https://doi.org/10.23873/2074-0506-2019-11-3-201-208

Experience of using polymethyl methacrylate membranes for anti-HLA antibodies' elimination by hemodialysis in renal transplant recipients

E.I. Pervakova*[1], V.V. Vasilets[1], O.N. Rzhevskaya[1,2],
N.V. Borovkova[1], A.V. Pinchuk[1,2,3]

[1]*N.V. Sklifosovsky Research Institute for Emergency Medicine,*
3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia;

[2] *Department of Transplantology and Artificial Organs, A.I. Yevdokimov Moscow State University of Medicine and Dentistry,*
1 Bldg. 20 Delegatskaya St., Moscow 127473 Russia;

[3] *Research Institute for Healthcare Organization and Medical Management,*
30 Bolshaya Tatarskaya St., Moscow 115184 Russia

Correspondence to: Elsa I. Pervakova, Cand. Med. Sci.,
Head of the Intensive Care Unit with Dialysis Methods for Patients after Organ Transplantation, N.V.Sklifosovsky Research Institute for Emergency Medicine,
e-mail: p-elza@yandex.ru

Introduction. *In recipients with pre-existing sensitization with incompatible antigens of the major histocompatibility complex, the kidney graft survival after retransplantations directly depends on the level of anti-HLA antibodies. Despite many years of experience in using various methods: plasmapheresis, cascade filtration, immunosorption, intravenous administration of immunoglobulins, the use of polyclonal anti-lymphocytic agents, the search for more acceptable ways to reduce the level of anti-HLA antibodies still remains relevant nowadays.*

The purpose of the study *was to assess the effect of polymethyl methacrylate membrane-based dialyzers on the decrease in anti-HLA antibody level in renal transplant recipients.*

Material and methods. *The study included 20 kidney transplant recipients. The main study group consisted of 10 patients who underwent early postoperative hemodialysis using polymethyl methacrylate membrane-based dialyzers to decrease anti-HLA antibody level. A total of 53 hemodialysis procedures were performed, an average of 5.3 per patient. The comparison group included 10 recipients in whom plasmapheresis had been performed at similar timing after kidney transplantation aimed at reducing the anti-HLA antibody titers and whose data were studied retrospectively. A total of 38 plasmapheresis sessions were performed, an average of 3.8 per patient.*

Results. *In the main study group, a day after the hemodialysis* procedure *using polymethyl methacrylate membrane-based dialyzers the level of anti-HLA antibodies decreased by an average of 28.3% in 6 of 10 patients (60%), and increased in 4 cases. Meanwhile, in the comparison group, the level of anti-HLA antibodies in venous blood after a plasmapheresis* session *decreased average by 44.6% in 8 patients of 10 (80%), and increased in 2 cases, on the contrary. Of note, there were no significant differences between the patients of the two compared groups either in the number of positive results ($p > 0.05$, Fisher's exact test), or in terms of the decrease in anti-HLA antibody level ($p > 0.05$, Mann – Whitney test).*

On days 2 and 5, in 50% of cases both after the hemodialysis procedure using polymethyl methacrylate membrane-based dialyzers and after the plasmapheresis session, the patients showed an increase in the

anti-HLA antibodies level compared to the baseline values. In the remaining cases, the level of anti-HLA antibodies in both groups was recorded at a lower range compared to the baseline values.

Conclusion. *The use of polymethyl methacrylate membrane-based dialyzers in the renal allograft recipients having a high level of preexisting anti-HLA antibodies seems promising for the period of oligoanuria until the renal allograft function is restored, since both hemodialysis and the sorption of pre-existing (and also newly synthesized) antibodies take place simultaneously.*

Keywords: kidney transplantation, anti-HLA antibodies, hemodialysis, polymethyl methacrylate, plasmapheresis

