Original Article

Plasmapheresis; Reasons & Results, An Epidemiological Study on the Indications and Outcome of Therapeutic Plasma Exchanges in a Tertiary Care Hospital — One Year Single Center Experience

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Background : Therapeutic Plasma Exchange (TPE) is a commonly accepted procedure used to remove circulating antibodies against specific antigens which are causative to a variety of diseases mediated by the reaction of these Antigen and Antibodies and activation of the complement cascade thereafter. It is also used as a part of the desensitization protocol in case of ABO incompatible renal transplant where circulating donor specific auto antibodies against the donor's blood group is removed.

Methods : This is a longitudinal observational study which assess the indication, complication and outcome of TPE in the hemodialysis unit of Rabindranath Tagore International Institute of Cardiac Sciences, a Tertiary Care Center for Nephrology and a Renal Transplant Unit. Total 91 patients underwent TPE during study period. The number of TPE sessions varied from 19 to 2 with a mean of 5.28(2.92) per person. Combination of FFP+5% Human Albumin was uses as replacement fluid in majority of patients (86.36%). Fresh Frozen Plasma (FFP) and 5% Human Albumin (HA) was used as isolated replacement solution in (11.36% patients) and (2.37% patients) respectively. 38 patients underwent TPE for Antibody mediated rejection (AMR), 4 patients for CAN/ATN ,4 patients for chronic AMR(CAMR) and 1 patient for Hyper Acute Rejection (HAR) post live donor renal transplantation.TPE was used pre operatively in 23 patients undergoing ABO incompatible renal transplantation. 5 patients underwent plasma exchanges for Hemolytic Uremic Syndrome and Anti Glomerular Basement Membrane Disease.

Results : Hypotension was the commonest complication seen in 62.63% patients followed by anaphyllactoid reaction (0.06%) and parasthesia (0.02%). There was no significant association between anaphyllactoid reaction and the replacement fluid, (OR=0.2; CI=0.5-1.2). TPE was successful in 28 patients having AMR. Partial success was achieved in 6 patients who could be discharged with a mean Creatinine of 2.1(0.4) mg/dl.TPE failed in 8 patients. 23 patients underwent TPE for ABOi KT and all the 23 cases could be successfully transplanted with an uneventful post operative period. Partial success was achieved in all the 5 cases of HUS and Anti-Glomerular Basement Membrane disease (anti-GBM disease).

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Key words **: Therapeutic Plasma Exchange, Fresh Frozen Plasma, Desensitization.**

Apart from regular hemodialysis, one major role of the dialysis machine is therapeutic plasma exchange (TPE) commonly known as plasmapheresis (PE). In this process the plasma component of the whole blood is separated from the cellular components and is either discarded or re infused following appropriate procedure to desensitize the necessary components (endotoxin, Antibodies etc).This job is usually performed by a dialysis machine using specific exchange filters which separates the necessary factor according to their size and hence the job befalls the nephrologists.

TPE is indicated in a wide range of disorders viz

Editor's Comment :

- Therapeutic plasma exchange(TPE) is a safe and effective way to treat antibody mediated rejection in renal allograft Transplantation.
- The usage of TPE is not only restricted to the field of Nephrology but it has a wider spectrum of usage.
- The complications of TPE are usually limited and can be managed easily.

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Good Pasteur's Syndrome, Thrombotic Thrombocytopenic Purpura, Chronic Inflamatory Demyelinating Poly neuropathy, Desensitization for ABO Incompatible renal transplantation, Rejection of Antibody mediated rejection in solid organ transplantation[1].

The replacement fluid may be colloids like Fresh frozen plasma, Albumin, Hydroxy ethyl starch or crystalloids like Ringer's Lactate or a combination of two[2]. From beginning the choice of replacement fluid depends upon the nature of disease and the final aim of plasmapheresis[3]. Factor Concentrates such as K Centra containing Vitamin K dependant factors, Protein C and Protein S; Ria Stap,a fibrinogen concentrate; Humate P containing Factor 8 and Von Willibrand Factor and Thrombate containing Anti thrombin 3 are being used to treat specific deficiencies avoiding dilution related complications[4].

Usually in each cycle 1-1.5 liters of plasma is removed[5]. The efficacy of TPE depends on the PV removed in relation to the patient's PV, the distribution of the pathogenic substance to be removed (intra versus extra-vascular spaces), and the synthesis and equilibrium rate of that substance between the compartments[6]. Immunoglobulin M(Ig M) is mostly distributed in intravascular compartment where as Immunoglobulin G(IgG) is mobile and there is a constant replenishment into the intravascular compartment from the extra vascular spaces[7]. The treatment volumes and regimens depend on the disease[8].

