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Role of therapeutic plasma exchange in acute humoral rejection patients undergoing live-related renal transplantation: A single-center experience

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Abstract:

BACKGROUND AND AIM: Renal transplantation (RT) is the most successful and ideal renal replacement therapy for end-stage renal disease patients. Renal allograft rejection has always been one of the major barriers in successful RT. Our aim was to report the role of therapeutic plasma exchange (TPE) in acute humoral rejection (AHR) patients who underwent live-related RT (LRRT) and their renal allograft outcome at our center.

MATERIALS AND METHODS: A prospective observational study was conducted from July 1, 2014, to December 31, 2016. Patients with biopsy-proven AHR and treated with TPE along with other lines of treatment after undergoing LRRT were included in the study. ABO-incompatible individuals, pediatric patients, and patients undergoing second transplants were excluded from the study. Clinical history, donor and graft details, management, and patient and graft survival were noted.

RESULTS: Of the 1608 patients who underwent LRRT, 49 (37 males, 76%; 12 females, 24%; mean age 39.5 ± 13.3 years) had biopsy-proven AHR (3.04%) and were treated with TPE. A total of 281 TPEs were performed with an average of 5.7 TPE/patient (range 2–12). Of the 49 patients, 38 patients (78%) with favorable response underwent 213 (75.8%) TPEs (average of 5.6 TPE/patient; range: 2–12), whereas 11 patients (22%) with unfavorable response underwent 68 (24.2%) TPEs (average of 6.2 TPE/patient; range: 3–8). Blood urea ($P = 0.012$) and serum creatinine ($P = 0.038$) levels at the time of rejection were significant predictors of response to TPE therapy. The average length of stay in our study population was 33 ± 22 days. Six months posttransplant, the patient and graft survival were 93.3% and 89.5%, whereas at 12 months, they were 89.3% and 81.5%, respectively.

CONCLUSION: TPE is a safe and effective adjunct therapy for treating AHR patients.

Keywords:

Acute humoral rejection, graft survival, renal transplantation, therapeutic plasma exchange

Introduction

Renal allograft rejection is broadly classified into three major types: hyperacute rejection, acute rejection (cellular or humoral), and chronic rejection. Acute humoral rejection (AHR) is characterized by graft dysfunction often manifesting within the 1st week after transplantation, resulting in graft loss due to preformed donor-specific antibodies (DSAs) or "*de novo*" DSA production after transplantation.[1] The incidence of AHR among renal transplant recipients ranges from 3% to 10% and 1-year graft survival for these patients does not

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exceed 15%–50%, with a significant number of patients being at a high risk of graft loss.[2]

The treatment options available for AHR are based on the following four basic concepts: (1) suppression of the T-cell response (i.e., antilymphocyte antibody, mycophenolic acid-derived drugs, and calcineurin inhibitors [CNI]), (2) elimination of circulating antibodies (i.e., therapeutic plasma exchange [TPE] or immunoadsorption techniques), (3) inhibition of residual antibodies (i.e., intravenous immunoglobulin [IVIg] or cytomegalovirus hyperimmune globulin), and (4) suppression or depletion of B-cells (i.e., rituximab).[3,4]

Despite the introduction of better immunosuppression, the risk of acute rejection still remains, therefore more emphasis is being laid on timely treatment of these patients, as worse long-term prognosis along with an increased risk of graft failure has been reported.[4] The graft loss due to AHR can be prevented by following an early and aggressive treatment approach.[5,6] An adequate treatment strategy is still ill defined for such patients, and the long-term complications associated with antirejection therapy are unknown.[7] Our aim was to report the role of TPE in AHR patients undergoing live-related renal transplantation (LRRT) and their renal allograft outcome at our center.

