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Case Series on use of Ulinastatin in Moderate to Severe COVID Illness

Roopa Rani K[1],Deepak TS[2],Thejeswini[3],Vikas KN[3]

[1]Associate Professor, Department of Anaesthesiology, MS Ramaiah Medical College, Bangalore, Karnataka, India.
[2]Associate Professor, Department of Emergency Medicine, MS Ramaiah Medical College, Bangalore, Karnataka, India.
[3]Assistant Professor, Department ofAnaesthesiology, MS Ramaiah Medical College, Bangalore, Karnataka, India.

Abstract

Background: Find the use of ulinastatin as a treatment option which is safe as well as potentially useful for the patients suffering from COVID-19.**Material and Methods:**In COVID-19 many authors have proposed Ulinastatin historically as an anti-inflammatory and anti-oxidation agent which has also been clinically utilized for the treatment of circulatory shock, acute respiratory distress syndrome (ARDS) and severe sepsis.**Results:**Clinical and laboratory data in critically ill ICU patient with COVID-19 in this case series, received treatment with Ulinastatin 1 lakh units i.v Q12h on day 1 of admission, was added and continued for 3 to 5 days and had a remarkable clinical improvement.**Conclusion:**In this case series the use of Ulinastatin was found to be safe & potentially helpful for patients affected with moderate to severe COVID illness with fast improvement in clinical condition.

Keywords:COVID 19, Ulinastatin, Pro-inflammatory cytokines, Inflammatory markers, acute respiratory distress syndrome.

Corresponding Author: Dr. Vikas KN, Assistant Professor, Department of Anaesthesiology, MS Ramaiah Medical College, Bangalore, Karnataka, India. Email: vikas.vikas7@gmail.com

Introduction

Corona virus disease 2019 (COVID-19) is a contagious disease which is caused by Corona virus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The majority of these patients have mild or moderate symptoms, nearing 14% of patients can progress to have severe pneumonia as well ashave high fatality rate.[1] Cytokine storm is suspected to be having critical role in COVID progression and sometimes death.[1] Severe COVID can cause uncontrolled systemic inflammation leads to Multiple organ failure including acute kidney injury, respiratory failure and septic shock.

Ulinastatin is acid resistant proteasinhibitor majorly found in human urine.It inactivates most of the serine proteases. However, even though ulinastatin is a protease inhibitor the activity of it toward many proteases is mostly weak. Ulinastatin historically demonstrated to be a important anti-inflammatory and anti-oxidation agent, it has also been clinically utilized for thetreatment of circulatory shock, acute respiratory distress syndrome (ARDS)and severe sepsis.[2-4] Patients will be given one to two lakh I.U. of ulinastatin (which is reconstituted with 100ml 5% dextrose) by intravenous route over 30 to 45 minutes, 2-3 times a day for 3-5 days.

In this case series, our intention is to describe the use of ulinastatin as an treatment option which safe as well as potentially useful for all the patients suffering from COVID-19. Here we present our experience at a tertiary care medical college teaching hospital.

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CASE 1

A 42 year old male patientwith no known co-morbidities was admitted to our hospital with complaints of fever & shortness of breath from 3 days. The patient got tested positive for COVID reverse transcription polymerase chain reaction (RT-PCR). Thehistory of the patient had no significant findings. On examination, he had a temperature of 1010F, a blood pressure of 110/70mmHg, pulse rate of 130 per minute, respiratory rate of 42 per minute, oxygen saturation (SPO2) at room air was 80% and 90% with 10 liters of oxygen giventhrough non-rebreathing face mask (NRBM). Respiratory system examination showedthere was adecreased in bilateral air andbilateral crepts.

Patient was evaluated with blood investigations including inflammatory markers, blood cultures etc and Imaging done including CT scan. 25-point CT severity score was 20.2D echo was normal. Patient was started on broad spectrum empiric antibiotics and other supportive medications as per ICMR guidelines and as per requirement of the patient. Patient was put on NIV with plans to intubate him if required due to tachapnea. Inj.Ulinastatin 1 lakh units i.v Q12h on day 1 of admission, was added and continued for 5 days. The clinical condition of this patient improved mainly respiratory rate (26 per minute)oxygen requirement reduced (5 L per minute) to maintain SPO2 95%after 8days.Serial chest x ray monitoring showed resolution of patches and inflammatory markers started reducing in blood test. At the time of discharge on 16 th day after admission, patients respiratory rate was 18 per minute and SPO2of 90% in room air.

CASE 2

A 54 year old female patientwith no known co-morbidities was admitted to our hospital with complaints of loss of smell,cough & shortness of breath from 6 days. The patient got tested positive for COVID RT-PCR in outside hospital. Thehistory of the patient had no co-morbidities. On examination, he had a temperature of 1000F, a blood pressure of 130/90mmHg, pulse rate of 110 per minute, respiratory rate of 30 per minute,SPO2 at room air was 86% and 97% with 6 liters of oxygen giventhrough NRBM. Respiratory system examination showedthere was adecreased in bilateral air and basal crepts.