Plasmapheresis is associated with its own complications apart from the complications related to the vascular access and citrate related toxicity[8]. The separated plasma is replaced by replacement fluid. The volume removed is such that if it were not replaced, significant hypovolemia resulting in vasomotor collapse would occur[2]. Other complications include hypocalcemia and anaphyllactoid reactions. However it is found that serious complications like adverse cardiac event, death hemorrhage, severe hypotension do not commonly occur[7]. Derangement of coagulation factors, prolonged neuromuscular blockade due to removal of acetyl choline esterase, urticaria, parasthesia, hypotension is seen in varying incidences[8-10].

Aims and Objectives

Primary Outcome :

To determine

(1) The total number of patients undergoing TPE during the study period.

(2) The indication of TPE

(3) Outcome of TPE

(4) Complication of TPE

(5) Replacement fluid used.

Secondary Outcome :

To determine the total number of TPE sessions performed during study period.

Materials and Methods

Study Design : It is a retrospective, observational study carried out at the Department of Hemodialysis of Rabindranath Tagore International Institute of Cardiac Sciences, Kolkata, India.

Study Period : The study was carried out between 01.01.2017 to 31.12.2017.

Inclusion Criteria :

All patients who consented to the study.

Exclusion Criteria :

(1) In situation where the session had to be pre terminated or transferred out to the unit for completion of the sessions.

(2) Carried over patients.

(3) Patients with venous hematocrit less than 60%.

Formal consent was taken from the participant. Data were collected from the patients in a predesigned questionnaire, the centralized software of the Medical Records Department using the unique hospital Identity number (MRN Number) and from the duplicate hard copy of dialysis sheet.

Outcome was defined as -

Success : Target achieved at the end of treatment.

Partial Success : The aimed target could not be achieved; however there was significant clinical improvement

Treatment Failure : Target not achieved.

No clinical or biochemical improvement

Mortality at the end of the treatment due to the cause for which TPE was initiated.

The data obtained were tabulated and analyzed.

Frezenius 4008S dialysis machine was used for the purpose.

Plasmapheresis was performed using Plasma filter PF 2000N (Gambro), maintaining a Trans membrane Pressure of 100(20) mm Hg at a blood flow rate of 200(20)ml/min.

3000 IU of Low molecular weight heparin was used to prevent extracorporeal coagulation. The procedure (PE) was performed with a blood flow rate of 100 ml/min (20) and a TMP of 80(10) mm of Hg.

Colloids like Fresh Frozen Plasma (FFP); 5% Human Albumin (HA) and crystalloids like Ringer's Lactate Solution (RL), Normal Saline(NS) were used

as substitution fluid

Since Antibody Mediated Rejection and ABOi Renal Transplantation were the commonest etiology, in light of pre determined parameter the Outcome was defined as -

	AMR	ABOi KT
Success	Creatinine value reduced to base line	Renal Transplantation was done with normal graft function
Partial Success	Creatinine reduction achieved but <30% of NADIR	Renal transplantation done but i) Partial recovery of graft function ii) Post operative AMR needing further PE
Treatment Failure	Creatinine reduction not achieved Graft Nephrectomy Re initiation of Hemodialysis	Transplantation aborted Hyper acute rejection
For other clinical condition the following definition was used :		
	Creatinine	Urine Output
Success	Returned to normal level.	Became non oliguric
Partial Success	Did not return to normal level but >30% reduction of NADIR was achieved	Urine output started/ increased but <400 ml/day
Failure	1. Creatinine reduction <30% of NADIR 2. Rise in Serum Creatinine level	1. Urine output persistently <100 ml/day 2. Further reduction in urine output

AMR = Antibody Mediated Rejection;
ABOi KT = ABO incompatible kidney transplantation (ABOi-KT)
Statistical Tools : Descriptive statistics was used with the help of SPSS software version 21.

Results

Total 91 patients underwent TPE during study period.

52 patients were males and 39 patients were female. (p=0.17)

The mean age of the study population was 43.3 years (13.76)

AVF was used in 76 patients (83.51%). CVC was used in 10 patients (10.98%). Double lummened uncuffed catheter was used in 5(5.49%) patients.

There were 482 sessions of TPE at the study center during study period.

The number of TPE sessions varied from 19 to 2 with a mean of 5.28(2.92) per person.

