

COMPLICATIONS OF PLASMAPHERESIS IN COVID-19 PATIENTS AT PAKISTAN AIR FORCE HOSPITAL MUSHAF

Hania Afzal, Muhammad Asif Naseer, Muzammil Khalid

Pakistan Air Force Hospital Mushaf, Sargodha Pakistan

ABSTRACT

Background: Plasmapheresis is a method of blood purification in which blood plasma and components are removed and treated from blood circulation. With advances in treatment of COVID-19, plasma exchange was found effective against disease complicated by cytokine storm syndrome. Plasmapheresis was started in our setup in January 2021. Study was conducted to observe adverse events related to procedure.

Material and Methods: A hospital based descriptive case series was conducted from January 2021 to June 2021, in Pakistan Air Force Hospital Mushaf, Sargodha, Punjab, Pakistan. Adverse events like hypocalcemia, hypotension and cardiac arrest were observed in 44 plasmapheresis sessions. Data was collected by generating a proforma and was analyzed by using IBM SPSS. v.24.

Results: Data from our study revealed that complications were seen in 25% of plasmapheresis sessions with most of the complications being minor and easy to manage and fatal events in 0.04% cases only. Complication during maintenance of Intra Venous line was seen in only one session, during procedure in 2 sessions and after procedure in 8 sessions. The only complication related to maintenance of Intra Venous access was atrial fibrillation in a single case^[1]. Complications seen during procedure included hypotension in 1 session and cardiac arrest in one. Adverse events seen after plasmapheresis were apprehension & palpitation in one case, drowsiness in one, drowsiness and Surgical Emphysema at Intra Venous access site in one, Hypocalcemia in three, Hypocalcemia with drowsiness in one and Hypomagnesemia in one case.

Conclusion: After interpretation of analysis and reviewing literature, it was seen that plasmapheresis is a safe procedure if it is used with caution and professional expertise.

Key Words: Plasmapheresis, Cytokine Storm, Adverse Effects, Complications, COVID-19

BACKGROUND

Plasmapheresis is a method of blood purification in which blood plasma and components with large molecular weight are removed and treated from blood circulation and then returned to it.² This method is being used as a treatment modality in different disease states for many decades. Plasmapheresis was well established in late 70's. Dr. Emil Freireich was the pioneer in using this procedure in different types of leukemias and other malignancies³

With advances in treatment of Corona Virus Disease of 2019 (COVID-19), plasmapheresis was found effective against disease complicated by cytokine storm syndrome.^{4,5,6}

Cytokine Storm, being predictor of mortality and

disease severity, is frequently seen in severe infections with *SARS*, *MERS* and *Influenza* as well as in *COVID-19*.^{7,8} Cytokine storm is the release of excessive amounts of cytokines (tumor necrosis factors, chemokines, interleukins, interferons, colony stimulating factors etc.) from cells of immune system into blood.

After receipt of data regarding its efficacy, plasmapheresis is being used in critically ill COVID-19 patients, complicated by cytokine storm and respiratory failure in PAF Hospital Mushaf after taking informed consent from patient's attendants. This treatment modality was started in this setup in January, 2021 by using Spectra Optia Apheresis system (an alternate to COBE spectra device).⁹ Fresh frozen plasmas are being used as an exchange fluid.

A case study of 31 patients was conducted in Oman which revealed beneficial role of therapeutic plasma exchange in COVID-19 patients with higher extubation rate and decreased mortality.⁵ A study was published in Dec 2020 which reviewed the beneficial role of therapeutic plasma exchange in COVID-19 patients and its complications.¹⁰

Correspondence: Dr. Hania Afzal, Department of Medicine, Sargodha Pakistan

Email: haniaafzal96@gmail.com

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A hospital based descriptive case study was conducted at PAF Hospital Mushaf to assess the adverse events and complications in patients while preparing for plasmapheresis, during the procedure and after completion of the process. So that, the effective treatment modality against the novel corona virus disease can be used in a safer way. A separate study was conducted in same setup to assess beneficial role of plasmapheresis in COVID-19 patients.

