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Comparison of Sepsis in Covid 19 Infected Patients on Therapeutic Plasma Exchange Vs Tocilizumab

Amina Hussain, Imran Fazal, Sana Uruj, Asim Saleem, Natasha Sarwar

Department of Medicine, Pak Emirates Military Hospital Rawalpindi/ National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To compare the presence of sepsis in COVID 19 infected patients on therapeutic plasma exchange vs Tocilizumab managed at Pak Emirates Military Hospital Rawalpindi

Study Design: Comparative Prospective study

Place and Duration of Study: Pak Emirates Military hospital Rawalpindi, from Feb 2021 to May 2021

Methodology: Patients who were diagnosed with COVID-19 on polymerase chain reaction and were oxygen dependent but not mechanical ventilation dependent were included in the study. They were randomly divided into two groups. Group I received 3-5 sessions of plasma exchange while group II received 1-2 doses of Tocilizumab. They were followed up for 10 days to look for presence of sepsis on basis of pro-calcitonin. Type of treatment used and other factors were correlated with presence of sepsis among the target population.

Results: Out of 350 patients included in the study 201 (57.4%) were male while 149 (42.6%) were female. Mean age of the study participants was 49.69 ±9.456 years. 287 (82%) had procalcitonin within range and no evidence of bacterial sepsis while 63 (18%) were diagnosed as having sepsis on the basis of raised pro-calcitonin levels. Advanced age, presence of comorbidities and use of Tocilizumab had statistically significant relationship (p-value<0.05) with presence of sepsis among the patients managed for severe COVID 19.

Conclusion: Bacterial sepsis was found in significant number of patients with severe COVID 19 illness undergoing therapeutic plasma exchange or receiving Tocilizumab. Patients more than 40 years of age or having comorbid medical illnesses or receiving Tocilizumab instead of plasma exchange were more at risk of sepsis.

Keywords: COVID 19; Plasma exchange; Sepsis; Tocilizumab

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INTRODUCTION

Pandemics have always been included as dark chapters in the history of mankind.[1] COVID 19 was the viral pandemic illness which started from China in 2019 and spread through the whole world affecting millions of people across the globe.[2] As this hierarchy climbs up from taking precautions to managing complications, suffering of patient and burden on health system increase manifold.[3] Anti-virals, antibiotics, multivitamins, antipyretics and oxygen supplementation have been commonly used in patients with mild to moderate illness.[4] Patients with severe form of illness may require critical care support and mechanical ventilation.[5] Immunomodulatory medications and therapeutic plasma exchange have also been used in a a large number of patients with a basis that they have a protective role in managing the immune storm generated by the COVID-19 virus in human body.[6]

Correspondence: Dr Amina Hussain, Department of Medicine, Pak Emirates Military Hospital Rawalpindi Pakistan

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As this pandemic is just eighteen months old, so still clinicians and researchers trying to find out the suitable management options for COVID 19. Guaraldi et al. in 2020 concluded that this agent is useful in reducing the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia.[7] ElSeirafi et al. published five case reports in this regard, 4 of their patients had excellent response in reducing the COVID 19 symptoms but one patient had bacterial sepsis after use of Tocilizumab.[8] Valk et al. in 2020 published a rapid review for evaluation of convalescent plasma or hyper-immune immunoglobulin for people with severe COVID 19. They concluded that this therapy is effective in reducing almost all the symptoms of COVID 19 in critically ill patients including hospital and intensive care unit admission time.

Fever and anaphylactic shock was seen in two patients from the cohort they studied.[9]

Third wave of COVID 19 had struck badly in some parts of Pakistan since April 2021. A lot of patients have been presenting with severe form of

illness requiring oxygen supplementation. Clinicians have been using all the available options but very limited data has been published in this regard and that too mostly regarding the efficacy of options instead of adverse effects.[10] A clear idea regarding risk of adverse effects need to be in mind of the physicians before use of an option. We therefore planned this study with the rationale to compare the presence of sepsis in

COVID 19 infected patients on therapeutic plasma exchange vs Tocilizumab managed at Pak Emirates Military Hospital Rawalpindi.

METHODOLOGY

This comparative prospective study was planned and conducted at Pak Emirates Military Hospital Rawalpindi between February 2021 and May 2021. Sample size was calculated by using the WHO sample size calculation by using the population prevalence of sepsis in COVID 19 patients as 9.5%.[11] Non probability consecutive sampling was used to gather the sample. **Inclusion Criteria:** All the COVID-19 PCR positive patients between age of 18 and 70 years diagnosed with severe illness and required oxygen supplementation were included in the study.[12]

Exclsuion Criteria: Patients with evidence of bacterial or fungal sepsis before the administration of plasma exchange or tocilizumab or those who were on any immunosuppressant agents before the diagnosis of COVID 19 were excluded from the study. Those with any contraindication for plasma exchange or tocilizumab or refused to undergo any of these treatment options were not included in the study. Pregnant or lactating women were excluded as well. Those who required mechanical ventilation or critical care support were not included in the study as well.

Ethical approval was taken from the ethical committee of hospital via letter no

A/28/ECL27312021. Patients diagnosed with COVID-19 with severe illness requiring oxygen supplementation but not mechanical ventilation, were included in the study. They were randomly divided into two groups via lottery method. Group I received 3-5 sessions of therapeutic plasma exchange.[12] while group II received 1-2 doses of Tocilizumab (8mg/kg body weight) as per protocol.[13] As almost all the inflammatory markers get raised in patients with severe COVID 19 therefore diagnosis of bacterial sepsis was made on the basis of serum pro-calcitonin levels. Bacterial sepsis was diagnosed if serum pro-calcitonin levels were more than 0.1 ng/mL within 10 days of start of treatment.[14] Comorbid medical conditions included in the analysis were type II diabetes mellitus, Ischemic heart disease and Hypertension.