Materials and Methods

A prospective observational study was conducted in the Department of Transfusion Medicine in a tertiary care hospital from July 1, 2014, to December 31, 2016, after approval from the institutional ethical committee. All the patients underwent ABO-compatible LRRT after a negative T- and B-cell complement-dependent lymphocytotoxicity antihuman globulin cross match. The living donors were not paid for the donation of the organ and the procedures were performed as per the Indian Transplantation of Human Organs Act.[8]

Acute humoral rejection diagnosis

AHR was diagnosed when patients fulfilled all the following three criteria: (i) presence of acute graft dysfunction (sudden rise in serum creatinine of >20% of baseline, after exclusion of other causes of graft dysfunction); (ii) histological features showing neutrophils in peritubular capillaries, vasculitis, and/or fibrinoid necrosis of vessels; and (iii) positive for C4d by immunofluorescence. Patients meeting the above-said criteria and treated with TPE along with other lines of treatment (triple immunosuppression, IVIg, and/or rituximab) were included in the study. Patients undergoing ABO-incompatible transplants, pediatric patients (<18 years), those with biopsy features suggestive only of acute cellular rejection (ACR), and patients undergoing second transplants were excluded from the study. All procedures were done after due consent from the patients.

Immunosuppression protocol

All patients were on triple immunosuppression consisting of tacrolimus (0.2 mg/kg; adjusted to trough levels, 8–12 ng/ml), mycophenolate mofetil (1000 mg twice a day; adjusted according to white blood cell and platelet counts), and prednisolone (intravenous methylprednisolone 500 mg daily for 3 days followed by 20 mg/day).

Acute humoral rejection treatment protocol

As per our hospital policy, AHR treatment consisted removal of 1.5 plasma volume (3–5 consecutive sessions). The replacement fluid used was 5% human albumin (20% human albumin reconstituted in saline) and at least two units of fresh frozen plasma (FFP; blood group specific) at the end of each session to replenish the lost coagulation factors. After every session of TPE, IVIg (100 mg/kg/dose) was given and a minimum of 12-h gap was maintained after IVIg dose and before the start of the next TPE. All the procedures were performed on Haemonetics MCS plus, Braintree, MA, USA, using central venous access and ACD-A as anticoagulant (ACD-A: Blood ratio of 1:12–1:16). Rituximab (dose 375 mg/m^2) was administered to patients not responding to TPE (3–5 consecutive sessions), steroid, and IVIg therapy, before labeling them as unfavorable response. A single course of methylprednisolone pulses (dose – 3–5 mg/kg for 3 days) was also administered to all the patients between the AHR diagnosis and TPE. Concomitant T cell-mediated rejections were treated with antithymocyte globulin (ATG; 1–2 mg/kg/dose).

The response to AHR treatment (TPE therapy) was graded as favorable when patients showed increase in urine output and significant reduction in serum creatinine (at least 50% reduction from creatinine level at the time of AHR diagnosis). Unfavorable response was considered when patients showed no improvement in graft function (no documented increase in urine output and/or fall in serum creatinine level) despite undergoing 3–5 consecutive TPE sessions along with IVIg and/or rituximab administration followed by dependence on dialysis posttransplant and/or graft nephrectomy or mortality. Patients were followed up for a period of 1-year posttransplant.

Data collection and statistical analysis

The data collected from patient records included age; gender; donor details (age and gender); cause of end-stage renal disease (ESRD); prior history of blood transfusion; dialysis duration; average length of

stay (ALOS); human leukocyte antigen (HLA) mismatch; graft biopsy details; antirejection therapy received along with TPE; laboratory parameters (blood urea, serum creatinine, serum sodium, and serum potassium) and urine output at the time of AHR diagnosis, at the time of TPE therapy, and at the time of discharge; number of TPE sessions; complications related to TPE; and response to TPE therapy.

