ORIGINAL ARTICLE

Complications of Therapeutic Plasmapheresis in Patients with Neurologic Diseases at A Tertiary Care Hospital

Naveed Ahmed[1*], Imran Ahmad[1], Fuad Ahmad Siddiqi[2], Khurram Haq Nawaz[1], Jahanzeb Liaqat[1], Fawad Ahmad[1]

ABSTRACT

Objective: To determine the complications of therapeutic plasmapheresis in patients with neurological diseases at a tertiary care hospital.

Study Design: Cross-sectional study.

Place and Duration of Study: The study was carried out at Department of Neurology, Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan from August 2021 to July 2022.

Methods: This study was carried out on patients diagnosed with various neurologic diseases where therapeutic plasmapheresis was performed which involves the replacement of patient plasma with donor plasma. A total of 680 therapeutic plasmapheresis treatments were performed on patients with a variety of neurologic diseases. Ppatients with hemodynamic instability, active sepsis, coagulopathy, and known allergies to fresh frozen plasma were excluded from the study. Data was recorded from consenting patients on a pre-designed proforma recording various parameters.

Results: Among 680 treatments,76.2% were carried out in males and 23.8% in females.

Guillain Barre Syndrome (42.06%) was the most common disease followed by chronic inflammatory demyelinating polyneuropathy (13.82%), neuromyelitis optical spectrum disorders (10.29%), and myasthenia gravis (7.94%) being the most common ones. In total 157 (23%) adverse events were noted, with fever (2.9%), pruritis (2.8%), urticaria and mild hypotension (2.5% each), tachycardia (2.2%), and DVT (1.3%) being commonly encountered complications. Anaphylaxis was recorded in 0.1%. The majority of the reactions were mild 118 (17.3%), some moderate 21 (3%), and few were severe 11 (1.6%). Serious, life-threatening events were seen in 0.1% and none had a fatal outcome. Prophylactic use of calcium resulted in lower electrolyte imbalance-related complications.

Conclusion: Therapeutic plasmapheresis is a safer treatment option for various neurologic diseases when performed by trained staff.

Keywords: *Anaphylaxis, Complications, Neurologic Diseases, Therapeutic Plasmapheresis*

***How to cite this**: Ahmed N, Ahmad I, Siddiqi FA, Nawaz KH, Liaqat J, Ahmad F. Complications of Therapeutic Plasmapheresis in Patients with Neurologic Diseases at A Tertiary Care Hospital. Life and Science. 2024; 5(2): 259-265. doi: http://doi.org/10.37185/LnS.1.1.538*

Introduction

Therapeutic Plasmapheresis is a technique of blood purification by exchanging patient plasma with allogeneic or autologous plasma or albumin. The cellular constituents of blood are returned to circulation.[1] The substances removed from plasma include immunoglobulins, autoantibodies, cytokines, immune complexes, myeloma light chains, and endotoxins.[2] The primary goal is to stop the disease progression due to the presence of inflammatory mediators. This procedure is of therapeutic choice in the pathogen being highly toxic with no available effective treatment; the pathogen being large enough to be removed by other techniques; Extended half-life of the pathogen where early removal acts therapeutically.[3] There are two types of techniques available for therapeutic plasmapheresis, filtration, and centrifugation with

[1]*Department of Neurology*
Pak Emirates Military Hospital, Rawalpindi, Pakistan
[2]*Department of Medicine*
Combined Military Hospital (CMH), Rawalpindi, Pakistan
Correspondence:
Lt Col. Naveed Ahmed
Resident, Neurology
Pak Emirates Military Hospital Rawalpindi, Pakistan
E-mail: naveedahmed2194@gmail.com
Funding Source: NIL; Conflict of Interest: NIL
Received: Nov 29, 2023; Revised: Feb 12, 2024
Accepted: Feb 20, 2024

similar adverse reactions profile.[4] Compared to hemodialysis, a high flow rate is not required and peripheral veins cannulation or central double lumen catheter can provide a vascular approach. The selection of exchange solutions depends on availability, primary pathology, and affordability. Fresh frozen plasma is a common exchange solution in most patients whereas albumin is used when fresh frozen plasma cannot be used. Citrate is used as an anticoagulant in centrifuge machines, whereas with membrane devices heparin is used. The therapeutic effectiveness of plasmapheresis is dependent upon the volume of fluid exchanged, the volume of distribution of pathogenic molecules in intra and extravascular spaces, and the equilibrium rate within the body. Therapeutic plasmapheresis has become a preferred treatment choice, especially after the identification of various autoantibody-mediated neurological disorders.[5]