Statistical analysis was done by SPSS 24.0. Frequency and percentage were calculated for the qualitative variables like gender and presence of bacterial sepsis whereas mean and standard deviation was calculated for the quantitative variables like age of the patients included in the study. Chi-square test was used to compare the type of treatment used and other variables in patients of COVID 19 with and without sepsis after the therapeutic plasma exchange or Tocilizumab use. The *p*-value less than or equal to 0.05 was used to establish statistically significant difference.

RESULTS

A total of 350 patients with severe COVID 19 illness were included in the final analysis. Out of these 350, 201(57.4%) were male while 149(42.6%) were female. Mean age of the study participants was 49.69 ±9.456 years. Table-I summarizes the general characteristics of patients of COVID 19 included in the study. 287(82%) had pro-calcitonin within range and no evidence of bacterial sepsis while 63(18%) were diagnosed as having sepsis on the basis of raised pro-calcitonin levels. Table-II shows the results of chi-square analysis. It was revealed that advanced age (*p*-value-0.015, presence of comorbidities (*p*-value<0.001) and use of Tocilizumab (*p*-value<0.001) had statistically significant relationship with presence of sepsis among the patients managed for severe COVID 19 while gender had no such relationship (*p*-value-0.372).

Table-I: Characteristics of Study Participants

Study parameters	n(%)
Age (years)	
Mean±SD	49.69 ±9.456 years
Range (min-max)	20 years – 63 years
Gender	
Male	201 (57.4%)
Female	149 (42.6%)
Treatment received	
Therapeutic plasma exchange	201 (57.4%)
Tocilizumab	149 (42.6%)
Presence of sepsis	
No	287 (82%)
Yes	63 (18%)
Presence of Comorbidities	
No	259 (74%)
Yes	91 (26%)

Table-II: Comparison of Various Variables Including Type of Treatment Used Among Patients of Severe Covid 19 With And Without Sepsis

Factors studied	Patients without sepsis	Patients with sepsis	*p*-value
Age			
<40 years >40 years	119(41.5%) 168(58.5%)	16(25.4%) 47(74.6)	0.015
Gender			
Male Female	168(58.5%) 119(41.5%)	33(52.4%) 30(47.6%)	0.372
Type of treatment			
Tocilizumab Therapeutic plasma exchange	105(36.5%) 182(63.5%)	44(69.8%) 19(30.2%)	<0.001
Presence of comorbidities			
No Yes	225(78.4%) 62(21.6%)	34(53.9%) 29(46.1%)	<0.001

DISCUSSION

Mankind has always suffered from pandemics and millions of lives have fell prey to them over the years.1 COVID 19 is no exception to this and initially considered as similar to viral flu has now caused significant mortality and morbidity among individuals of all age groups across the globe.[2] Various management options both supportive and curative have been tried in last few months for these patients especially those with severe form of illness. Various trials have been published to establish the efficacy of these agents but limited data is available regarding the adverse effects related to them.

Mushtaq *et al*.[15] published their experience of Agha Khan University Hospital Karachi regarding outcome of COVID-19 patients with use of Tocilizumab. They revealed that more than 2/3rd of their patients showed significant improvement in oxygen requirement, inflammatory parameters and chest x-rays. They recommended that this medication could be promising treatment option for patients with severe COVID illness but with keeping a close eye on adverse effects. They did not study any specific adverse effects but results of our study concluded that risk of bacterial sepsis may increase with use of this agent.

Vu *et al*.[16] in 2020 published a study in Bio Medical Central infectious diseases to look for effects of Tocilizumab in COVID-19 patients. They found out that it was an effective management strategy for patients with severe symptoms of COVID 19 but infection rate was slightly higher and around 26% of their patients had developed infectious complications during the course of treatment. We did not study efficacy of Tocilizumab among our study participants but our results supported results of Vu et al. in a sense that our patients also had significant infectious complications or sepsis during the course of treatment.

Balagholi *et al*.[17] in 2020 published an interesting paper regarding role of therapeutic plasmapheresis in treatment of COVID-19 patients. They found out that this procedure is effective for managing these patients especially patients with severe illness. They concluded that adverse effects related to this procedure are usually mild. They did not mention sepsis or infectious complication as a significant side effect related to use of this procedure in COVID 19 patients. Very few of our patients undergoing therapeutic plasma exchange developed sepsis. It was significantly less as compared to use of Tocilizumab.

Research has been done to look for complications of therapeutic plasma exchange. Lu *et al*.[18] in 2019 summarized that usually mild complications occur among patients undergoing plasma exchange. Out of 435 patients undergoing 1201 procedures they found only one patient suffering from Cryptococcus infection leading to sepsis. Our results also revealed that sepsis was seen less in patients treated with plasma exchange as compared to use of Tocilizumab.

Cause and effect relationship with therapeutic modalities and presence of sepsis is very difficult to establish with this design and that is one of the main limitations of this study. Though we tried to control the confounders by strict inclusion/exclusion criteria but still multiple factors in patients with severe COVID admitted in hospital may contribute to infectious complications among these patients.

CONCLUSION

Bacterial sepsis was found in significant number of patients with severe COVID 19 illness undergoing therapeutic plasma exchange or receiving Tocilizumab. Patients more than 40 years of age or having comorbid medical illnesses or receiving Tocilizumab instead of plasma exchange were more at risk of sepsis.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AH & IF: Data acquisition, data analysis, critical review, approval of the final version to be published.

SU & AS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

NS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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