PLASMAPHERESIS IN TRANSPLANTATION

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Abstract

The problem of organ transplants is still far from being resolved. Until now, to eliminate both acute and chronic rejection of transplanted organs used drugs with many side complications. At the same time, methods of efferent therapy aimed at the removal of antibodies did not get enough proper and timely application. Among them is the leading value plasmapheresis.

Key words: transplantation, rejection, antibodies, plasmapheresis.

Despite all the advances in modern transplantation still remains the problem of acute or chronic rejection of transplanted organs. These processes have many reasons which can not always be eliminated.

In cases coming transplantation without removing the remaining autoantibodies in the body, the transplanted kidney is at risk of the same autoimmune destruction as remote. On the other hand, the removal of the affected kidney with "pseudo-heterogenous" antigenic structure that encourages the constant reproduction of autoantibodies may contribute to remission and this pathological process [1].

Immune conflict after **kidney transplantation** may be the result of the emergence of anti-HLA antibodies as a result of isoimmunization in connection with previous transplants, blood transfusions or pregnancy. Despite the crossmatch with the donor organ, the presence of such HLA-antibodies leads to early rejection. Growth of donor-specific alloantibodies occurs within the first few weeks [2]. In some cases, under the influence of natural autoantibodies of IgG and IgM isotypes of complement system activation and endothelial cells can develop hyperacute rejection reaction in the next hours or even minutes [3].

Recurrence of focal segmental glomerulosclerosis in the transplanted kidney is observed in 30-80% of cases and deaths transplant within three years and up to 90% and only systematic conventional or cascade plasmapheresis after surgery prevents such complication [2, 4, 5, 6, 7]. Sometimes it takes a weekly plasmapheresis for nearly four years [8, 9, 10].

In cases with prolonged growing hypoproteinemia plasma exchange rates move to immuno-adsorption [11]. When combined taking courses plasmapheresis with rituximab (antilymphocyte immunoglobulin) or bortezomib achieved a longer remission of proteinuria [12, 13]. Nevertheless, we must bear in mind that rituximab itself can lead to serious complications that have to neutralize as by plasmapheresis [14].

R.M. Higgins et al. (1996), 9 patients had an immuno-adsorption before transplantation, which improved results and prognosis, even in cases where the previous rejection of transplanted kidneys. However M.D.Stegall et al. [15] believed that repeated sessions of plasmapheresis more reliably prevent rejection of the transplanted kidney than high doses of immunoglobulins. High frequency of graft rejection with hemolytic-uremic syndrome also requires prior course of plasmapheresis with ekulizumab [16].

Significant problems arise when forced kidney transplant under the **ABO incompatibility**. One reason is the presence of antigens A or B not only on the membranes of erythrocytes, but also on the walls of blood vessels, including transplanted kidney [17]. In this case, the recipients antibody (α or β) begin to interact with the antigens on the vascular wall, leading to disturbances of the microcirculation, and subsequent rejection of the transplanted organ ("large incompatibility"). "Shallow incompatibility" occurs as a result of generation of donor lymphocytes remaining in the transplanted organ as a "passenger", against the recipient erythrocytes, causing hemolysis of [18].

In these cases, a preliminary removal of anti-A or anti-B antibodies by plasma exchange substantially reduces the concentration of these antibodies, thereby smoothing rejection [19, 20, 21]. In cases of organ transplantation upcoming family donors, ABO incompatible, A.A. Ragimov et al. [22] performed courses of plasmapheresis to reduce the titer of antibodies to the respective levels of 1:2 - 1:4. In the case of the initial antibody titer 1:32 had to be removed to 350-550% CPV and repeated cases rise in antibody titer to 1:32 in the post-transplant period had again resorted to plasmapheresis with removal of up to 400% CPV. A.A.Tobian et al. (23) also reported the important role of plasmapheresis course, both before and after kidney transplantation with ABO-incompatibility, which eliminates episodes overactive antibody-dependent allograft rejection. Moreover, during the year the transplanted kidney proved viable in 100% of cases. Positive results were obtained when using the course immunoadsorption using columns Adsopak ABO-A production NPF POKARD [24].

When **liver transplant** under the ABO incompatibility plasmapheresis was also used before surgery [25] and T. Ashizawa et al. [26] – both before and after surgery. Shimoda M. et al. [27] reported that preoperative administration of rituximab alone (without plasmapheresis) was unable to block the production of antibodies. Plasmapheresis should be used immediately, as soon as the first signs of organ rejection [28].

The same problems with ABO incompatibility arise in hematopoietic **stem cell transplantation** in oncology and a course of plasmapheresis before transplantation largely prevents rejection crises [29].

When transplanting organ to blood incompatibility ABO system has been used successfully also cascade plasmapheresis [30, 31]. At the same time, for 3-4 sessions cascade plasmapheresis managed to reduce the titer of anti-ABO antibodies to a concentration of 1:32, which is quite acceptable criterion for subsequent kidney transplantation in ABO incompatibility.