The data were collected and entered in the Microsoft Excel (Redmond, WA, USA). For statistical analysis, the patients were divided into two groups based on response to TPE therapy, as follows: favorable (Group 1) and unfavorable (Group 2). Wilcoxon rank-sum test was used for measuring the correlation between the continuous variables, and Chi-square test was used for measuring the association between the categorical variables. Statistical significance was assumed at $P < 0.05$. Statistical analysis was performed using IBM Statistics software version 17.0 and R-3.2.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, a total of 1608 LRRTs were performed. Of these, 49 patients (37 males, 76%; 12 females, 24%) had biopsy-proven AHR (3.04%) and were treated with TPE. The mean age at the time of rejection was 39.5 years (21–79 years). The most common cause of ESRD in our study population was diabetic nephropathy (32.7%) followed by hypertensive nephropathy (14.3%) [Table 1]. The most common clinical feature at the time of rejection was oliguria (100%; defined as urine output <400 ml/day) followed by fever (58%), fluid overload (12%), and accelerated hypertension (2%). Graft Doppler ultrasound was performed in all the patients, which showed complete diastolic cutoff. Table 2 shows the details of graft biopsy (histological and immunofluorescence) performed in our patients. Concomitant T-cell-mediated rejection was noted in 17 patients (35%).

Table 3 summarizes the details related to patient demographics and laboratory parameters. A statistically significant difference was noted among patients' age (P = 0.016) and ALOS (P = 0.016), on comparing the response of TPE therapy [Table 3]. No significant difference was noted among the groups for recipient's gender, duration of dialysis, prior history of blood transfusion, HLA mismatch, and donor's age and gender [Table 3].

A total of 281 TPEs were performed with an average of 5.7 TPEs/patient (range: 2–12). The most common venous access utilized was central venous access (jugular venous catheter – 27, 55%; femoral catheter – 15, 31%) followed by peripheral venous access (arterovenous fistula – 7, 14%).

Table 1: Distribution of patients according to the underlying cause of end-stage renal disease

Cause of end-stage renal disease	Number of patients, *n* (%)
Diabetic nephropathy	16 (32.7)
Hypertensive nephropathy	7 (14.3)
CGN	6 (12.2)
Unknown	6 (12.2)
FSGS	5 (10.2)
CIN	5 (10.2)
APCKD	4 (8.2)

CGN=Chronic glomerulonephritis, FSGS=Focal segmental glomerulosclerosis, CIN=Contrast-induced nephropathy, APCKD=Adult polycystic kidney disease

Table 2: Graft biopsy details for acute humoral rejection patients

Histopathological and immunohistochemical features	Number of patients, *n* (%)
ATN	31 (63)
Neutrophils and/or mononuclear cells in PTC and/or glomeruli and/or capillary thrombosis	49 (100)
Fibrinoid necrosis/intramural or transmural inflammation in arteries	35 (71)
C4d in PTCs (>50% positivity)	49 (100)

ATN=Acute tubular injury, PTCs=Peritubular capillaries

The average plasma volume removed/procedure was 4000 ml (range: 2000–6000 ml). The average delay between AHR diagnosis and start of TPE was 3.65 ± 5.67 days. Complications related to TPE therapy were citrate toxicity (two patients, six TPE procedures, 2.13%) and allergic reaction to FFP transfused at the end of procedure (one patient, two TPE procedures, 1.06%).

Of the 49 patients, 38 patients (78%) with a favorable response underwent 213 (75.8%) TPE procedures with an average of 5.6 TPEs/patient (range: 2–12), whereas 11 patients (22%) with an unfavorable response underwent 68 (24.2%) TPE procedures with an average of 6.2 TPEs/patient (range: 3–8). Blood urea (P = 0.012) and serum creatinine (P = 0.038) levels at the time of rejection were statistically significant predictors of response to TPE therapy [Table 3]. Owing to low urine output, higher baseline blood urea, and serum creatinine levels, among the 11 patients with an unfavorable response, an average of 6.2 TPE sessions were performed, which led to increased length of stay (P = 0.011) in comparison to the favorable group (unfavorable 47 ± 22 days; favorable 27 ± 21 days), and yet no recovery of graft function was noted in them [Table 3]. On comparing Groups 1 and 2, antirejection therapy (combination of TPE with IVIg and/or rituximab) given had no effect on the outcome [Table 3]. The ALOS in our study population was 33 ± 22 days.