Conflict of interest Authors declare no conflict of interest

Financing. The study was performed without external funding

Pervakova EI, Vasilets VV, Rzhevskaya ON, Borovkova NV, Pinchuk AV. Experience of using polymethyl methacrylate membranes for anti-HLA antibodies' elimination by hemodialysis in renal transplant recipients. *Transplantologiya. The Russian Journal of Transplantation.* 2019;11(3):201–208. (In Russ.). https://doi.org/10.23873/2074-0506-2019-11-3-201-208

ARC, acute rejection crisis

aHLAa, anti-HLA antibodies, antibodies to HLA histocompatibility complex

CKAT, cadaveric kidney allotransplantation

DBP, diastolic blood pressure

EH, extracorporeal hemocorrection

ESRD, end-stage renal disease

FLCs, plasma levels of immunoglobulin free light chains in patients with ESRD

FSGN, focal segmental glomerulonephritis

HD-PMMA, hemodialysis using polymethyl methacrylate membrane-based dialyzers

HLA, human leukocyte antigens

Ig, immunoglobulin

IST, immunosuppressive therapy

KAG, kidney allograft

MAP, hemodynamic mean arterial pressure

MFI, mean fluorescence intensity

PMMA, polymethyl methacrylate

PPH, plasmapheresis

SBP, systolic blood pressure

WL, waiting list

β_2M, β_2-microglobulin

Rationale

Among the patients on the waiting list for transplantation, the number of those with pre-existing anti-HLA antibodies has recently increased significantly. According to various authors, more than 30% of recipients from the WL are positive for anti-HLA antibodies (aHLAa) at baseline. At the same time, more than 50% of patients awaiting kidney retransplantation are sensitized against HLA class I and class II [1]. Anti-HLA antibodies are formed due to a prior sensitization by incompatible major histocompatibility complex antigens as a result of blood transfusions, previous transplantations, history of pregnancies, etc. [1]. Anti-HLA antibodies are class G

immunoglobulins (Ig) with a molecular weight of about 160 kDa, which are synthesized by mature B lymphocytes and plasma cells and constitute the bulk of blood serum Ig. They account for 70–80 % of all serum Ig, with about 50% being contained in the tissue fluid.

The presence of preexisting anti-HLA antibodies in the recipient is the main etiological factor of the delayed graft function, and in more severe cases may cause the kidney graft loss in the early post-transplant period due to a hyper-acute or acute rejection crisis (ARC) [2]. However, a high level of aHLAa in recipients is not an absolute contraindication to kidney transplantation. In this regard, the ability to reduce the aHLAa titer is of a paramount importance for the survival and full recovery of kidney allograft function (KAG) in sensitized recipients. Currently, desensitization may be undertaken in a planned manner either at the stage the potential recipient being on the WL or during the preparation for a kidney transplantation from a living donor. Also the desensitization may be conducted on urgent indications immediately before the cadaveric kidney allotransplantation (CKAT). In such cases, the desensitization is continued in the postoperative period, as a rule. For this purpose, the extracorporeal hemocorrection (EH) methods with proven efficiency such as plasmapheresis [PPH], cascade filtration, immunosorption, or intravenous Ig administration are used before CKAT and in the early postoperative period in most clinics [1, 3–6]. However, the high cost of EH, the need for repeated EH procedures, and in some cases limited technical capabilities, do not allow using these tools in routine practice. On the other hand, the use of polyclonal antithymocyte drugs (ATGAM®, timoglobulin®, etc.) for the ARC prevention in sensitized recipients is limited because of the formation of antibodies against these drugs [7]. Therefore, the search for more acceptable ways to reduce the