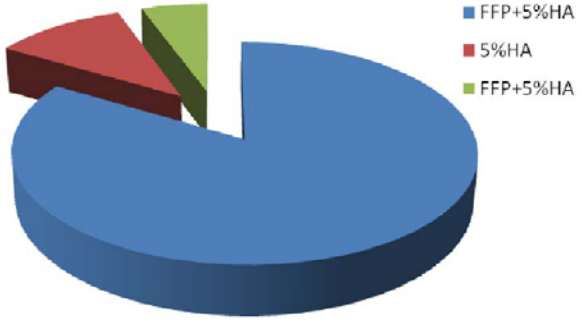
Combination of FFP+5% Human Albumin was uses as replacement fluid in 76(83.51%) patients.

Fresh Frozen Plasma(FFP) and 5% Human Albumin (HA) was used as the only replacement solution in 10 patients (10.9%) and 5 patients (5.45%) respectively (Fig 1).

In 42 (46.15%) patients underwent TPE for Antibody mediated rejection (AMR), 4(4.3%) patients for CAN/ ATN, 7(7.6%) patients for chronic AMR (CAMR) and 1(1.09%) patient for Hyper Acute Rejection(HAR) post live donor renal transplantation. Standard triple drug immune suppression protocol consisting of Tacrolimus, Mycophenolate and Prednisolone was continued. TPE was used pre operatively in 32(35.16%) patients undergoing ABO incompatible renal transplantation. All patients undergoing ABO Incompatible renal transplantation got Rituximab 100 mg(single dose) and Intravenous Immunoglobulin @1 gm/kg body weight as adjuvant therapy.3(3.2%) and 2(2.18%) patients underwent plasma exchanges for Hemolytic Uremic Syndrome (HUS) and Anti Glomerular Basement Membrane Disease (Anti Gb M disease) respectively (Fig 2).

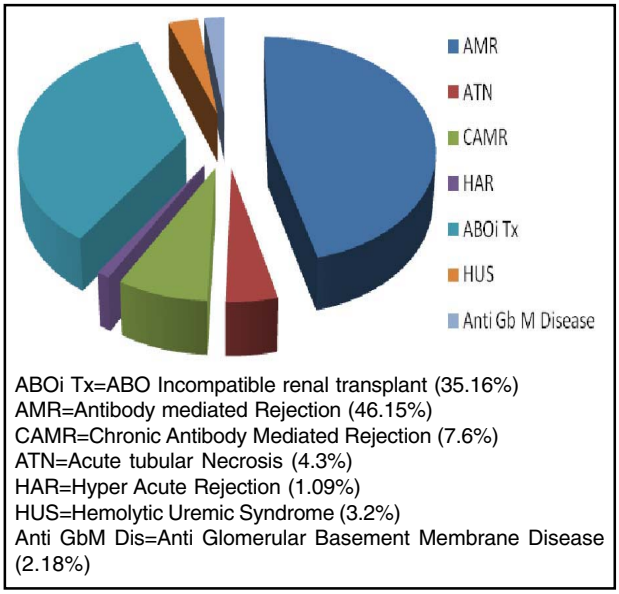
Total 68 episodes of complications (14.1%)were seen during study period. Hypotension was the commonest complication seen in 57(83.8%) with a mean trough MAP of 70(5) mm Hg, followed by anaphyllactoid reaction in 6(8.82%) and parasthesia in 4(0.02%) patients. Coagulation of extracorporeal circuit happened in 1(1.4%) session. There was no significant association between anaphyllactoid reaction and the replacement fluid.(OR=0.2;CI=0.5-1.2). Anaphyllactoid reaction responded to IV Hydrocortizone therapy (Fig 3).

TPE was successful in 30(71.4%) patients having AMR. Partial success was achieved in 6(14.28%)



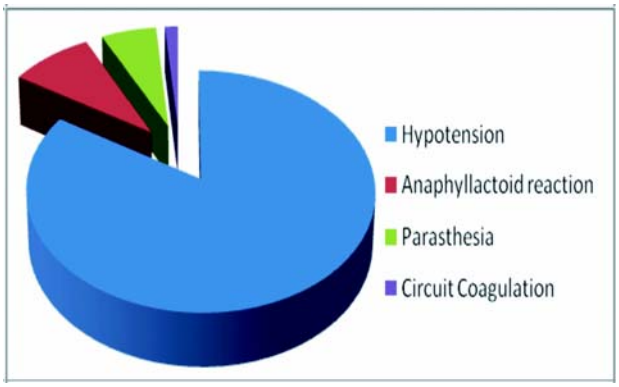
FFP+5%HA = Combination of Fresh Frozen Plasma + 5% Human Albumin (83.51%)
5%HA = Only 5% Human Albumin (10.9%)
FFP = Fresh Frozen Plasma (5.45%)

