International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 11 November 2023

Page No: 2717-2722

DOI: https://doi.org/10.47191/ijmscrs/v3-i11-33, Impact Factor: 6.597

Early and Timely Use of Hemofiltration Therapy with Poly Methyl Meth Acrylate (PMMA) Filters in Severe COVID-19 Adult Respiratory Distress Syndrome Patients: A Single Centre Study in India

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ABSTRACT

A high Interleukin-6 (IL-6) level in COVID-19 plays a major role in the pathophysiology and is considered a reliable parameter in predicting the adversity of the disease. In COVID-19. Extracorporeal blood purification has been proposed as an adjuvant therapy and it aims at controlling the dysregulation in the immune system. Essentially, it lowers the upregulated levels of several mediators and therefore controls the cytokine storm, instead of actively targeting individual pathways of inflammation. Positive IL-6 balance post-Polymethyl methacrylate (PMMA) filter used for Cytokine storm in COVID-19 patients with dialysis has shown to be an independent predictor of mortality. A retrospective analysis of seventeen patients wherein hemofiltration was used for cytokine storm with dialysis, sepsis, and septic shock. The inflammatory markers post-hemofiltration sessions were supervised to understand hemofiltration's efficacy. The average age of the patients was 70.2 (18.2) years. They were classified as responders or non-responder groups based on the decrease or no change/ increase respectively between the pre-and post-filtration IL-6 levels. A 3.6-fold increase was noticed in non-responders (N=11) for IL-6 levels post hemofiltration. Responders demonstrated a 21.4% ($p<0.05$) reduction in IL-6 levels post hemofiltration. Of these, 4 who survived demonstrated a decrease in IL-6 levels of 66.2%. Of 10 non-responders, none survived. However, the survival rate was 71.43 percent among the responders. There was a significant statistical difference in the mortality rate between the two groups ($p= 0.003$).Cytokine storm, an overwhelming immunological response in COVID-19 patients, can be controlled successfully by the early and timely use of hemofiltration therapy with PMMA filters like Hemofeel. However, patients with higher positive IL-6 balance post-hemofiltration may be associated with limited outcomes.

KEYWORDS: Hemofeel, Respiratory Distress, Covid-19, Cytokine Removal, Adjunct Therapy

ARTICLE DETAILS

Published On:
13 November 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Severe Adult Respiratory Syndrome COVID 2 (SARS CoV-2) infections may be asymptomatic or cause only mild symptoms in the majority of the cases, moderate in few, and severe in nearly 10–20% of the inflicted, especially in the geriatric group, and comorbidities which may progress to interstitial pneumonia and acute respiratory distress syndrome (ARDS) [1]. These patients with ARDS present a dysfunctional immune system with an imbalanced immune response, leading to a typical "cytokine storm" associated with lung injury facilitating severe pneumonia with hypoxia and vascular injury [2]. Cytokine storm is typically modulated by interferon-gamma, tumor necrosis factor-alpha, interleukin (IL)-17, IL-8, and IL-6 released by host cells in response to damage-associated molecular patterns (DAMPS) and pathogen-associated molecular patterns (PAMPs) [3,4]. This immunological complication requires an anti-inflammatory treatment in addition to antiviral therapy [5]. The latter may have already been taken care of, but the residual unattended damage needs attention at the earliest. The immunosuppressive and immune modulatory drugs such as Corticosteroids (CS), Chloroquine (CQ), Hydroxychloroquine (HCQ), IL-6 receptor antagonists including Tocilizumab (TCZ), Interleukin-1 antagonists including Anakinra, TNF inhibitors, Janus kinase inhibitors, Itolizumab that binds to CD6 which modulates T-lymphocyte activation and proliferation, intravenous immunoglobulin (IVIG), and Colchicine are utilized for treatment [1,6,7]. Apart from these drugs, Removing PAMPS, such as endotoxin or cytokines, also seems promising. The removal of circulating immune modulatory mediators may prevent organ damage or mitigate organ failure in patients with COVID-19 [8]. IL-6 has a molecular weight of 22kDa which drives the overactive inflammatory response to induce the cytokine storm [9,10]. Meta-analysis of nine studies from January 1 to February 2020 demonstrated that increased IL-6 level on admission was associated with an increased likelihood of mortality in COVID-19 patients (Q: 0.01, 95% CI: 0.01-0.03; P = .03) [11,12]. Therefore, hemodialysis membranes that can clear these mediators may be of utility in reducing the cytokine storm and Thu the disease progression. The widely recognized cytokine removal using blood purification includes convection, diffusion, and adsorption. Poly Methyl Meth Acrylate (PMMA) based filters combine three mechanisms for removing cytokines like IL-6 and IL-8.9 These cytokines are filtered and adsorbed by the Hemofeel hollow fibers [9]. As a result, only minimal amounts of IL-6 and IL-8 are detected in the filtrate samples [9]. On the other hand, Quiroga et al. showed positive IL6 balance (i.e.-rising levels of IL6Post Dialysis with PMMA filter) from their study in COVID-19 patients to be an independent predictor of mortality [3]. Thus, not only should IL-6 be removed by specific membrane-based filters, but treatment should also be applied before it is accumulated. At our tertiary care center, patients were treated with continuous venovenous hemodiafiltration using a Poly Methyl Meth Acrylate (PMMA) (PMMA) membrane hemofilter (Hemofeel CH-1.8W; Toray, Tokyo, Japan) for acute kidney injury with cytokine removal therapy and ARDS.

