Utility of Double Filtration Plasmapheresis in Acute Antibody Mediated Renal Allograft Rejection: Report of Three Cases

Akut Antikor Aracılı Renal Allograt Rejeksiyonunda Çift Filtrasyon Plazmaferez: Üç Vaka Bildirimi

ABSTRACT

Plasmapheresis is an extracorporeal procedure, which is often employed to rapidly lower circulating titers of autoantibodies, immune complexes or toxins. There are two types of plasmapheresis namely, regular plasmapheresis (RPP) by centrifugation and membrane filtration, and double filtration plasmapheresis (DFPP) which is a special form of membrane filtration in which two membranes called as plasma separator and plasma fractionator are employed to filter macromolecules more selectively. DFPP have several advantages over RP. Despite widespread utilization of DFPP in the setting of ABO blood group incompatible kidney transplantation, there is no report regarding DFPP in patients with antibody mediated acute renal allograft rejection who are good candidates for beneficial effects of DFPP. Here we report three renal transplant recipients in whom DFPP was applied as a component of anti-rejection treatment regimen.

KEYWORDS: Kidney, Transplantation, Rejection, Plasmapheresis

ÖZ

Plazmaferez, dolaşımdaki antikor, immün kompleks ve toksin düzeylerini hızla düşürmek için kullanılan bir ekstrakorporeal yöntemdir.İki tip plazmaferez bulunmaktadır: Santrifüj ve membran filtrasyonu ile yapılan regüler plazmaferez (RP) ve büyük moleküllerin daha selektif olarak filtre edildiği, plazma ayırıcısı ve plazma fraksiyoneri olarak adlandırılan iki membranın kullanıldığı özel bir filtrasyon şekli olan çift filtrasyon plazmaferezdir (ÇFP).ÇFP'nin RP'ye göre bazı avantajları vardır. ABO uyumsuzluğunda böbrek nakli uygulamasında ÇFP yaygın olarak kullanılmasına rağmen, ÇFP'nin faydalı etkileri için iyi bir aday olabilecek antikor aracılı akut renal allograft rejeksiyonu olan hastalarda ÇFP ile ilgili vaka bildirimi yoktur. Burada rejeksiyon tedavisinin bir parçası olarak ÇFP uygulanan üç renal transplant hastasını bildirmekteyiz.

ANAHTAR SÖZCÜKLER: Böbrek, Transplantasyon, Rejeksiyon, Plazmaferez

Yalçın SOLAK[1]
Hüseyin ATALAY[1]
İlker POLAT[2]
Melih ANIL[1]
Kültigin TÜRKMEN[1]
Zeynep BIYIK[1]
Mehdi YEKSAN[1]

1 Selcuk University Faculty of Medicine, Department of Nephrology, Konya, Turkey
2 Selcuk University Faculty of Medicine, Department of Internal Medicine, Konya, Turkey

CASE REPORTS

Plasmapheresis is an extracorporeal procedure, which is often employed to lower circulating titers of autoantibodies, immune complexes or toxins rapidly(1). Acute antibody-mediated renal allograft rejection (AAMR) is among the relatively well established indications of therapeutic plasmapheresis (2). Basically there are two types of plasmapheresis namely, regular plasmapheresis (RPP) by centrifugation and membrane filtration. Double filtration (Cascade) plasmapheresis (DFPP) employs two membranes with different pore sizes, more selective in terms of removal of immunoglobulins and some specific molecules involves (cryofiltration, hemadsorption) and have some advantages over RPP. DFPP has been used largely for ABO blood group incompatible renal transplantation. Acute antibody-mediated renal allograft rejection is an important cause of graft loss and morbidity in early postoperative period (3). In contrast to RPP, experience with utilization of DFPP in the setting of acute antibody-mediated renal allograft rejection is scarce. We report three cases in whom we used DFPP for treatment of AAMR.

Received : 03.12.2010
Accepted : 10.03.2011

Correspondence Address:
Yalçın SOLAK
Selçuk Üniversitesi Tıp Fakültesi,
Nefroloji Bilim Dalı.
Konya, Turkey
Phone : +90 505 889 98 85
E-mail : yalcinsolakmd@gmail.com

We are presenting three patients in whom AAMR complicated the course of the renal transplantation. All cases were diagnosed by allograft biopsy. Although we could not use C4d staining in biopsy specimens due to inavailability of the stain, the histopathologic changes were characteristic for AAMR and other possible causes of allograft dysfunction were excluded. All of the patients responded favorably to AAMR treatment.