The median baseline serum creatinine posttransplant was 1.9 mg/dL (range – 0.8–2.4). The average time for serum creatinine levels to return to a baseline level

Table 3: Demographic (median, range) and laboratory parameter details of acute humoral rejection patients (mean±standard deviation)

	Overall (*n*=49)	Favorable (*n*=38; Group 1)	Unfavorable (*n*=11; Group 2)	*P*
Patient				
Age (years)	37 (21-79)	42 (21-79)	31.3 (21-45)	0.016
Gender (male/female)	37/12	31/8	6/4	0.108
Dialysis (months)	4 (0-72)	8.5 (0-72)	7.4 (0-36)	0.933
Prior history of blood transfusion	26	20	6	1.000
ALOS (days)	28 (6-97)	27.4 (6-97)	47 (26-80)	0.011
HLA mismatch	3 (2-6)	3.2 (2-6)	3.5 (2-6)	0.603
Donor				
Age (years)	47 (23-68)	45 (23-68)	51 (32-62)	0.675
Gender (male/female)	26/23	21/17	5/6	0.817
At time of rejection				
Blood urea (mg/dL)	96.4±44.2	89±43.4	122.2±38.2	0.012
Serum creatinine (mg/dL)	3.9±1.8	3.6±1.6	4.9±2.2	0.038
Serum sodium (mEq/L)	135.5±5.8	136.1±5.7	133.5±6.1	0.253
Serum potassium (mEq/L)	4.3±0.6	4.3±0.6	4.4±0.7	0.838
Urine output (ml)	81.5±45	86.1±45.9	65.9±39.7	0.27
At the time of the therapy				
Blood urea (mg/dL)	142.1±65.8	128.8±60.8	173.1±40.2	0.018
Serum creatinine (mg/dL)	4.2±1.8	3.6±1.5	5.5±1.6	0.0007
Serum sodium (mEq/L)	138.5±4.9	138.2±3.9	138.8±3.4	0.487
Serum potassium (mEq/L)	3.9±0.5	4±0.4	4±0.3	0.829
Urine output (ml)	2137.8±1281.1	2520.6±932.3	897.2±571.9	<0.001
At the time of discharge				
Blood urea (mg/dL)	103.4±65	86.5±47.4	167.3±74.9	0.00005
Serum creatinine (mg/dL)	5.6±19.6	2.1±0.9	5.2±1.6	<0.001
Serum sodium (mEq/L)	136±19.7	138.6±3.8	139.5±4.6	0.44
Serum potassium (mEq/L)	4.1±0.7	3.9±0.5	4.6±0.7	0.002
Urine output (ml)	2673±1575.3	3210.3±1116.6	1084.1±1659	0.004
Antirejection therapy				
TPE plus IVIg	38	31	7	0.117
TPE plus IVIg plus RTX	11	7	4	0.237

ALOS=Average length of stay, HLA=Human leukocyte antigen, TPE=Therapeutic plasma exchange, IVIg=Intravenous immunoglobulin, RTX=Rituximab

was around 24 ± 17 days. On comparing Groups 1 and 2, statistically significant difference was noted for the average time taken for serum creatinine levels to return to baseline level [Group 1 – 20 days; Group 2 – 38 days; P = 0.002; Table 3]. Six months posttransplant, the patient and graft survival were 93.3% and 89.5%, whereas at 12 months, they were 89.3% and 81.5%, respectively. Eight patients were lost to follow-up. Figure 1 summarizes the patient outcome.