MATERIALS AND METHODS

From August to December 2020, 162 infected severe COVID-19 pneumonia patients were admitted to the ICU at the Seven Hills facility of Sir H. N. Reliance Foundation Hospital and Research Centre,Mumbai. Among these, we retrospectively analyzed data from 17 patients in whom hemofiltrationwas used to remove rising IL-6 levels; some also required hemodialysis. Given the retrospective nature of the study, the Institutional Ethics Committee (IEC) waived off the requirement for written informed consent dated May 20, 2021, IEC number HNH/IEC/2021/ OCS/ CCM/53. The data was collected in the form of demographic variables, comorbidities, COVID-19 pneumonia severity index (APACHE II score, CT Severity Index - CTSI, PaO_2/FiO_2 (P/F ratio) on admission, ventilator-related data, vasopressor requirement, pre-as well as post-hemofiltration data on IL6, D:Dimer and CRP levels, dialysis duration, length of ventilator support, ICU, and hospital stay were also collected. During disease, patients with rising IL6 levels, worsening P/F ratio, increasing oxygen therapy, worsening renal parameters like rising creatinine levels, and drop in urine output requiring ventilatory support was subjected to hemofiltration along with pharmacological therapy, including immune-modulators like Tocilizumab (TCZ). We used a PMMA membrane hemofilter – Hemofeel, to remove IL6 and reduce terminal-organ damage. The majority of these patients also succumbed to acute kidney injury warranting hemodialysis at a later stage. Hemofeel was used intermittently for 6 to 8 hours and sometimes for an extended period of 12 hours in patients with higher IL-6 levels or worsening organ failure. We monitored the inflammatory markers post-hemofiltration session to understand hemofiltration's efficacy. Patients were subjected to two to three hemofiltration sessions twenty-four hours apart. Categorical data are expressed as numbers and percentages, and continuous variables are expressed as median and 25th and 75th percentile. Mann-Whitney test was used for continuous data to find any significant differences between the two groups. Within the group, statistical data analysis between pre- and post-hemofiltration was carried out using the Wilcoxon-Signed Rank Test. In contrast, the Chi-square Test for categorical data tested significant distribution differences. Yate's correction was used where at least one cell had a number less than 5. Data of survivors were analyzed in terms of increase or decrease in percentages as surviving patients were few. A two-tailed P-value of <0.05 for all analyses have been considered statistically significant. All statistical analyses have been performed using IBM SPSS 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

RESULTS

Patients whose plasma IL-6 levels were reduced post-hemofiltration sessions were categorized as **Responders (N=7).** The plasma IL-6 levels that continued to rise or remained persistently high were categorized as **Non–non-responders (N=10)**.

***Demographic and Comorbidity Variables*:** Table 1 presents demographic and comorbidity data of responders (N=7) or non-responder group (N=10). The average age of these patients was 71.3 (18.2) years. Within Responders, 6 out of

7 patients had IHD, while in the non-responder group, out of 10,only 1 had IHD.

COVID-19 pneumonia severity index: There was no significant difference in severity indices between the non-responders and responders as seen in Table 2.