We used DFPP in all three patients on alternate days along with other appropriate treatments for AAMR. We used Infomed HF-440 Hemofiltration device with LF-050 (Infomed SA, Switzerland) and Evaflux-2A (Kuraray Co., Ltd. Japan) membranes as plasma separator and plasma fractionator, respectively. Anticoagulation was provided by unfractionated heparin with monitoring of coagulation tests. Each DFPP session processed 1-1.2 plasma volume of the corresponding patient. We used human albumin solution as substitution fluid.

Case-1

A 52-year-old male who had been performing continuous ambulatory peritoneal dialysis for four years underwent deceased donor renal transplantation. Underlying renal disease was unknown. He was administered prednisolone, mycophenolate mofetil (MMF) and anti-thymocyte globulin (ATG Fresenius) as an induction agent. His periton catheter remained in place and periodic flushes were performed along with effluent white blood cell counts. At postoperative sixth day, urine output started to diminish. After exclusion of dehydration and a mechanical cause, percutaneous allograft biopsy was performed, which showed changes consistent with AAMR. Six DFPP sessions on alternate days were performed along with pulse prednisolone for three days. Urine output increased but did not exceed 500 ml/day. He was hemodialysed on alternate days. The patient developed severe Acinetobacter baumannii peritonitis which was susceptible only to tigecycline and died due to refractory septic shock.

Case-2

A 53-year-old female patient who had been on hemodialysis for seven years underwent deceased-donor renal transplantation. She had diabetes mellitus and chronic obstructive pulmonary disease. She was administered basiliximab for induction treatment. Her maintenance immunosuppressive regimen included tacrolimus, prednisone and MMF. On the second postoperative day her urine output diminished. Percutanous allograft biopsy revealed AAMR. Intravenous immunoglobulin (IVIG) along with alternate day DFPP (five sessions) were applied. The patient was disharged with normal graft function. She was followed for 20 months after transplantation. The last biochemical results were as follows: BUN: 53 mg/dl, creatinine: 1.04 mg/dl, Na: 126 mEq/lt, K: 4.2 mEq/lt, albumin: 3.1 g/dl, Hb: 9.4 g/dl, Htc: 40.7 %, Wbc: 8600 cell/mm3, platelet count: 202,000/mm3, creatinine clearance: 69 ml/min, spot urine protein/creatinine ratio: 0.12. Her treatment included tacrolimus 2mg bid, mycophenolate sodium 360 mg bid , prednisolone 5 mg/day, verapamil 240 mg/day treatment.

Case-3

A 59-year-old female patient who had been on hemodialysis for ten years due to diabetes mellitus underwent deceased-donor kidney transplantation. Basiliximab was used as induction agent. Her maintenance immunosuppression regimen included tacrolimus and MMF. On the first postoperative day, her urine output diminished. Percutanous allograft biopsy showed AAMR. DFPP five sessions on alternate days were applied along with IVIG and pulse prednisolone treatment. Urine output returned to normal in four days under this treatment and the patient was discharged with normal graft functions. She was observed for 18 months after transplantation. She was hospitalized in general surgery department for drainage of lymphocele two months after transplantation. Her latest biochemical and hemogram results were as follows: BUN: 21 mg/dl, creatinine: 1.2 mg/dl, Na: 137 mEq/lt, K: 3.5 mEq/lt, albumin: 4.2 g/dl, Hb: 13.3 g/dl, Htc:40.7 %, WBC: 5640 cell/mm3, platelet count: 187,000/mm3, creatinine clearance: 51.8 ml/min, spot urine protein/creatinine ratio: 0.20. Her treatment included tacrolimus 1 mg bid, mycophenalate mofetil 360 mg bid, prednisolone 5 mg/day, verapamil 120 mg/day, allopurinol 300 mg/day.

DISCUSSION

AAMR is defined as renal graft dysfunction in a patient who has morphologic evidence of acute tissue injury, immunopathologic evidence for antibody action (C4d staining), and serologic evidence of circulating donor spesific antibodies (DSAs) (4).

Treatment of AAMR is based on four major concepts, namely, supression of the T-cell response, elimination of circulating antibodies (via plasmapheresis), inhibition of residual antibodies and depletion of B-cells (2). Plasmapheresis is the fastest acting therapy among available treatments of AARM. By means of plasmapheresis DSAs are readily cleared from the plasma. Most of the time plasmapheresis is not sufficient when used alone in the AAMR setting. RPP can not eliminate all DSAs, some residual amount of DSAs persists, thus blocking of residual DSAs by intravenous immunoglobulin and preventing further DSA synthesis by immunosuppressive drugs and/or rituximab need to be implemented along with RPP (2).