Fig 1 — Types of Replacement Fluid Used



ABOi Tx=ABO Incompatible renal transplant (35.16%)
AMR=Antibody mediated Rejection (46.15%)
CAMR=Chronic Antibody Mediated Rejection (7.6%)
ATN=Acute tubular Necrosis (4.3%)
HAR=Hyper Acute Rejection (1.09%)
HUS=Hemolytic Uremic Syndrome (3.2%)
Anti GbM Dis=Anti Glomerular Basement Membrane Disease (2.18%)

Fig 2 — Indication of Therapeutic Plasma Exchange



Hypotension (83.8%), Anaphyllactoid reaction (8.82%)
Parasthesia (5.88%), Circuit Coagulation (1.4%)

Fig 3 — Complication during Therapeutic Plasma Exchange

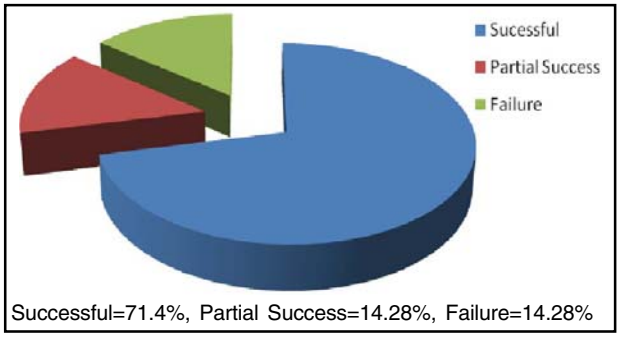
patients who could be discharged with a mean Creatinine of 2.1(0.4)mg/dl.TPE failed in 6(14.28%) patients of whom 1 patient died, graft nephrectomy was performed in 2 patients and hemodialysis was re initiated in 3 patients (Fig 4).

Partial success was seen in 5(71.42%) cases of CAMR. TPE failed in 2(28.57%) cases of CAMR with re initiation of Hemodialysis (Fig 5).

TPE was successful in 1 case of ATN. Partial success was achieved in 3 other cases.

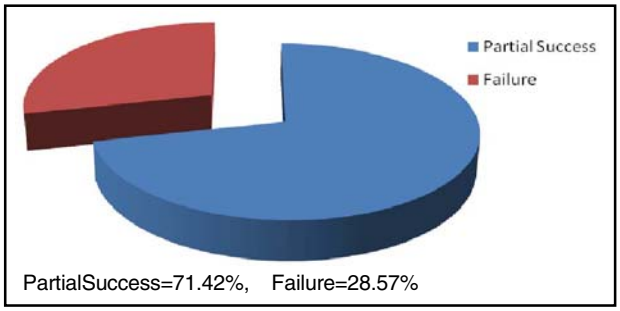
32 patients underwent TPE for ABOi KT and all the 32 cases could be successfully transplanted with an uneventful post operative period.

Partial success was achieved in all the 5 cases of HUS and Anti GbM disease. The mean reduction in Serum Creatinine was 75.2(3.2)% post procedure.



Successful=71.4%, Partial Success=14.28%, Failure=14.28%

Fig 4 — Outcome of Therapeutic Plasma Exchange in Antibody mediated Rejection



PartialSuccess=71.42%, Failure=28.57%

Fig 5 — Outcome of TPE in CAMR

Discussion

Compared to other study fresh frozen plasma was associated with lesser anaphyllactoid reactions. 20% vs 0.6 %(p>0.05)[11].

However hypotensive episodes were much higher compared to other trial 62.63% vs 1.5%[12,13].

Outcome of treatment of HUS/TTP was not yielding in our study compared to others[14].

Outcome of TPE (in conjunction with IvIg and Rituximab) in reducing antibody titer,thereby leading to successful renal transplantation was comparable to and at time better than international standards[15,16].

Conclusion

TPE is a safe mode of treatment and successfully removes the offending antibodies when used in conjecture with Rituximab and/or IV Ig. TPE is not a successful treatment of CAMR, however, more data and prolonged study is needed. Lack of complete success in case of Hemolytic Uremic Syndrome and Anti Glomerular Basement Membrane Disease could possibly be attributed to the time lag between onset of symptom and initiation of therapy. Hence more rapid detection and high index of suspicion is warranted. Complications associated with TPE could be easily manageable. FFP can be used as a safe alternative to Human Albumin which is more expensive in view of no significant association with the use of replacement fluid

and anaphyllactoid reaction.

Sessions should be closely monitored with more frequent measurement of Blood Pressure to detect and manage hypotension.

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Conflict of Interest : None

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