preexisting aHLAs levels has remained extremely relevant to date. From this point of view, the most interesting are the data on the effect of polymethyl methacrylate (PMMA) membrane-based hemofilters on the elimination of protein-bound uremic toxin of furan-2-carboxylic acid, the removal of β2-microglobulin (β2M) [9], homocysteine [10], total pentosidine, protein carbonyls, protein oxidation products, and cytokines (interleukin IL-1β, IL-6, and tumor necrosis factor α) [11] from plasma in dialysis patients. Moreover, it was shown that the BK-F model is distinguished by a maximum capacity for β_2M removal, the capacity that is greater than that of well-known polyacrylonitrile (AN-69 or PAN) and polysulfone, and the effect obtained is largely owing to the adsorption of β_2M on the dialysis surface of the PMMA membrane [12]. Recent studies have found that PMMA-membrane adsorption used in dialysis patients can remove the various protein complexes [13, 14] releasing histamine components with a molecular weight of 160 kDa [15], and also reduce plasma levels of free Ig light chains (FLCs) [16] and the level of soluble serum CD 40 [17]. PMMA membranes have also been shown to have a lower stimulating activity against the complement system [18].

All those factors formed the basis for our use of PMMA membrane dialyzers in the patients with high titers of anti-HLA antibodies.

Material and methods

Ten recipients sensitized to the major histocompatibility complex antigens were studied in the period of awaiting for kidney transplantation. These patients were included in group I (HD-PMMA) (See Table). Before CKAT, the aHLAa of both Class I, and Class II were identified in blood of all recipients, with an average fluorescence intensity (MFI) from 2,500 to

17,000 U. Given the delayed KAG function, hemodialysis was performed using PMMA-based membrane dialyzers (HD-PMMA) to all recipients in the short-term after transplantation. A total of 53 HD-PMMA procedures were given.

Table. Renal transplant recipient characteristics

Parameter	**Total** **N = 20**	**Group I (DH-PMMA) N = 10**	**Group II (PPH)** **N = 10**
Gender, m/f	9/11	4/6	5/5
Age, years	45.9 ± 5.1	43.1 ± 4.7	48.8 ± 5.9
ESRD origin:			
Chronic glomerulonephritis	9	6	4
Systemic lupus erythematosus	3	1	2
Chronic pyelonephritis, ICD	2	1	1
Congenital urogenital system malformation	3	2	1
Nephropathy of unknown etiology	2	-	2
Repeated CKAT	17	9	8

Notes: ESRD, end-stage renal disease; ICD, International Classification of Diseases

Hemodialysis was performed using the *Artificial Kidney* machine (Fresenius 5008, Germany). Hemodialysis mode characteristics:

• Dialyzer type: VK-2,1 FTORAY;

• Blood flow rate: 200–250 ml/min;

• Dialysis fluid flow rate: 500 ml/min;

• Vascular access (AV fistula, double-lumen central catheter 12.5 F);

• Procedure duration: 4 hours;

• Number of procedures: from 3 to 8 sessions (mean 5.3 per patient);

• Anticoagulation: Heparin 10–12 (U/kg/h).

For comparison, the results obtained from 10 other recipients were analyzed retrospectively; they comprised group II where PPH was performed on a Multi Filtrate machine in the early post-transplantation period in order to reduce the aHLA titer (see Table). A total of 38 PPH sessions were given.

PPH mode characteristics:

• Multi Filtrate Kit 6 IS MPS 2;

• Access: (AV fistula, 2-lumen central catheter 12.5 F);

• Procedure duration: 2–2.5 hours;

• The number of procedures: from 2 to 5 sessions (mean 3.8 per patient);

• Blood flow rate: 100–120 ml/min;

• Plasma removal rate: 650–900 ml/h;

• Plasma exfusion volume: 1200–1600 ml (25–30 ml per kg of patient's body weight);

• Volume replacement: fresh frozen plasma, albumin, crystalloids;

• Anticoagulation: Heparin 10–20 (U/kg/h).