To the best of our knowledge, there is no report in the literature describing use of DFPP in the AAMR setting. In contrast, there is considerable experience about utilization of DFPP in preperation of patient to ABO blood group incompatible renal transplantation with success rates up to 97% (5, 6). In addition, DFPP has been successfully used in various conditions among which are cryoglobinemia (7), Goodpasture syndrome (8), Guillian Barre syndrome and multiple sclerosis (9).

DFPP tecnique, first described by Agishi (10), utilizes two membranes. A patient's blood first pass through plasma separator which separates plasma. Then separated plasma is further processed by a second filter called as plasma fractionator. This membrane is used to separate principally immunoglobulins from the plasma. Rest of the plasma deprived of immunoglobulins then is sent back into blood (11). Fractionators differ in pore sizes, consequently have different filtration capabilities for agents such as IgA, IgG, cytokines, IgM and LDL (12).

DFPP has several advantages over RPP. First, DFPP selectively removes macromolecules while RP is nonselective in this regard. Second, there is no deficiency syndrome with DFPP since it conserves immunoglobulins and coagulation factors, and patients are less likely to develop sepsis due to conservation of IgG. Third, DFPP requires little or no replacement fluid in the form of albumin and/or fresh-frozen plasma (FFP). Thus, there is no or little infection transmission risk related to FFP use. Fourth, despite the cost of the membranes, DFPP is more cost effective in the long run because it requires no replacement fluid. Fifth, DFPP utilizes a closed end system with less chance of contamination. Lastly, more than one plasma volume can be processed without increasing cost and risk of deficiency syndromes (12). Despite its advantages, DFPP membranes may cause some allergic reactions ranging from mild to severe anaphylaxis, especially in patients taking ACE inhibitors.

CONCLUSION

In these three cases we did not observe any allergic reaction, hypotension, or bleeding. Our latter two cases responded favorably to anti-rejection treatment which also incorporated DFPP into treatment regimen. Despite showing a benefit in the first patient, severe peritonitis and sepsis related patient death precluded further benefit of DFPP in this patient. We believe that considering potential benefits, DFPP should be compared with RPP in a randomized clinical trial. Less infecion tendency and less volume load potential may be very important considerations in patients experiencing AAMR.

REFERENCES

1. Madore F: Plasmapheresis. Technical aspects and indications. Crit Care Clin 2002; 18: 375-392
2. Singh N, Pirsch J, Samaniego M: Antibody-mediated rejection: Treatment alternatives and outcomes. Transplant Rev (Orlando) 2009; 23: 34-46
3. Colvin RB: Antibody-mediated renal allograft rejection: Diagnosis and pathogenesis. J Am Soc Nephrol 2007; 18: 1046-1056
4. Colvin RB, Nickeleit V: Renal transplant pathology. In Jennette JC, Olson JL, Schwartz MM, Silva FG (eds). Pathology of the Kidney (6th ed). Philadelphia: Lippincott-Raven, 2006; 1347-1490
5. Shimmura H, Tanabe K, Ishikawa N, Tokumoto T, Fuchinoue S, Takahashi K, Toma H, Agishi T: Removal of anti-A/B antibodies with plasmapheresis in ABO-incompatible kidney transplantation. Ther Apher Dial 2000; 4: 395-398
6. Tanabe K: Double-filtration plasmapheresis. Transplantation 2007; 84(12): 30-32
7. Ramunni A, Lauletta G, Brescia P, Saliani MT, Montrone M, Chironna M, Sansonno D, Dammacco F, Coratelli P: Double-filtration plasmapheresis in the treatment of leg ulcers in cryoglobulinemia. J Clin Apher 2008; 23: 118-122
8. Hajime N, Michiko A, Atsunori K,Tatsuo K, Yuko N, Naoki O, Katsuhiko S: A case report of efficiency of double filtration plasmapheresis in treatment of Goodpasture's syndrome. Ther Apher Dial 2009; 13: 373-377
9. Ramunni A, De Robertis F, Brescia P, Saliani MT, Amosuro M, Prontera M, Dimonte E, Trojano M, Coratelli P: A case report of double filtration plasmapheresis in an acute episode of multiple sclerosis. Ther Apher Dial 2008; 12: 250-254
10. Agishi T, Kaneko I, Hasuo Y Hayasaka Y, Sanaka T, Ota K, Amemiya H, Sugino N, Abe M, Ono T, Kawai S, Yamane T: Double filtration plasmapheresis. 1980. Ther Apher Dial 2000; 4: 29-33
11. Mineshima M, Akiba T: Double filtration plasmapheresis in critical care. Ther Apher 2002; 6: 180-183
12. Siami GA, Siami FS: Membrane plasmapheresis in the United States: A review over the last 20 years. Ther Apher 2001; 5: 315-320