It was possible to significantly (80-90%) reduce the content of group antibodies and using 3-4-selective immunoadsorption sessions using columns Ig-Adsopak for IgG-apheresis made NPF POKARD in Russia [32].

After transplantation, a new situation – of the transplanted kidney comes antigenic signal, in response to which begin to form new antibodies with peak acute "crisis of rejection" in 1-2 weeks. And here efferent therapy can smooth these immune responses at lower levels of immunosuppressive therapy. The courses of plasmapheresis in such cases helps to restore urine output, decrease in serum creatinine and a gradual recovery of graft function, that 60% of patients allowed avoid "transplant-ectomy" [33].

In recent years, steel plasmapheresis spend even intraoperatively immediately after inclusion the transplanted kidney to blood flow, because it was found that major levels of proinflammatory cytokines (IL-6 , IL-8 , IL-10), the middle molecular weight toxins, and the lipid peroxidation products increases and reaches maximum by the end of the operation [34]. In addition to reducing the blood levels of endotoxin, the initial recovery of nitrogen and excretory renal function occurred significantly faster – to 5 - 6th day instead of 12-18 days in cases without the use of plasmapheresis [35]. Immunosuppressive therapy with plasmapheresis is able to block rejection reaction after transplantation also loops of the **small intestine** [36].

Moreover, the transplanted organ, whether the kidney, heart, lung, liver, or bone marrow, is a constant driving force reproduction antibodies throughout their lives, making this process one of the options of autoimmune diseases. So antimyosine antibodies are often found at the rejection of the transplanted heart [37]. Graft rejection may occur even after 10 years. Alloreactive antibody formed against the graft, and they are retained, and after its rejection, which reduces the chances of subsequent engraftment of the graft. Disturbance of function of B-cells are one of the reasons for such resistant alloimmunization or hyperreactivity. Wherein the leading role belongs not so much of the T-cell regulation, as uremia in renal failure [38].

Sometimes the after-effects of **bone marrow transplantation** are the liver, which is among the reasons vein-occlusion isolated liver disease, chronic rejection reaction, viral or fungal infection and cholestatic disorders [39]. Hepatitis C among survivors after transplantation occurs from 5 to 70% of cases, and cirrhosis developed in 3.8% of patients [40].

In such reactions, as **graft-versus-host disease** (GVHD) occurs an accumulation of inflammatory cytokines such as TNF-α, IL-1β, IL-6, and this "cytokine cascade" activates other

effector cells – natural killer and macrophage, causing direct damage to skin tissue, liver and gastrointestinal tract [41]. All this makes indicate plasmapheresis and our own experience convinced of its efficacy in the treatment of GVHD [47].

It should be noted, that may develop chronic GVHD and 50% of these patients with a mortality rate of up to 25% [42], which once again underlines the urgency of this problem and the need for more active treatment involving and plasmapheresis also.

Frequent complication of stem cell transplantation is the development of thrombotic microangiopathy with edema of the intima and fibrinoid necrosis of the vessel wall. To this leads too high doses of chemotherapy conditioned, irradiation, calcineurin inhibitors (used in prophylaxis and treatment of GVHD), and infection [43]. The kidneys are affected in this case in the first place and the development of acute renal failure seems a poor prognostic factor in the level of detail 44-90% [44, 45]. And plasma exchange, performed in such cases every day before effect, able to stop such a complication [46, 47].

Modern immunosuppressive therapy consists of a combination of three drugs – cyclosporine, azathioprine and prednisolone, and in recent years – rituximab also. They improve the outcomes of transplantation, but consider that immunosuppression that occurs during prolonged administration rituximab, is fraught with the development of septic complications (up to 50-60% for the year) and, in particular, cytomegalovirus infection, for which relief is sometimes necessary to remove the transplanted kidney [48].

And at the same time not able to completely prevent the crises of acute or chronic rejection – transplant vasculopathy [49]. Processes of chronic rejection of transplanted lungs according to two transplant centers ranged from 60 to 80%. Use of antilymphocyte antibodies during episodes of graft rejection is associated with activation of viral infections and lymphoproliferative disorders. Methotrexate also promotes lymphopenia and infectious complications [50]. Furthermore, the known nephrotoxic and neurotoxic effects of cyclosporine, which often negates the results of operations and leads to the most adverse effects [51]. One of the consequences is receiving cyclosporine A is also a hypertriglyceridemia, developing after transplantation of bone marrow cells and which can be eliminated with plasmapheresis or cascade plasma filtration [52, 53].

Widely used in transplantation and calcium-nevrin inhibitors (Tacrolimus, Sirolimus), but their use is also fraught with serious complications such as thrombotic microangiopathy with the development of nephropathy (acute tubular necrosis), cholestasis, encephalopathy (headache, visual disturbances, seizures), greater frequency limfoproliferativnyh tumors [54, 55].