The postoperative patient management, both in the main and in the comparison group, was carried out according to a standard diagnostic and treatment protocol. The schemes of immunosuppressive therapy (IST) in the patients of both groups were similar. Polyclonal antithymocyte antibodies (thymoglobulin or ATGAM) were used as induction IST. The maintenance IST protocol included calcineurin inhibitors (tacrolimus or cyclosporin), lymphocytoselective inhibitors of purine synthesis, i.e. the mycophenolic acid derivatives, and steroid hormones. Steroid hormones were administered intravenously (250 mg/day) for the first 2 days after CKAT, later they were given orally. Patient's examinations included: an assay for anti-HLA antibody and standard clinical and laboratory tests for hemoglobin, erythrocytes, leukocytes, platelets, total protein, creatinine, urea, electrolyte level and acid-base status before and after the EH, using the standard techniques. Hemodynamic parameters were also monitored with a timely correction of abnormalities. The central hemodynamics status was assessed by taking the systolic blood pressure (SBP), diastolic blood pressure (DBP), calculating the mean hemodynamic pressure (MAP = (SBP – DBP)\3 + MAP). All patients also underwent X-ray, ultrasound, Doppler sonography studies, dynamic nephroscintigraphy. In all recipients, the whole blood levels of calcineurin inhibitors were determined 3 times a week to assess whether the received IST dose was sufficient.

Anti-HLA antibodies in the serum of the recipients were assessed before hemodialysis, and at days 1, 2, and 5 after the procedure (PPH or HD-PMMA). Anti-HLA antibodies were detected using a multiplex assay on the Luminex platform using Lab Screen Mixed kits (One Lambda, USA). The serum reactivity was assessed by the fluorescent signal from each microsphere, after the correction of non-specific binding with a negative

control by the microsphere. If MFI did not exceed 500 units, the result was considered negative; with MFI values of 500–3000 units, a medium degree of sensitization to HLA was recorded, and a high degree was recorded with MFI over 3000 units.

Statistical analysis of the data was performed using Statistica 10 software package (StatSoft, Inc., USA). The groups were compared using Fisher's exact test and the Mann–Whitney test. The threshold level of significance was assumed to be 0.05.

Results

A day after the HD-PMMA procedure, 60% of patients (6 of 10) in the main group had the aHLAa level decreased by an average of 28.3%, and in 4 cases the aHLAa level increased. Meanwhile, after the PPH session, 80% of patients (8 of 10) in the comparison group had the aHLA level in venous blood decreased by an average of 44.6%; and in 2 cases an increase in the antibody content was observed. We noted no significant differences between the patients of the compared groups in terms of the number of positive results ($p>0.05$, Fisher's exact test), and in terms of the aHLA content decrease ($p>0.05$, Mann–Whitney test). .

On the 2nd and 5th day, in 50% of cases, both after the HD-PMMA procedure and after the PPH session, the patients had an increase in the aHLAa content as compared to baseline. In the rest of the cases, the levels of the antibodies to the major histocompatibility complex antigens in both groups were lower compared to the baseline. We present a clinical case report.

Clinical Case Report

Patient G., 25 years old, had a diagnosis of focal segmental glomerulonephritis (FSGN) and an end-stage renal disease; condition after repeated CKAT (2007 and 2011); chronic allograft nephropathy, Grade 2A; the acute rejection crisis of the humoral type; hepatitis C (de novo) experienced in 2013; secondary arterial hypertension (controllable); secondary anemia; chronic gastritis.

The previous history: the patient had been ill since the age of 3 months old when her urinalysis revealed proteinuria for the first time. She was hospitalized for treatment several times. In 1999, a kidney biopsy was performed that identified FSGN. In July 2007, having a high level of nitrogenous slag, she was hospitalized and a renal replacement therapy was started. In September of the same year, a live-related kidney transplantation was performed (the donor was her father). An immediate graft function was noted. In May 2008, a biopsy-confirmed ARC occurred; the pulse therapy with methylprednisolone was performed with a simultaneous conversion of calcineurin inhibitors from cyclosporine A to tacrolimus. In 2009, a program hemodialysis was resumed for the recurrent ESRD of the graft and increasing azotemia. In August 2011, the patient underwent a repeated kidney allotransplantation (from a posthumous donor) in the Sklifosovsky Research Institute for Emergency Medicine. In the early post-transplantation period, a delayed KAG function was observed, and a renal replacement therapy was performed. Diuresis resumed from day 11 after CKAT. For the purpose of ARC prevention, basiliximab (simulekt) 20 mg, was administered twice as an induction IST: intraoperatively and on day 4 after CKAT. A three-component maintenance IST with tacrolimus of extended release, mycophenolate mofetil, and prednisolone was given. Considering a high titer

