care hospital. The study was double blind.

Inclusion criteria:

All patients above the age of 16 years, both males and females, admitted with a diagnosis of mild or moderate COVID-19 based on RT-PCR report

Exclusion criteria:

- Patients with a known allergy to or adverse drug reaction with montelukast
- Patients unwilling to participate in the study
- Patients included in any other ongoing studies & Pregnant and lactating females

A total of 80 patients were calculated as the sample size considering the recovery rate of 40%, with 5% precision and 80% power. The patients were equally divided in both the groups.

Patients were categorized into Group A (Montelukast 10mg), Group B (Placebo). The patients in intervention group A were given one tablet of 10 mg of montelukast once daily at bedtime for 10 days from the time of admission. The patients in placebo group B received one similar looking placebo tablet with identical packaging. Since it was double blind, neither the doctor nor the patient were aware of the medicine. Apart from this, standard treatment was provided to all patients in both the arms, according to their clinical needs and as per the ICMR protocol and SOP of the institute. Patients were discharged as per the guidelines prescribed in SOP of the institute.[11]

Following the acquisition of signed informed permission, the patients were randomized using block randomization with variable allocation to the intervention or placebo group, block sizes produced by sealed envelope. At the time of admission, every patient's age, sex, pre-existing conditions, presenting symptoms, and other prescribed medications—such as steroids, heparin, remdesivir, convalescent plasma therapy, tocilizumab, antibiotics; as well as vital signs like heart rate, blood pressure, temperature, respiratory rate, oxygen saturation, mental status (AVPU), and qSOFA score were recorded (both the scores recorded at the time of admission and at least once a day).

Mild: No evidence of breathlessness or hypoxia (normal saturation).

Moderate: Breathlessness and/or hypoxia (saturation 90-94% on room air), respiratory rate of 24 or more and no features of severe disease.

Severe: Any of the following – severe respiratory distress, oxygen saturation <90% on room air, respiratory rate >30, shock, or evidence of a life-threatening organ dysfunction.

Ten days after the onset of symptoms, three days of afebrile condition, and four days of maintaining oxygen saturation above 94% without further medication were the requirements for discharge. These were used in combination with the judgement of the treatment team. The progression of the illness to a severe grade was the major outcome, and the following outcomes were measured - admission to the intensive care unit, need for mechanical ventilation, in-hospital death, and discharge on or before 10^{th} day of admission.

Statistical Analysis:

Epi-info 7 was used for analysis. The means were used to express all descriptive data and (SD) as well as frequency (%). Fischer's exact test and the chi-square test were used to evaluate how the primary and secondary outcome measures differed from one another in both the groups. In terms of statistics, a “p” value less than 0.05 was deemed significant.

RESULTS

	Montelukast Group N=80	Placebo Group N=80	'p' Value
Mean age (years)	54±4.3	52±4.2	0.50
Male	68	71	0.18
Female	32	29	0.88
Mean days from the onset of symptoms	5.4	7	0.12
Fever	72.3	66.7	0.43
Shortness of breath	35.2	35.6	1
Cough	56.8	46.7	0.21
GI symptoms	6.7	13.3	0.85
Hypertension	42.2	42.9	1
Type II DM	46.7	45	0.23
IHD	12.3	8.7	0.45
COPD	4.7	2	0.94
Asthma	11.3	6.9	0.45
Hypothyroidism	13.7	11.7	0.78
Severity at the time of admission			
Mild	68	82	0.11
Moderate	30	17	0.13
History of smoking	2	1	0.21
Treatment given			
Heparin	95.8	86.4	0.04
HCQS	20.8	28.6	0.32
Corticosteroid	84.8	90.6	1
Azithromycin	82.4	76.8	0.41
Remdesivir	14.6	10.1	0.55

Table 1- Comparison of Demographic and Clinical Characteristics of Montelukast and Placebo groups

As per table 1; among 160 patients during the study period, all patients were equally divided in both the groups (80 in Montelukast and 80 in Placebo). The study was male preponderance and mean age was nearly same above 50 years which clearly suggests that due to more work outside, the males were more exposed and above 50 were at high risk. The most common symptoms in both the groups were fever followed by cough and shortness of breath. Among the co-morbidities, most of the patients were diabetic and hypertensive in both groups. At the time of admission, in those treated with montelukast, 68% were mild cases and 30% moderate & in placebo group, 82% were mild cases and 17% were moderate. Heparin, corticosteroid and azithromycin were commonly given in both the groups, but it was not statistically significant ($p>0.05$).

Primary Outcome			
Progression to severe disease	20.22	15.78	0.58
Secondary Outcomes			
ICU admission	2.2	4.6	0.61
Mortality	0	0	1
Intubation	0	0	1
Discharge by 10th day	52.32	52.10	1

Table 2- Comparison of primary and secondary outcomes in both the groups

As per table 2; progression to severe disease was the primary outcome which was higher in montelukast group (20.22%) as compared to placebo group (15.78%) but it was not statistically significant. Among the secondary outcomes, ICU admission was higher in placebo group, but discharge rate was nearly similar in both the groups.