Discussion

The published literature on the treatment of AHR patients differs from center to center,[6,7,9-11] with each center utilizing different permutation and combination of treatment modalities available along with the experience of the center. TPE is the cornerstone of the treatment for AHR, as it is the fastest and most effective method for the elimination of circulating antibodies, particularly DSA.[7] Other treatment options available for these patients are immunosuppressive drugs (CNIs, mycophenolic acid-derived drugs, and antilymphocyte antibody) for controlling the T-cell-dependent B-cell responses, IVIg by inhibiting or blocking the residual antibodies, and rituximab by suppressing the antibody production.[3,7]

The incidence of AHR in our study was 3.04%. Similar results have been reported by Stalinska *et al*.[9] (3.7%). Abraham *et al*.[6] reported a higher incidence of 4.5% in their study. They followed an aggressive treatment approach that included TPE along with intensification of immunosuppressants but without IVIg and rituximab, whereas in our study, the combination of IVIg and/or rituximab with TPE was used, which might have resulted in better response in our patients, thus a lower incidence of AHR. Abraham *et al*.[6] also observed that frequency of TPE sessions along with daily treatment in early stages resulted in better graft survival, possibly by maximizing DSA clearance, thus increasing the likelihood of response to treatment. Thus, in our study, the average gap between the AHR diagnosis and start of TPE therapy was 3.6 days, which might

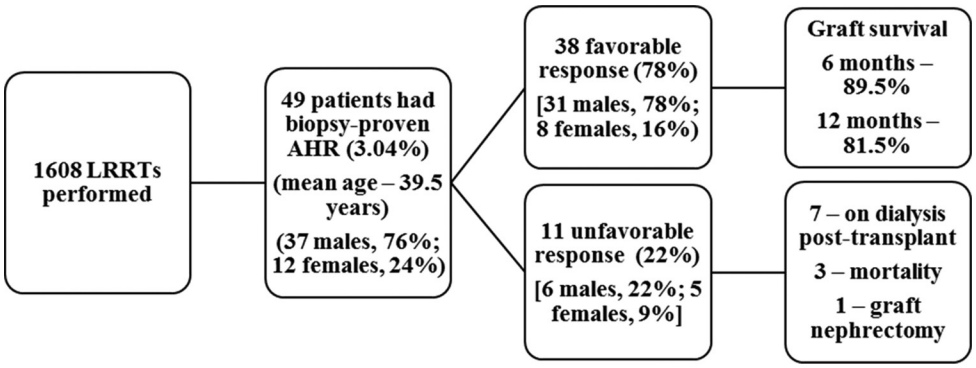

Figure 1: Flowchart summarizing the patient outcome. LRRT = Live-related renal transplantation, AHR = Acute humoral rejection

have resulted in better response in our patients due to the early start of TPE in combination with IVIg and/or rituximab. Larpparisuth *et al*.[12] also reported a higher incidence (5.36%) compared to our study. They observed that majority of their patients (68%; 17/25 patients) were highly sensitized, which further increases the inherent risk of rejection. However, in our study, 26 patients had a prior history of blood transfusion, which would probably increase their risk of rejection; however, we were unable to test our patient population for DSA in pretransplant and after diagnosis of AHR. Therefore, we cannot comment on the risk of rejection due to the presence of DSA *per se* in our study.

von Moos *et al*.[13] have reported that younger kidney transplant recipients have a higher risk of developing AHR due to heightened immune responses, resulting in increased levels of DSA. We observed that patients with an unfavorable response were younger in comparison to those with a favorable response (P = 0.016). The most common presenting symptom at the time of rejection in our study was oliguria (100%) followed by fever (58%); similar findings have been reported by Gupta *et al*.[11] Abraham *et al*.[6] reported that the median serum creatinine at the time of rejection might influence the number of TPE being performed. Compared to their study (median serum creatinine at the time of rejection – 5.96 mg/dL; average 8.1 TPE procedures), the median serum creatinine at the time of rejection (3.85 mg/dL) and the average number of TPE performed (5.7 TPE procedures) in our patient population were lower. They also observed that patients responding to the treatment required more sessions of TPE, which was also statistically significant, but we did not observe this in our study. Another major difference was that they processed 1–1.4 calculated plasma volumes; however, in our study, we processed a standard of 1.5 plasma volumes for all our patients. Therefore, we were able to process a larger plasma volume and provide a standardized treatment to all the patients in every sitting, which might have led to lesser number of TPEs being performed for our patients.