of aHLAa, a pronounced KAG enlargement seen at ultrasound, and deteriorating intraorgan blood flow, ATGAM was administered and 5 sessions of the PPH were also performed for 15 days (from day 2 to day 17 after CKAT). At discharge from hospital, the KAG function was satisfactory. Subsequently, the patient was followed-up at Moscow City Nephrology Center of Municipal Clinical Hospital № 52.

The hospitalization in May 2016 described in the present paper was due to unstable blood levels of tacrolimus in the patient and the necessity to differentiate the diagnosis between an acute rejection crisis and the nephrotoxicity of calcineurin inhibitors. A puncture biopsy of KAG was performed that revealed the humoral rejection signs; a 3-day pulse therapy with metipred was performed, thymoglobulin 25–50 mg was administered daily for 6 days, and the baseline IST was intensified. Due to high levels of aHLAa class I and class II (1465 U and 5637 U, respectively) and patient's azotemia, hemodialysis was started using PMMA-membrane-based hemodialyzers (BK-2,1 F). After the three procedures of HD-PMMA, the patient showed a decrease in aHLAa of both class I, and class II (to 948 U, and 2672U, respectively). On day 23, the patient was discharged home having a satisfactory KAG function (creatinine decreased from 255 mmol/L to 209 mmol/L, urea decreased from 17.34 mmol/L to 13.73 mmol/L, diuresis increased from 1800–3400 ml). At discharge from the hospital, there was a slight increase in aHLAa class I (1238 U) and class II (3948 U), but those values did not reach the baseline values (Fig. 1).

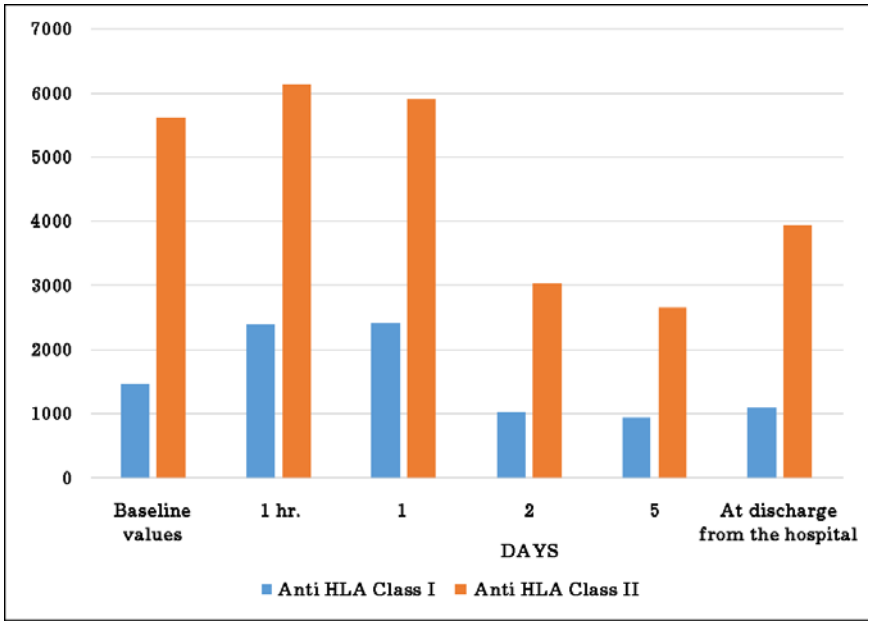

Figure. Changes in the level of anti- HLA antibodies in blood over time in patient G