Since the same under similar autoimmune processes, and virtually the only truly pathogenetic treatment is efferent therapy, and among its most effective methods is

plasmapheresis, and then in transplantation should extend **the principle of periodic courses of plasmapheresis** to remove antibodies against the transplanted organ [56, 57].

That, of course, remains an urgent immunosuppressive therapy, but plasmapheresis helps take it to the sub-toxic doses without risk of adverse complications. The best effect is achieved with a combination of courses of plasmapheresis with intravenous immunoglobulin [58].

Relief of organ dysfunction after liver transplantation carrying both conventional plasmapheresis, and on system MARS (molecular adsorbent recirculating system) was equally effective [59].

A.A.Ragimov et al. [1], in particular, reported that immunosuppressive therapy after **heart transplantation**, even in cases where the cause was not transplant coronary artery disease but dilated cardiomyopathy, leads to significant violations of blood lipid and the emergence of ischemic lesions in the transplanted heart. As one of the most effective methods of treatment of hyperlipidemic conditions is plasmapheresis, and it was after 2-7 years after surgery in the treatment program included 8 patients who underwent orthotopic heart transplantation. After courses of plasmapheresis, held twice a year, there was a marked improvement in the state of hemorheology and lipid metabolism. Significantly reduced blood levels of total cholesterol and low density lipoprotein without significant changes in the concentration immunosuppressants. On scintiograms was significant improvement in myocardial perfusion in ischemic areas.

Especially true plasmapheresis was for the relief of acute rejection crises, even in unstable hemodynamics [60, 61, 62]. Moreover, O.Grauhan et al. [63] emphasized that after 7 rejection episodes in 7 patients treated without plasmapheresis, only two survived, and after 11 such episodes in 6 patients survived everybody. Plasmapheresis was successfully used during crises rejection of the transplanted heart, even in children from the age of 3.5 months [64].

At the same time, despite the removal of large volumes of plasma, has seen no significant lowering of drugs immunosupressive. Given the development allo-sensitivity to HLA-antigens in "candidates" for a heart transplant, and plasmapheresis is advisable to carry out prior to transplantation [65]. Moreover, removal of used antibodies by plasmapheresis was performed during cardiopulmonary bypass during heart transplant surgery [66].

Nevertheless, there were also attempts to directly suppress hyperactive T-lymphocytes producing antibodies, using extracorporeal photopheresis, when the irradiation with ultraviolet rays of the isolated cells [67]. However, there was not delete the already accumulated autoantibodies, which makes such procedures inadequate.

We must bear in mind that with organ transplants inevitably raises a number of disorders that should require efferent therapy. Indeed, virtually all patients who need organ transplants at

the time of surgery are very significant disturbances of homeostasis and endotoxemia caused by failure of the body. It's either renal or cardiac, or pulmonary, or even multiple organ failure.

Organ donor, who had just suffered a seizure during hypoxia and transportation, and before that the stress and endotoxemia dying donor, after transplantation hits the best conditions of the internal environment of the new owner, which makes it problematic to the proper functioning of the new location. I.N.Soloveva et al. [68] noted that the content of an average molecular weight toxins and malondialdehyde before surgery were higher than normal values and they continued to increase during the operation, peaking at 1 hour after the start of blood flow in the graft (kidney).

Therefore, it seems relevant efferent therapy and detoxification of the recipient in the preoperative period, and ideally the donor before removal from the body. Expedient the efferent therapy also in the postoperative period for the rehabilitation of the internal environment of intraoperative stress agents, which should facilitate the "inclusion" of the transplanted organ [68]. Plasmapheresis in volume 1 CPV in the next 2-3 hours after inclusion the transplanted kidney into the bloodstream reduces the level of middle molecules by 25% below the preoperative level, prevented oligoanuria, need dialysis, facilitated a more rapid normalization of creatinine and increased actuarial graft survival [34, 68]. Plasmapheresis performed immediately after liver transplantation, also prevented its dysfunction [69]. The same tactic of intra-and postoperative plasmapheresis was used also in a heart transplant in a high content of reactive antibodies and tissue incompatibility [70].

E.G.Moseshvili et al. [71] turned out well to stop the acute rejection that has occurred within 10 days after kidney transplantation, using anti-CD3 murine monoclonal antibody in combination with an intensive course of plasmapheresis (7 sessions with the removal of 2.5-3 liters of plasma per procedure).

Currently, the optimal tactic to prevent transplant rejection is considered a combination of plasmapheresis with intravenous immunoglobulin (sometimes with the addition of rituximab) [12, 28, 72]. Along with plasmapheresis immunoadsorption is also used [57]. **Cascade plasmapheresis** is the most effective and safe treatment of acute rejection crises transplanted organ [73].