Therapeutic Plasmapheresis-related complications can be due to vascular access, exchange solution, and the treatment itself.[6] Unawareness of the possible severe adverse reactions is a major barrier for health care professionals in considering therapeutic plasmapheresis in patients who are seriously ill.[7] There is a scarcity of local data about the safety and complications of therapeutic plasmapheresis. Only few case reports or case series are available. The aim of present study was to prospectively analyze various therapeutic plasmapheresis-related adverse side effects and their severity. We evaluated 680 procedures and assessed associated adverse side effects and classified them according to severity. We performed a prospective assessment of therapeutic plasmapheresis-related complications in seriously ill patients with various neurologic diseases.

Methods

The cross-sectional study was conducted at Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan from August 2021 to July 2022. Permission from the hospital Ethical Review Committee was taken on 2nd August 2021 vide letter number A/28. Informed written consent was obtained after the investigational role of therapeutic plasmapheresis was explained to all patients and their families. Sample size (n) was calculated keeping a confidence level ($Z^2_{1-\alpha/2}$) of 95%, a margin of error (d) of 5%, and taking an expected percentage of complication (P) as 45.05%[7] A total of 680 plasmapheresis treatment sessions were included in the study through consecutive non-probability sampling techniques.

Plasma Exchange Procedure: A total of five therapeutic plasmapheresis treatment sessions were performed for every patient. We used the 7th version of the COBE Spectra machine which works on the centrifugation principle. Femoral venous cannulation was used for intravenous access. Nadler's formula was applied to calculate the blood volume of the patient.[8] Flow rates were 30–60 ml/minute and anticoagulant acid dextrose was used in a 1:10 ratio. Proper aseptic measures were taken during venous access and therapeutic plasmapheresis as per the hospital infection control policy. Pulse oximetry, temperature, and blood pressure monitoring were done at the start, during, and after the completion of each treatment. Each treatment was carried out for 120 - 180 minutes with an exchange volume of 1.5 times the plasma volume. The exchange solution is composed of normal saline (1 part) and fresh frozen plasma (2 part) at body temperature. Hypocalcemic complications associated with citrate were prevented by using a 10ml calcium gluconate (10%) solution. All treatments were carried out in critical care settings including high dependency and intensive treatment units by trained staff. Heparin anticoagulation was used to keep a double-lumen catheter patent. The catheter was taken out after final treatment with manual compression for 30 minutes to prevent bleeding complications.

Classification of Complications: All therapeutic plasmapheresis-related complications were recorded on a predesigned proforma. The rate and severity of various complications associated with treatment were evaluated. They were categorized as mild, moderate, and severe. Mild reactions were without any clinical consequence. Whereas reactions that were of little clinical significance but required medical intervention and were resolved completely were considered Moderate and life-threatening complications were classified as Severe.

Data Collection Procedure: The demographic profile of all patients including name, medical record

number, gender, age, and clinical parameters including vital signs, weight, and complications were entered in a predesigned Performa. Heart rate and blood pressure were measured during pretreatment, post-treatment, and at 30-minute intervals during plasmapheresis. Temperature and saturation were recorded at the start and end of treatment. All clinical events described by the patient or observed by staff during the procedure were confirmed and documented by resident medicine on proforma. A total of 26 potential complications or adverse effects as mentioned in Table 1 were recorded.

Operational Definitions

Tachycardia- pulse rate greater than 100 beats per min.

Mild Hypotension- Systolic blood pressure greater than 85 mmHg but less than 95 mmHg.

Severe Hypotension - Systolic blood pressure less than 95 mmHg.

Fever – rise in core body temperature beyond 100°F during treatment.

Hypocalcemic symptoms- Facial, perioral, hands or feet paresthesia.

Exit site infection – venous access site positive culture growth.

Septicemia - the life-threatening invasion of the bloodstream by microbes from a local source (e.g. venous catheter, skin) associated with systemic ailment.[9]

Anaphylaxis – life-threatening systemic allergic reaction with hyperacute onset and manifestations. It may result in death in severe cases.[10]

Inclusion Criteria: All patients with severe neurologic diseases consenting to therapeutic plasmapheresis treatment.