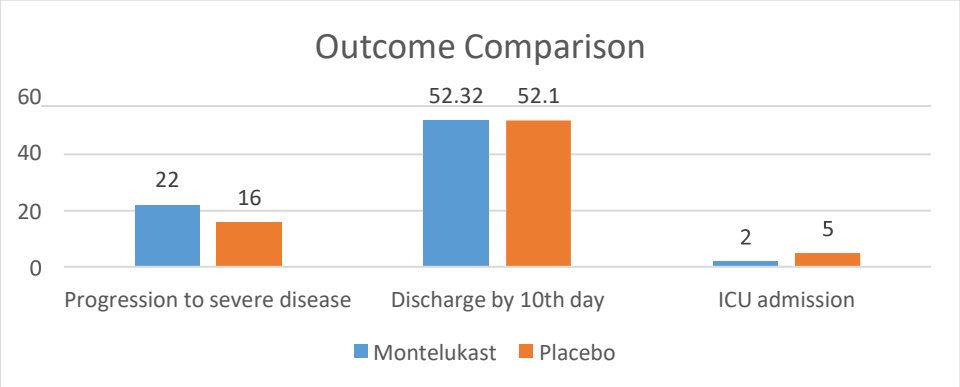

Figure 1- Outcome comparison of both the groups

As per figure 1; the outcome comparison includes both primary and secondary outcomes. In the primary outcome, progression to severe disease was higher in patients treated with montelukast (22%) in comparison to placebo group (16%). But both the groups showed almost similar discharge rates by 10th day of admission (52%).

DISCUSSION

The main goal of this study is to demonstrate the efficacy of montelukast, a previously approved drug in COVID symptoms. In comparison to placebo, in mild to moderate disease, this study found no improvement in the primary endpoint of progression to severe disease with the use of montelukast. Moreover, using montelukast did not enhance the secondary outcomes of death, ICU hospitalization, discharge on or before 10th day, or need for mechanical ventilation.

According to a preliminary study, asthma patients receiving montelukast in addition to other medication were less likely to get COVID-19 infection than those not receiving montelukast. In addition, there was a lower chance of hospitalization for those who had contracted the virus.[12]

Due to putative antiviral and anti-inflammatory actions, montelukast has recently been suggested for therapy in the acute phase of COVID-19 in several articles. It has been suggested that montelukast may obstruct entrance of SARS-CoV-2 into the cells because of its affinity for the ACE receptor. As a result, montelukast may lessen both the intensity and duration of acute COVID-19. Furthermore, montelukast may shorten the replication cycle of the virus, according to theory.[13,14]

The effectiveness of montelukast in treating acute SARS-CoV-2 infection in out-patients was assessed in two previous studies.[14] One attempt seeks to assess if montelukast is effective in lowering the frequency of hospital admissions and ER visits.[15] The effectiveness of Favicovir and montelukast in reducing the number of hospital admissions was assessed in the second study.[16] In a prior retrospective study, patients receiving montelukast in addition to conventional standard medication showed a lower risk of clinical worsening compared to the patients who were not given montelukast. However, compared to the patients who were not treated with montelukast, there was no discernible decrease either in hospital stay or in laboratory values of inflammatory markers.[17]

For extended-COVID, no therapies have been investigated. The severity of the COVID-19, its enormous financial and human cost, and the expected protracted COVID wave necessitates quick, efficient treatments to lessen SARS-CoV2 infection-related problems. Drawing from prior clinical experience[18], we anticipate producing data regarding the impact of montelukast on enhancing the quality of life associated with respiratory symptoms in patients with extended-COVID-19.

There were several restrictions on the study, which could have had an impact on the outcomes. Since most of the instances were mild and relatively a few of them progressed to the point where an ICU admission was needed, we were unable to obtain statistically significant samples to evaluate this specific outcome. Furthermore, in severe situations, we were unable to evaluate the effectiveness of the drug. Severe cases were not included in the study; hence results might not be applicable to those patients. As there was no mortality rate, some of the primary outcome measures could not be assessed. As inflammatory markers were not reviewed, the effect of treatment on cytokine storm could not be quantitatively measured.

Furthermore, it was not possible to quantify and objectively evaluate the effectiveness of the drug in reducing the cytokine storm because we did not correlate its use with the levels of inflammatory markers. These restrictions may be addressed further by larger studies measuring the inflammatory markers both before and after montelukast usage.

CONCLUSION

No statistically significant difference was observed in any of the outcomes between the montelukast-treated group and the placebo-treated group in the current study. The discharge rate is the same in both the groups.

Conflict of Interest: None declared.

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