Patients with AHR can present with mixed features suggestive of concomitant ACR, which responds well to methylprednisolone pulse therapy. In case of no response to pulse therapy, ATG might be given to attain better graft function and save the graft.[3,6,10] In our study, we observed 17 patients (35%) presenting with features of cellular rejection along with AHR. They responded well to pulse therapy and ATG. Similar results have been reported by Abraham *et al*.,[6] Larpparisuth *et al*.,[12] and Gubensek *et al*.[10]

TPE is considered a safe procedure; however, it is known to be associated with variable rates of side effects such as bleeding diathesis, volume contraction, allergic reactions, citrate-related effect/toxicity, and blood-borne pathogen transmission.[14] Of the total 281 TPEs performed in our study, we observed citrate-related effects in six procedures (2.13%; treated with intravenous calcium gluconate) and allergic reactions in two procedures (1.06%) among three patients. Of these three patients, two had lower body weight, whereas another had known allergic history and complained of mild allergic reaction (urticarial rashes) to FFP transfused (treated with intravenous antihistaminic) toward the end of the procedure. Gubensek *et al*.[10] performed 237 TPEs and reported mild allergic reaction (0.4% procedures) followed by significant metabolic alkalosis induced by citrate and FFP as the complications related to TPE in their study.

Of the 49 patients, 78% (n = 39) had a favorable response that is recovery of the renal function with dialysis independence (increase in urine output and significant fall in serum creatinine level). However, 22% (n = 11) of the patients had an unfavorable response, as no improvement in graft function was seen in them despite undergoing 3–5 consecutive TPE sessions along with IVIg and/or rituximab administration. The probable reason for patients with unfavorable response not responding to TPE therapy could be the presence of the underlying tubular atrophy and interstitial fibrosis or another acute kidney injury that was not rejection,

which was not investigated in our patient population by performing repeat biopsy, neither these patients were monitored for DSA levels, which again would have provided evidence to determine no response to TPE therapy. Of the 11 patients with an unfavorable response, 7 patients were put on hemodialysis post transplantation despite treatment. As these patients were already on potent immunosuppressants, the chances of infection increased, therefore we observed mortality due to sepsis-related multiorgan failure in two patients and bleeding with wound infection in another patient. Graft nephrectomy was performed in one of these patients and subsequently, he was put back on hemodialysis. At 6 months, the patient and graft survival were 93.3% and 89.5%, whereas at 12 months, they were 89.3% and 81.5%, respectively. Similar results have been reported in the published literature.[5-7,9-11]

The several limitations encountered in our study are: (i) it was a prospective observational single-center study with a limited sample size and follow-up duration, (ii) almost 16.3% of the patients were lost to follow-up, (iii) DSA monitoring pre- and post-interventions (TPE plus IVIg and/or rituximab) was not done which would have provided evidence for efficacy of the treatment given, (iv) difficult to comment on the efficacy of TPE as patients were also given IVIg and/or rituximab which might have affected the response to TPE therapy, (v) around 35% of the patients presented with concomitant ACR, (vi) lack of group of AHR patients who were treated with TPE only, (vii) no repeat graft biopsy being performed to document the AHR reversal and effectiveness of the treatment given, and (viii) patient follow-up after AHR treatment consisted of biochemical parameters only (serum creatinine), as no graft biopsies or DSA monitoring was performed which might lead to misdiagnosis of chronic AHR.

As the number of patients undergoing renal transplantation is increasing annually in India, studies documenting the effectiveness of different treatment modalities may help in better management of patients with AHR, as it is the most severe form of rejection, which can be reversed with timely and aggressive treatment approach. In our study, we found TPE to be a safe and effective adjunct therapy for treating AHR patients.

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Conflicts of interest

There are no conflicts of interest.

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