Exclusion Criteria: Patients with the following conditions were excluded from the study: hemodynamic instability, active sepsis, coagulopathy, and known allergies to fresh frozen plasma.

Data analysis was done using IBM Statistical Package for the Social Sciences (SPSS) version 20. For quantitative variables (e.g. Age) we calculated mean and standard deviation. The frequency of each complication was also determined.

Results

From August 2021 to July 2022, 680 therapeutic plasmapheresis treatments were carried out at Pak Emirates Military Hospital Rawalpindi on patients with various neurologic diseases mentioned in figure.1. Treatment was administered to 518 males and 162 females (Table-1 for percentages). The mean age was 58.7 ± 14.5 years with a range of 23 – 82 years. In total 157 complications were observed making up 23 % of all treatments. The majority of the reactions were mild 125(18.4%), some moderate 21(3%), and severe reactions were seen in 11(1.6 %) treatments including nine cases of Deep vein thrombosis (DVT) and one case of anaphylaxis (Figure.2).

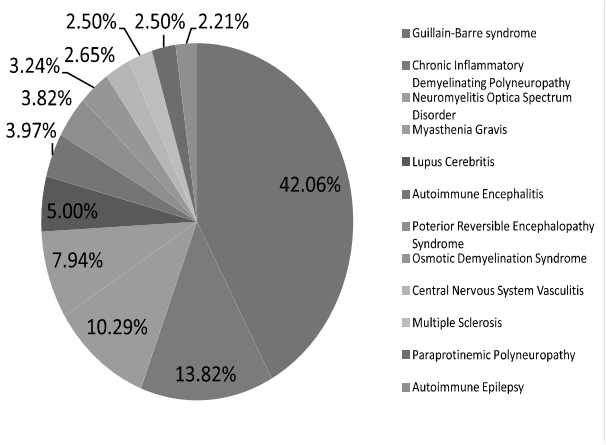

Fig.1: Neurologic Diseases for which therapeutic plasmapheresis was carried out

Table-1: Gender wise distribution

Gender	Number	Percentage
Male	518	76.2
Female	162	23.8
Total	680	100

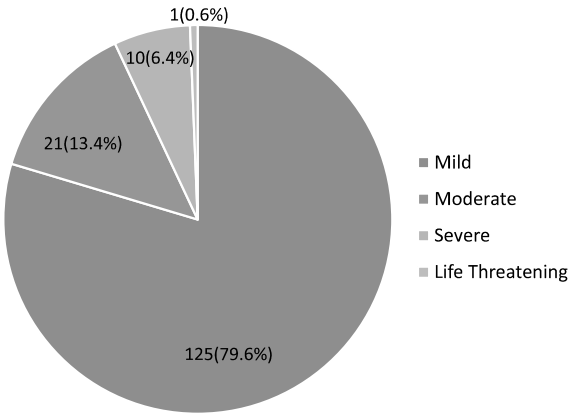

Fig.2: Severity-wise Complications of Therapeutic Plasmapheresis

Venous access complications

Common femoral vein catheter placement was carried out in all cases. In nine cases, indwelling catheters caused deep vein thrombosis (1.3%) but none had a pulmonary embolism. A slightly higher rate of deep vein thrombosis was probably due to increased hypercogubality associated with immobility due to neurological weakness. For patients who developed deep vein thrombosis their catheters were removed and started on therapeutic anticoagulation for three months. Catheter exit site infection was observed in six cases (0.9%), and one (0.1%) developed septicemia which was treated with broad-spectrum antibiotics. One patient (0.1%) had exit site bleeding which was controlled with local compression.

Complications associated with Fresh Frozen Plasma / therapeutic plasmapheresis

Mild adverse reactions were the most commonly observed complication. Fever was recorded in 20(2.9%) managed with oral antipyretics. Pruritis in 19(2.8%) and urticaria in 17(2.5%) were managed with oral antihistamines. Mild hypotension in 17(2.5%) & tachycardia in 15(2.2%) which responded to adjustment of flow rates (Table-2).