MATERIAL AND METHODS

A hospital based descriptive case series was conducted for six months duration i.e. from January 2021 to June 2021 in COVID ITC of PAF Hospital Mushaf to observe adverse effects of plasmapheresis in COVID-19 patients. Study included all plasmapheresis sessions performed during the study interval i.e. 44 sessions performed in 13 COVID-19 patients complicated by cytokine storm and having respiratory failure. Procedure was performed after taking informed written consent from attendants of all patients.

Patients who received plasmapheresis therapy were observed for complications along with review of their medical records. For plasmapheresis, Spectra Optia apheresis system was used. Fresh Frozen Plasma from healthy donors was used as an exchange fluid with anticoagulant and normal saline. Data was collected by using a self-generated Performa filled while directly observing patients and with review of their medical records. Data was analyzed by using IBM SPSS.V.24. Study included critically ill patients with COVID-19 pneumonia having

- Positive/negative PCR for SARS COV-2
- >50% lung involvement on CT Chest and
- Raised inflammatory markers including IL-6, serum ferritin, LDH and D-Dimers

Operational Definitions:

Adverse events: Any unexpected medical problem related to technique, instrument or procedure of plasmapheresis.

Serious Adverse event: Any adverse event leading to death or directly causing death of patient.

Causality of adverse event with procedure: Causes of adverse events related to procedure.

RESULTS

In our study 44 plasmapheresis sessions were performed in 13 critically ill COVID-19 patients. In 27 sessions, patients had positive PCR for SARS COV 2. In other cases patients had negative PCR but were diagnosed as case of COVID-19 pneumonia clinically. The positive percentage was 61.4% while the negative percentage was 38.6%. All sessions were performed in patients with greater than 50% lung involvement on CT scan chest. For twenty-two Plasmapheresis sessions IV access was secured in Right Femoral Vein, for twenty-one sessions in Internal Jugular Vein, and for only a single session IV line was maintained in Right Subclavian vein. Complication during maintenance of IV access, developed in only one case, i.e. atrial fibrillation ^[1], in which IV line was placed in Right Subclavian vein i.e. 2.3% (Figure-I).

No anaphylactic reaction was observed. Complications were found during two out of 44 sessions (Table-I), i.e. 4.5%. One of the complications was hypotension, which was managed with IV Phenylephrine. The other was sudden cardiac arrest just after starting plasmapheresis leading to death of patient. Cause of death could not be confirmed as consent for autopsy was not granted by attendants.

Prophylactic Calcium Gluconate was given before 7 plasmapheresis sessions only.^{14,15} Adverse events seen after plasmapheresis were, apprehension & palpitation in one case, drowsiness in one, drowsiness and Surgical Emphysema at IV-line site in one, Hypocalcemia in three, Hypocalcemia with drowsiness in one case and Hypomagnesemia in one case (Figure-II).

Data compilation of all 44 sessions revealed that adverse events were observed in 11 plasmapheresis sessions with a cumulative percentage of 25%. Most of them are minor and can easily be dealt with. Fatal events were seen in 2 sessions only i.e 0.04%.

Table-I: Complications during Plasmapheresis (cross tabulation)

		What was the complication			Total
		Hypotension	Cardiac Arrest		
Complications during procedure	Yes	2	1	1	2
	No	42	0	0	42
Total		44	1	1	44

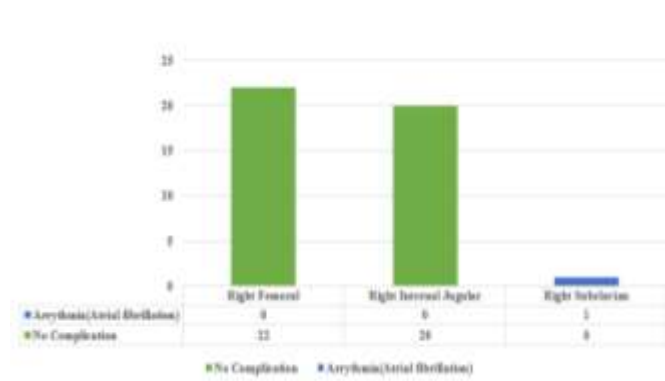


Figure-I: IV access and complications related to the site of insertion.