Patient was evaluated with routine blood investigations including inflammatory markers, blood cultures etc and Imaging done including CT scan. 25-point CT severity score was 16. 2D echo was normal. Patient was started on broad spectrum empiric antibiotics and other supportive medications as per ICMR guidelines and requirement of the patient. Patient was continued on 6 L per minute oxygen. Inj.Ulinastatin 1 lakh units i.v Q12h, was added on day2 and continued for 3 days. The clinical condition of this patient improved mainlydrastically respiratory rate 18 per minute,oxygen requirement also reduced to maintain SPO2 98% in room air.Serial chest x ray monitoring showed resolution of patches and inflammatory markers started reducing in blood test. At the time of discharge on 11 th day after admission patient was comfortable.

CASE 3

A 27-year-old male patient with history of no chronic diseases was admitted to our hospital with complaints of easy fatiquablity, cough & breathlessness from 4 days. The patient got tested positive for COVID RT-PCR. Thehistory of the patient had exposure to his uncle with COVID. On examination, he had a temperature of 990F, a blood pressure of 120/80mmHg, pulse rate of 140 per minute, respiratory rate of 54 per minute, oxygen saturation (SPO_2) at room air was 60% and 86% with 15 litres of oxygen giventhrough nonrebreathing face mask (NRBM). Respiratory system examination showedthere was adecreased in bilateral air andbilateral crepts.

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Patient was evaluated with blood investigations including inflammatory markers, blood cultures etc and Imaging done including CT scan. 25-point CT severity score was 22. 2D echo was normal. Patient was started on broad spectrum empiric antibiotics and other supportive medications as per ICMR guidelines and as per requirement of the patient. Patient was put on NIV with plans to intubate him if required due to tachapnea. Inj.Ulinastatin 1 lakh units i.v Q12h on day 1 of admission, was added and continued for 5 days. The clinical condition of this patient slowly improved mainly respiratory rate 28 per minuteoxygen requirement reduced 10 L per minute to maintain SPO2 90%after 10days.Serial chest x ray monitoring showed improvement and inflammatory markers started reducing in blood test. At the time of discharge on 20 th day after admission, patients respiratory rate was 24 per minute and $SPO_2$of 92% with 2 litre oxygen. Patient was advised home oxygen and was weaned off home oxygen after 32 days.

CASE 4

A 48-year-old male patient with no known co-morbidities was admitted to our hospital with complaints of fever & shortness of breath on mild exertion from 2 days. The patient got tested positive for COVID RT-PCR in our hospital. The history of the patient had no co-morbidities. On examination, he had a temperature of 1020F, a blood pressure of 120/80mmHg, pulse rate of 98 per minute, respiratory rate of 28 per minute, SPO2 at room air was 88% and 98% with 5 liters of oxygen given through NRBM. Respiratory system examination showed there was a decreased in bilateral air and basal crepts.

Patient was evaluated with routine blood investigations including inflammatory markers, blood cultures etc and Imaging done including CT scan. 25-point CT severity score was 14. 2D echo was normal. Patient was started on broad spectrum empiric antibiotics and other supportive medications as per ICMR guidelines and as per requirement of the patient. Patient was continued on 4 L per minute oxygen. Inj.Ulinastatin 1 lakh units i.v Q12h, was added on day3 and continued for 3 days. The clinical condition of this patient improved mainly at a faster phase respiratory rate 16 per minute, oxygen requirement also reduced to maintain SPO2 99% in room air.Serial chest x ray monitoring showed resolution of patches and inflammatory markers started reducing in blood test. Patient was discharge on 9 th day after admission.

Discussion

Patients with COVID-19 have been found to show high level of pro-inflammatory cytokines. There by emphasizingexistence and also impact of so-called “cytokine storm” in viral respiratory infection that can cause deterioration inclinical course of the disease. It is being researched as a reason to cause rapid multi-organ failure.[5] The study of SARS-CoV-2 has shownthat virus can infect lung epithelial cellsand produce IL-8 in along with IL-6. IL-8 is a well-known chemo-attractant to neutrophils and T cells. That’s why modulating immune response or else suppressing cytokine production might prove vital in majority of sick cases.[6] Ulinastatin the drug which is intrinsic broad spectrum protease inhibitor might inhibit many type of cell proteolytic enzymes, also can impact on multifunctional mechanisms. Ulinastatin inhibits effect production of proinflammatory cytokines.[7] Treatment using ulinastatin hasreduced blood levels of TNF-α & IL-1β. TGFβ1.There are many studies which have shownulinastatin does inhibitexpression of TNF-α &IL-1β also increaseslevels of IL-2 & IL-10.[8,9] In our cases we could clearly see the improvement in the clinical condition of the patients who were started on ulinastatin and no adverse drug reaction was noted. Even though Large scale randomized controlled trials will beneeded specially in covid 19 patients regarding its usefulness we were able to see the improvement which is contrary to the anticipated results.

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Conclusion

All our patients showed significant improvement in clinical condition and oxygenation index. Treatment with ulinastatin was found to be safe & potentially helpful for patients affected with moderate to severe COVID illness with fast improvement inclinical condition, inflammatory markers andpulmonary lesions. Multiple studies will be required in future to confirm our findings.

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