Inflammatory markers: Pre- and post-hemofiltration data of inflammatory markers are shown in Table 3**.** Compared to non-responders, pre-hemofiltration levels of IL-6 and CRP were lower in responders, while D-Dimer was higher. However, the differences are not statistically significant. Post-filtration, the level increased to 408.95 among the non-responders and reduced to 16.35 among the responders. Post hemofiltration, CRP increased to 15.10 among the non-responders and reduced to 5.94 among the responders. Additionally, post-filtration, D-Dimer levels increased to 1115.18 for non-responders and reduced to 750.96 for the responders.As shown in Figure 1 shows the mortality difference between the two groups. Of 10 non-responders,none of them survived. However, the survival rate was 71.43 percent among the responders. The two groups can see a significant statistical difference in the mortality rate (p= 0.003).

Treatment Variables: Present data on non-invasive ventilation, ventilation, and hemofiltration treatment is shown in Table 4. Responders required Oxygen therapy, Non-invasive ventilation (NIV), and Mechanical ventilator (MV) support for 5, 6, and 1 day respectively. Conversely, the non-responders were on Oxygen therapy, NIV, and Mechanical ventilation for 1, 1, and 4 days respectively.The median time to initiate hemofiltration after ICU admission for non-responders was four days,compared to 6 days for responders and survivors before intubation. The duration of hemofiltration of non-responders was 24 hours compared to 16 hours for responders and survivors. Among non-responders, all the patients required vasopressors pre- and post-hemofiltration. None of the patients in the responder group required a vasopressor before hemofiltration.

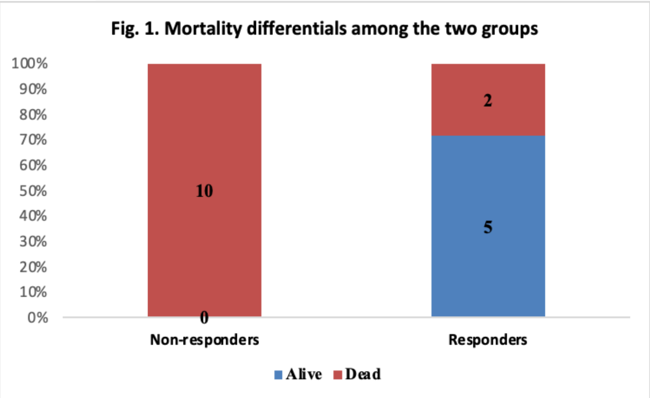

Figure 1. Mortality differentials among the two groups.

DISCUSSION

Increased serum IL-6 in COVID-19 has been established as a marker and an effector of the disease [12]. In the present study, we have seen that patients who demonstrated reduced IL-6 levels and survived and were subjected to hemofiltration before intubation. Thus, removing IL-6 before its accumulation and subsequent damage helped the patient handle the disease well.While ten out of eleven non-responders were those in whom hemofiltration was taken as a last resort when they were already on the ventilator, in these patients post-hemofiltration, IL-6 levels had increased notably, suggesting that production of this cytokine exceeded the clearance and there wascollateral damage.Tocilizumab (TCZ), an IL6 blocker, was used in both groups; however, the reduction in IL-6 levels was observed only in the responders, likely on account of hemofiltration. Although patients treated with TCZ treatment demonstrated symptomatic improvement in the resolution of hypoxemia [5, 13-16], this drug has also shown a tendency for infections and hepatotoxicity [17]. Therefore, another viableoption for IL-6 removal is hemofiltration therapy with the help of PMMA-based filters. Hemofeelcombines the properties of convection, diffusion, and adsorption to remove IL-6 and IL-8 molecules 137[18].There is no homogeneity in terms of their inflammatory phenotype amongst patients and they havewidely varying levels of cytokines in their blood (e.g., IL-6 can range from <10 to >1 million pg./mL)[19]. Applying hemofiltration to all patients may be beneficial only for some, have no effect, or eveninjure others. Therefore, specific criteria should be defined. Quiroga et al., in their prospective single-center study of 16 patients, dialyzed using a PMMA filter, did observe a reduction of IL-6 in survivorspost hemofiltration but not in non-survivors [3], which was similar to our findings. Banshodani et al.conducted a combination of pharmacological treatments and renal replacement therapy (RRT) withPMMA filters for hemodialysis (HD) patients with COVID-19 and demonstrated positive findings [20].Blood purification has been proposed as a possible adjuvant therapy for critically ill patients with COVID-19. In the present study, the use of Hemofeel before hemodynamic compromise improved by reducing IL-6 and vasopressor support. Moreover, the use of hemofiltration before the onset ofincremental use of oxygen or organ damage like lung, reduction in IL-6 levels, reduction in progress of organ failure, reduction in requirement of invasive ventilation, and mortality.With the evolving guidelines on the treatment of COVID-19 ARDS, we employed hemofiltration as an adjunct to steroid therapy for cytokine removal. An invasive procedure accompanied by a financial burden; it was opted in a few patients. Some of these patients were already on the ventilator with multiple vasopressor support & they progressed to multi-organ failure, likely due to severe cytokine storm, and showed no