Severe anaphylactic reaction requiring intravenous medication and temporary cessation of treatment occurred in one patient (0.1%) due to an allergic reaction to fresh frozen plasma transfusion. None of the patients died due to the therapeutic plasmapheresis procedure itself. Nausea in 12(1.8%) and vomiting in 4(0.6%) treatments. The majority responded to oral anti-emetics, and few required intravenous medication. Severe hypotension was seen in 5(0.7%), which required additional fluid replacement. Hypocalcemic symptoms including perioral, hand, and feet paresthesia, and numbness were recorded in 5(0.8%), leg cramps in 4(0.6%) procedures, and additional doses of calcium gluconate, and potassium were given for these complications. Anxiety was noted in 5(0.7%) cases which were managed with counseling and anxiolytics. Headache in 4(0.6%), pharyngitis & dyspnea in 2 each (0.3%), Abdominal and chest pain, and Lower Back Pain each in one (0.1%) treatment (Table-2).

Discussion

Most neurologic diseases have category I/II recommendations for therapeutic plasmapheresis. It has become an acceptable and quite safe treatment option for various neurologic diseases, even for critically ill patients on mechanical ventilation.[11] The most common neurological diseases were Guillain-Barré syndrome (42.1%), Chronic Inflammatory Demyelinating Neuropathy (13.8%), Neuromyelitis Optica Spectrum disorders (10.3%), and Myasthenia Gravis (7.9%) for which therapeutic plasmapheresis was done (Figure.2 for details).

In our study, the incidence of all types of procedure-related complications of therapeutic plasmapheresis was 23%, with 18.4% mild, 3% moderate 1.5% severe, and 0.1% life-threatening. Our results are comparable to a study by Lemaire, et al.in which the rate of all types of complications were 26.9%.[12] Bramlage CP, et al. reported a similar outcome with an adverse events rate of 25.6%. The majority were mild (13.7%), some moderate (11.0%), and very few (0.7%) were severe.[13] In another study by Kumar R, et al. complication rates ranging from 1.6% to 25% was observed with severe reaction frequency of 0.5% to 3.1%.[14]

Routine calcium replacement led to a low incidence of hypocalcemia symptoms (tingling, paresthesias) despite using fresh frozen plasma as replacement fluid. Severe hypocalcemia leading to cardiac arrhythmia was not observed in any patient. Vascular access-related catheter infection without septicemia was seen in a few cases; however therapeutic plasmapheresis itself was not associated with

Table-2: Severity-wise Complications of Therapeutic plasmapheresis

S/N	Complication	Number	Percentage (%)
Mild			
1.	Fever	20	2.9
2.	Pruritis	19	2.8
3.	Urticaria	17	2.5
4.	Mild hypotension	17	2.5
5.	Tachycardia	15	2.2
6.	Nausea	12	1.8
7.	Dizziness	5	0.8
8.	Anxiety	5	0.8
9.	Leg cramp	4	0.6
10.	Headache	4	0.6
11.	Pharyngitis	2	0.3
12.	Dysponea	2	0.3
13.	Abdominal pain	1	0.1
14.	Chest pain	1	0.1
15.	Lower Back Pain	1	0.1
Moderate			
16.	Exit site infection	6	0.9
17.	Hypocalcemic symptoms	5	0.8
18.	Severe hypotension	5	0.7
19.	Vomiting	4	0.6
20.	Exit site bleeding	1	0.1
21.	Hemoptysis	0	0.0
22.	Epistaxis	0	0.0
Severe			
23.	Deep Vein Thrombosis	9	1.3
24.	Anaphylaxis	1	0.1
25.	Sepsis	1	0.1
26.	Arrhythmia	0	0.0
	Total Complications	157	23
	Total Treatments	680	

infection. Fever, urticaria, pruritis, and hypotension characterized allergic reactions to fresh frozen plasma, which were mostly mild. A slightly high risk of deep vein thrombosis is due to immobility, and indwelling catheter which can be mitigated by keeping the patient on prophylactic thromboprophylaxis.[15]

Our results show that therapeutic plasmapheresis imposes a lower risk of complications when performed by trained staff. Furthermore, it is cost-effective when compared to available alternative treatment options – intravenous immunoglobulins (IVIG). Based upon a very low rate of serious

Our study has a few limitations. It was a single-center study targeting a specific set of diseases for plasmapheresis and our results cannot be generalized to patients with other indications for plasmapheresis as a rescue therapy. We prospectively collected data following each treatment therefore all adverse events were

accurately recorded. Further studies to explore the predictors of complications and assessment of outcomes are recommended.