DISCUSSION

Plasmapheresis and other modalities to overcome cytokine storm were found effective in life threatening COVID-19 infections^{11,4,6,12} but there are few complications which are related to procedure and can cause morbidity and mortality. Different studies have been conducted across the globe for decades to assess the complications of plasmapheresis in different settings and diseases. Our study and literature revealed that different factors can have impact on adverse effects related to plasmapheresis like underlying disease, type of vascular access, type of replacement fluid and type of anticoagulation. Vascular access complications can be infections and others as for vascaths. Procedural problems can be hypocalcemia (due to citrate anticoagulants), hypotension due to vasovagal response, hemolysis and air embolism. Replacement fluid effects can be transfusion related reaction, coagulopathy, removal or dilution of drugs, hypothermia, infections, anemia, hepatitis, electrolyte imbalance, sepsis and hypoproteinemia.

A study in Iran showed role of plasmapheresis in COVID-19 and concluded that main factor in success of therapy is in starting therapy at early stages of inflammation. Study also revealed, safety of technique in COVID-19 patients. In this study use of albumin as an exchange fluid was considered to be associated with complications like reduction of immunoglobulins and coagulopathy as COVID-19 patients are already at risk of coagulopathy and use of albumin instead of FFPs may increase the risk of bleeding and depletion of procoagulant factors. Study suggested that a potential complication with plasmapheresis was removal or dilution of antivirals or steroids. So these drugs must be administered after procedure.¹⁰

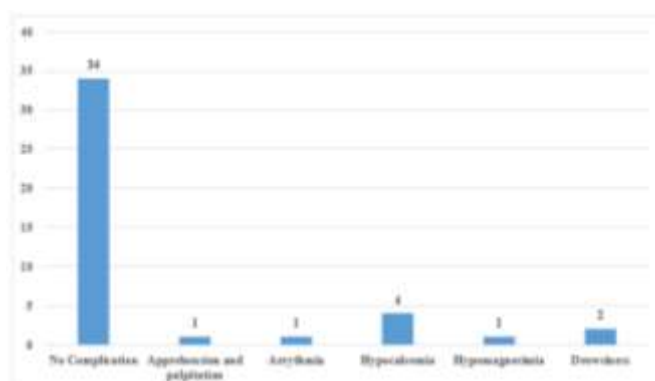


Figure-II: Side effects of plasmapheresis.

Keeping in view of all available data plasmapheresis was started in our setup in patients of Novel Corona Virus, complicated with cytokine storm and respiratory distress syndrome.

We used Calcium Gluconate prophylactically in 7 plasmapheresis sessions as it was supported by previous studies. A study published in 2018 compared two methods of Calcium gluconate administration during therapeutic plasma exchange, one method was use of 5ml of 10% Calcium Gluconate in 500ml of replacement fluid and other was IV infusion of 2g Calcium Gluconate in 50mL normal saline at 25ml/hr. First method was found better with lesser hypocalcemic events but more use of Calcium Gluconate.¹⁴ In other study, 2g of Calcium Gluconate was given in 50ml Normal saline either at rate of 1.0 or 1.6 g/hr. Hypocalcemic events were seen in 5 of 17 sessions with 1.0g/hr but in 0 of 17 with 1.6 g/hour.¹⁵ In our setup we used 10ml of 10% calcium gluconate in 100ml of Normal Saline.

Complications related to plasmapheresis were studied in past for different diseases but no such studies are conducted in patients of COVID-19, so complications are compared with procedure done in other diseases.