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change in their outcomes. These patients were also found to have a positive IL-6 balance post hemofiltration, rendering the therapy futile. However, hemofiltration was used inn some patients before intubation or even before the initiation of vasopressor support to curtail the overproduction of cytokines, and we found a better response. We could avoid intubation and prevent progression to multi-organ failure, although there are limited survivors.The limitation of our study is the sample size; given the benefit, we believe that the therapy could have a good potential and safety margin in the treatment of such conditions as COVID-19, rather than the unknown long-term effects of immunosuppression therapy. Being a retrospectiveobservation study, we are unable to cut off the value for Hemofiltration with Hemofeel at this point, however clinical worsening of the disease was used as a surrogate marker for inititation of hemofiltration.

CONCLUSION

Cytokine storm, an overwhelming immunological response in COVID-19 patients, can be controlled successfully using hemofiltration therapy with PMMA filters like Hemofeel. However, patients with higher positive IL-6 balance post hemofiltration may be associated with limited outcomes.

ACKNOWLEDGMENT

The authors are thankful to Sir HN Reliance Foundation Hospital and Research Centre for giving the necessary permission to conduct the study.

REFERENCES

I. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020; 39(7): 2085-2094. doi: 10.1007/s10067-020-05190-5.

II. Wong CK, Lam CW, Wu AK, Ip WK, Lee NL, Chan IH, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin. Exp. Immunol. 2004; 136: 95–103.

III. Quiroga B, Muñoz Ramos P, Giorgi M, de Santos A, Núñez A, Ortiz A, et al. Dynamic assessment of interleukin-6 during hemodialysis and mortality in coronavirus disease-19. Ther Apher Dial. 2021; 25(6): 908-916. doi: 10.1111/1744-9987.13626.

IV. Feng Y, Peng JY, Peng Z. Blood purification in sepsis and systemic inflammation. Curr Opin Crit Care. 2021; 27(6): 582-586.
doi: 10.1097/MCC.0000000000000890.
PMID: 34581298.

V. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti- inflammatory treatments. Lancet Infect Dis. 2020; 20(4): 400–402. doi: 10.1016/S1473-3099(20)30132-8.

VI. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol. 2020; 38(2): 337–342.

VII. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the experience of clinical immunologists from China. Clin Immunol 2020; 108393.

VIII. Nadim MK, Forni LG, Mehta RL, Connor MJ, Liu KD, Ostermann M et al. Publisher correction: COVID-19-associated acute kidney injury: consensus report of the 25(th) Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020; 16: 765.

IX. Harm S, Schildböck C, Hartmann J. Cytokine Removal in Extracorporeal Blood Purification: An in vitro Study. Blood Purif. 2020; 49(1-2): 33-43. doi: 10.1159/000502680.

X. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B et al. COVID-19: immunopathogenesis and Immunotherapeutics. Sig Transduct Target Ther 2020; 5: 128. https://doi.org/10.1038/s41392-020-00243-2.

XI. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. J Med Virol. 2020; 92(11):2283-2285.
doi: 10.1002/jmv.25948..

XII. Ulhaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Med Mal Infect. 2020; 50(4): 382-383.
doi: 10.1016/j.medmal.2020.04.002.

XIII. Ferro F, Elefante E, Baldini C, Bartoloni E, Puxeddu I, Talarico R, et al. COVID-19: the new challenge for rheumatologists. Clin Exp Rheumatol. 2020; 38(2): 175–180.