Discussion

Hemodialysis is the main treatment option at pretransplantation stage for the patients with ESRD. Hemodialysis provides the removal of low molecular weight substances (urea, creatinine, etc.) through a semipermeable membrane. The clinical implementation of dialyzers with synthetic biocompatible membranes (AN-69, PAN, and polysulfone) with a high permeability to water and to the substances with higher molecular weights made it possible to increase the overall efficacy of hemodialysis in removing "medium" molecules, some enzymes, bacterial endotoxin [19], as well as the so-called small proteins (β_2M, myoglobin) [20], however, the permeability of these membranes for high-molecular substances remains very limited. The ability of PMMA-membrane dialyzers to remove by adsorption various complexes with a molecular weight of 160 kDa from

dialysis patients [15], as well as to reduce the plasma levels of free Ig light chains (FLCs) [16], described by a number of researchers, was the basis for our use of such dialyzers (primarily, the BK-F models) in HLA sensitized patients.

After the hemodialysis procedure using the BK-F PMMA-membrane dialyzers, 60% of the studied patients showed a definite decrease in the levels of anti-HLA antibodies of both classes compared to the baseline values. The resulting positive effect is comparable with the results obtained when removing antibodies by means of PPH. The reduced anti-HLA antibody levels in 50% of cases maintained in the patients until their discharge from the hospital. The preliminary results we obtained at this stage showed that the use of PMMA membrane BK-F dialyzers during hemodialysis in patients with the delayed KAG function was obviously more preferable. That was related to the need of providing the renal replacement therapy for these patients for the period of oligoanuria until the restoration of the KAG function. The use of PMMA membrane hemodialyzers in sensitized recipients after kidney transplantation might be economically more appropriate compared to hemodialysis with conventional dialyzers, since the former technique could simultaneously provide the hemodialysis and the sorption of preexisting (as well as newly synthesized) antibodies.

Further studies in this direction are likely to give more complete evidence on the feasibility of using PMMA-based membrane dialyzers in the recipients from the WL at the outpatient stage. Defining the mechanisms of antibody elimination was beyond our study tasks. Our fundamental task was to answer the question whether the dialyzers with the above characteristics could, in principle, contribute to decreasing the aHLAa level. Nevertheless, taking into account the molecular weight of anti-HLA antibodies (~ 160

kDa), one can assume that the adsorption processes of the latter prevail on the PMMA membrane, which undoubtedly requires further research.

Conclusion

The polymethyl methacrylate membrane dialyzers appear promising to be used for the period of oligoanuria in the renal allograft recipients with a high level of preexisting anti-HLA antibodies until renal allograft function has been restored, since both the hemodialysis and the sorption of preexisting (as well as newly synthesized) antibodies take place simultaneously.

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Information about authors

Elza I. Pervakova, Cand. Med. Sci., Head of the Intensive Care Unit with Dialysis Methods for Patients after Organ Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-2163-5537

Vladimir V. Vasilets, Anesthesiologist-Critical Care Physician of the Intensive Care Unit with Dialysis Methods for Patients after Organ Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-5975-2907

Olga N. Rzhevskaya, Dr.Med. Sci., Leading Researcher of the Kidney and Pancreas Transplantation Department, N.V. Sklifosovsky Research Institute for Emergency Medicine, Professor of the Department of Transplantology and Artificial Organs, A.I. Yevdokimov Moscow State University of Medicine and Dentistry, https://orcid.org/0000-0001-6849-1457

Natalya V. Borovkova, Dr. Med. Sci., Head of the Scientific Department of Biotechnologies and Transfusiology, N.V. Sklifosovsky

Research Institute for Emergency Medicine, https://orcid.org/0000-0002-8897-7523

Aleksey V. Pinchuk, Cand. Med. Sci., Head of the Scientific Kidney and Pancreas Transplantation Scientific Department, N.V. Sklifosovsky Research Institute for Emergency Medicine, Assistant Professor of the Department of Transplantology and Artificial Organs, A.I. Yevdokimov Moscow State University of Medicine and Dentistry, Head of the Organizational and Methodological Department for Transplantology, Research Institute for Healthcare Organization and Medical Management, https://orcid.org/0000- 0001-9019-9567

Received: May 23, 2019

Accepted for publication: June 19, 2019