A study was published in Journal of Clinical apheresis in which retrospective review of 3624 sessions in 401 patients was done. In 67.7% of those procedures 80% albumin and 20% saline was used, while in remaining procedures albumin alone was used as replacement fluid. It was concluded that partial use of saline was associated with greater risk of hypotension.¹³

A prospective observational study was conducted in India regarding effect of Double filtration plasmapheresis on various plasma components. Study revealed that bleeding complications were seen in only

those cases in which fibrinogen level was lesser than 50% and hypocalcemic events were lesser with use of effluent albumin concentration as replacement fluid ^[16]. A paper was published in 2014, which revealed complications of plasma exchange in patients with Thrombotic Thrombocytopenic purpura and related microangiopathic anemias. Results showed that overall percentage of complications was low with 6.45% venous thrombotic events, 6.45% allergic plasma reactions with only 1 acute anaphylaxis, 9.6% citrate reactions and 8.3% line associated infections.¹⁷

A study was conducted to analyze incidence of plex related complications in ICU patients. Study documented episodes of hypotension in 8.4%, arrhythmia in 3.5%, fever with chills in 1.1% and paresthesias in 1.1% procedures.¹⁸

A study was published in 2012, which was based on concepts, mechanisms and overview of apheresis guidelines. Study revealed that frequency of complications with plasma exchange is different in literature and depends on whether an effect is considered complication or not. Study reported that in an older study, rate of complications was 17% with 6.14% severe reactions and newer studies had more divergent data ranging between 4.75% and 36%.¹⁹

An article was published in Journal of Clinical Apheresis in which 883 plasma exchange sessions were analyzed retrospectively for complications and their causes. Study concluded that adverse events were present in 25.6% procedures, with 13.7 % being mild, 11.0% moderate and only 0.7% were severe adverse effects including 0.4% anaphylaxis and 0.3% sepsis. Complications were more common in patients with neurological disorders.²⁰

In an article data was compiled of prospective examination of 1727 plasma exchange sessions. Total 889 complications were observed in 614 or 36% of treatments. Most of the complications were minor with fever in 7.7%, urticaria in 7.4% and hypocalcemia in 7.3% treatments. Complications were seen in 42% of sessions with Fresh Frozen Plasma and in 30% with Albumin Saline as an exchange fluid. Hypotension was more common in sessions with Albumin saline as an exchange fluid.²¹

A study analyzed data of 4857 plasma exchange sessions retrospectively and reported that total 231(4.75%) adverse events were seen. Paresthesias being the most common was seen in 2.7%, hematoma

at site of IV access in 2.4%, clotting in 1.7%, urticaria in 1.6% and bleeding in 0.06% cases. The incidence of life threatening adverse effects was 0.12% and true anaphylactoid reactions were seen in only 5 cases. Use of prophylactic Calcium and potassium lead to lesser electrolyte disturbances.²²

It was revealed in a research that hemolysis was the most common complication of Double Filtration Plasmapheresis and occurred in 20% of patients. Hypotension was reported in 3.3% sessions and in 17% sessions Vascular-access-related complications were seen. One episode of bleeding was reported due to overt coagulopathy.²³

CONCLUSION

Based on literature and results of this study, it is concluded that plasma exchange is associated with adverse events which are related to technique, exchange fluid used and coagulopathy. Out of complications and adverse events most of the adverse events observed are of minor significance only. Patients can get more benefits and lesser side effects if plasma exchange is started earlier in COVID-19. Further benefits can be achieved with administration of electrolytes like calcium gluconate prophylactically.

CONFLICT OF INTEREST

Authors declare no conflict of interest

CONTRIBUTION

Hania Afzal: Conception, the acquisition, analysis, interpretation of data and manuscript writing.

Muhammad Asif Naseer: Conception, the acquisition, analysis, interpretation of data and manuscript writing.

Muzammil Khalid: Discussed the results and contributed to final manuscript.

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