XIV. McIntosh K (2020) Coronavirus disease 2019 (COVID-19). Edited by Martin S Hirsch. UpToDate, https://www.uptodate com/contents/coronavirus-disease-2019-COVID-19.

XV. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng V et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis 2020; ciaa478. 10.1093/cid/ciaa478

XVI. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020 May 19;117(20):10970-10975.
doi: 10.1073/pnas.2005615117.

XVII. Jones G, Ding C. Tocilizumab: a review of its safety and efficacy in rheumatoid arthritis. Clin Med Insights: Arthritis Musculoskelet Dis. 2010; 2010(3): 81–89. doi: 10.4137/CMAMD.S4864.

XVIII. Harm S, Schildböck C, Hartmann J. Cytokine Removal in Extracorporeal Blood Purification: An in vitro Study. Blood Purif. 2020; 49(1-2): 33-43. doi: 10.1159/000502680.

XIX. Kellum JA, Pike F, Yealy DM, Huang DT, Shapiro NI, Angus DC, et al. Relationship between alternative resuscitation strategies, host response and injury biomarkers, and outcome in septic shock: analysis of the protocol based care for early septic shock study. Crit Care Med. 2017; 45(3): 438–45.

XX. Banshodani M, Shintaku S, Kawanishi H. Combination therapy for COVID-19 in hemodialysis patients: Pharmacological treatments and renal replacement therapy based on the severity. Therapeutic Appheresis and Dialysis 2022; 26(2): https://doi.org/10.1111/1744-9987.13737.

Table 1: Demographic covariates and comorbidities

Covariates	Non-responders (n=10)		Responders (n=7)		Total (N=17)		
	N	%	N	%	N	%	p-value
Mean age and SD	71.00 ± 7.73		71.71 ± 9.21		71.29 ± 8.10		0.905
Gender							0.350
Females	7	70.00	3	42.86	10	58.82	
Males	3	30.00	4	57.14	7	41.18	
DM							0.304
No	5	50.00	1	14.29	6	35.29	
Yes	5	50.00	6	85.71	11	64.71	
HTN							0.603
No	3	30.00	1	14.29	4	23.53	
Yes	7	70.00	6	85.71	13	76.47	
CKD							1.000
No	8	80.00	5	71.43	13	76.47	
Yes	2	20.00	2	28.57	4	23.53	
IHD							0.004
No	9	90.00	1	14.29	10	58.82	
Yes	1	10.00	6	85.71	7	41.18	

Table 2: Severity scores in the two groups

Covariates	Non-responders (n=10)		Responders (n=7)		Total (N=17)		
	Median	IQR	Median	IQR	Median	IQR	p-value
APACHE Score	12.00	4.00	11.00	7.00	12.00	6.00	0.943
CTSI Score	13.50	14.00	18.00	6.00	16.00	7.00	0.402
CORAD Score	6.00	0.00	5.00	1.00	6.00	1.00	0.290
P/F (at admission)	107.50	37.00	102.00	63.00	105.00	37.00	0.905
P/F (at intubation	51.50	24.00	45.00	14.00	51.00	12.00	0.327
Base creatinine level	1.33	2.48	1.12	5.62	1.26	2.48	0.813

Table 3. Inflammatory markers, pre- and post-hemofiltration among the two groups.

Covariates	Non-responders (n=10)		Responders (n=7)		Total (N=17)	
	Median	IQR	Median	IQR	Median	IQR
Pre-IL6	166.65	712.23	46.06	216.56	139.70	183.44
Post-IL6	408.95	1193.60	16.35	196.20	151.00	574.73
Pre-CRP	9.42	7.96	7.82	10.00	8.47	7.59
Post-CRP	15.10	10.80	5.94	15.58	15.00	14.41
Pre-DDIMER	766.50	760.55	1367.00	3614.84	968.00	1196.77
Post-DDIMER	1115.18	7187.00	750.96	5057.37	1051.00	4647.37

Table 4. Outcome differentials among the two groups

Covariates	Non-responders		Responders		
	Median	IQR	Median	IQR	p-value
Days on ventilator	4	16	1	25	0.488
Days on oxygen mask	1	2	5	10	0.276
NIV days	1	1	6	8	0.247
Days after ventilation hemofiltration started	4	32	6	7	0.406
Duration of hemofiltration	24	36	16	12	0.441