Conclusion

We conclude that therapeutic plasmapheresis can be safely employed for various neurologic diseases as a suitable and cost-effective substitute for intravenous immunoglobulins without compromising the safety of the patients. We found various non-serious readily identifiable complications which can be managed without interrupting the procedure. Life-threatening and procedure-limiting complications were rare.

REFERENCES

1. Fernández-Zarzoso M, Gómez-Seguí I, de la Rubia J. Therapeutic plasma exchange: Review of current indications. Transfusion and Apheresis Science. 2019; 58: 247-53. doi: 10.1016/j.transci.2019.04.007
2. Lemaire A, Parquet N, Galicier L, Boutboul D, Bertinchamp R, Malphettes M, et al. Plasma exchange in the intensive care unit: Technical aspects and complications. Journal of Clinical Apheresis. 2017; 32: 405-12. doi: 10.1002/jca.21529
3. Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. Journal of Clinical Apheresis. 2016; 31: 149-62. doi: 10.1002/jca.21470
4. Strasser E. Principles of Therapeutic Apheresis in Neurological Disease. Transfusion Medicine and Hemotherapy. 2023; 50: 88-97. doi: 10.1159/000529463
5. Osman C, Jennings R, El-Ghariani K, Pinto A. Plasma exchange in neurological disease. Practical Neurology. 2020; 20: 92-9. doi: 10.1136/practneurol-2019-002336
6. Basic-Jukic N, Kes P, Glavas-Boras S, Brunetta B, Bubic-Filipi L, Puretic Z. Complications of therapeutic plasma exchange: Experience with 4857 treatments. Therapeutic Apheresis and Dialysis. 2005; 9: 391-5. doi: 10.1111/j.1744-9987.2005.00319.x
7. Ara F, Hassan MS, Yusuf MA, Nasreen Z, Islam A, Alam MB, et al. Complications of therapeutic plasma exchange in patient with neurological disorders. Journal of National Institute of Neurosciences Bangladesh. 2017; 3: 69-74. doi:10.3329/jninb.v3i2.36766
8. Nadler SB, Hidalgo JU, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962; 51: P224-32. doi: 10.5555/uri:pii:0039606062901666
9. Singer M, Deutschman CS, Seymour CW, Hari MS, Annane D, Bauer M, et al. The Third
10. International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315: 801-10. doi: 10.1001/jama.2016.0287.
11. Turner PJ, Worm M, Ansotegui IJ, El-Gamal Y, Rivas MF, Fineman S, et al. Time to revisit the definition and clinical criteria for anaphylaxis? World Allergy Organization Journal. 2019; 12: 100066. doi: 10.1016/j.waojou.2019.100066
12. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. Journal of Clinical Apheresis. 2019; 34: 171-354. doi: 10.1002/jca.21705
13. Lemaire A, Parquet N, Galicier L, Boutboul D, Bertinchamp R, Malphettes M, et al. Plasma exchange in the intensive care unit: Technical aspects and complications. Journal of Clinical Apheresis. 2017; 32: 405-12. doi: 10.1002/jca.21529
14. Bramlage CP, Schröder K, Bramlage P, Ahrens K, Zapf A, Müller GA, et al. Predictors of complications in therapeutic plasma exchange. Journal of Clinical Apheresis. 2009; 24: 225–31. doi: 10.1002/jca.20217
15. Kumar R, Birinder SP, Gupta S, Singh G, Kaur A. Therapeutic plasma exchange in the treatment of myasthenia gravis. Indian Journal of Critical Care Medicine. 2015; 19: 9-13. doi: 10.4103/0972-5229.148631

Authors Contribution

NA: Idea conception, study designing, data collection, data analysis, results and interpretation, manuscript writing, and proofreading

IA: Idea conception, data analysis, results and interpretation, manuscript writing, and proofreading

FAS: Idea conception, data analysis, results and interpretation, manuscript writing, and proofreading

KHN: Idea conception, data analysis, results and interpretation, manuscript writing, and proofreading

JL: data collection, data analysis, results and interpretation, manuscript writing, and proofreading

FA: data collection, data analysis, results and interpretation, manuscript writing, and proofreading