Therefore highly sensibilized 11 patients with high titer antibodies in kidney transplantation repeated immediately prior to the transplantation to eliminate intraoperatively was 30-40% CPV and 40-50% CPV when the graft was inclusion into the bloodstream (substitution remote plasma were of albumin and fresh frozen plasma). In all cases, the graft began to function normally even on the operating table with the normalization of the levels of creatinine and urea in 3-4 days without rejection crises. If necessary, repeated sessions of

plasmapheresis were performed at different times at postoperative period also [74]. For one of these patients plasmapheresis program was successfully held for three years at intervals of 4 months [74].

Such preventive efferent therapy is particularly relevant and for **lung transplant**. First, the donor lungs in principle can not be "normal", since at the time of death, a donor must be developed in such an endotoxemia, which can not but lead to the development of his lungs phenomena of respiratory distress, hypoxia and ischemia, and at the time of the donation and transporting it can not add additional damage. It was shown in the laboratory staff of Experimental Pathology Institute of Pulmonology by E.N. Danilov, G.M. Kudryashov and E.D.Shehunov back in 1980-1990 -ies . ☒

In addition, with the growth of lung tissue ischemia period increases release also of such toxic substances as "big histocompatibility complex» II class, in bronchoalveolar lavage fluid increases of interleukin-2 and interferon-γ which significantly increases the risk of rejection [75].

Second, immediately after transplantation and inclusion into the bloodstream it descend pathological metabolites recipient remains in a state of severe respiratory failure, together with intraoperative BAS. All this also requires detoxification in the early postoperative, and maybe even the intraoperative period. This confirms the fact that in almost all cases, lung transplants at pulmonology institute (St. Petersburg) evolved phenomenon of respiratory distress syndrome, which were the ultimately tanatogenesis and main causes of adverse outcomes of operations.

☒Risk of acute rejection of the transplanted lung during the first year is 55% [Martinu T. et al., 2009]. If the transplanted lung and avoid rejection, then a significant number (60-80%) of these patients develop progressive **bronchiolitis obliterans**, which is no less intractable problem [76]. It is revealed by the reduction in forced expiratory volume in 1 second to less than 80% compared with early (baseline) post-transplant period. This syndrome can be considered a kind of chronic rejection.

It is characterized by progressive fibroproliferative process *lamina propria* of bronchial wall with narrowing of the lumen of the last [77]. M.A.Smith et al. [78] concluded that the bronchiolitis obliterans which occurs during the first two years after lung transplantation is the result of an autoimmune process in which antibodies to the HLA (human leukocyte antigen) and cytomegalovirus play a leading role. This was revealed in seronegative (for CMV) recipients who were transplanted lungs from seropositive donors. Plasmapheresis, followed by administration of immunoglobulin or rituximab can not only prevent rejection crises, but also to prevent the formation of bronchiolitis obliterans [79] .

Promising results if not cure, then at least delay the progression of bronchial obstructive process using photopheresis obtained when after ingestion of the drug methoxsalen with 1 mg/kg

to achieve a plasma concentration of greater than 50 mg/dl. 90 minutes after leukapheresis was performed with extracorporeal irradiation of a thin layer of white blood cells by long-wave ultraviolet rays and subsequent reinfusion of leukocytes. Similar procedures were carried out 1-2 times a month to stabilize the effects of obliterating alveolitis [80].

M.L.Barr et al. [49] used a different technique of photopheresis, when the patient's blood was extracted and separated into packed red blood cells, which immediately returned to the patient, and leuco-rich plasma, which was exposed to UV radiation in the presence of extracorporeal added solutions methoxsalen or 8-methoxypsoralen. White cells are photoactive and covalently linked to molecules of a pyridine base membrane and cytoplasm of leukocytes, leading to fatal damage. These cells are then reinfused to patient and die within 1-2 weeks, however during this interval they induce the reaction of autosupression partially directed against T-cells, but nonirradiated and damaging the T-cell clones also. Using this method allowed us to reduce the frequency of crises both as rejection, and infectious complications.

M.L. del Rosario et al. [81] also performed the irradiation of venous blood mononuclear medium wave ultraviolet rays at a dose of 1.2 J/cm^2 open polypropylene container containing a cell suspension of 1 mm thickness. This procedure was carried out without the use of photoactivators. This procedure helped to suppress the release of cytokines of irradiated cells, reducing the formation of cell-membrane proteins such as large antigens of class II major histocompatibility complex and cell adhesion molecules, a decrease in their antigenicity. Return these lymphocytes increased tolerance to transplanted bone marrow cells.

Of course, it would be so tempting to influence specific T cells, damaging the graft, but this reaction is not selective and possibly lethal damage by ultraviolet irradiation of the remaining clones of lymphocytes can lead to unpredictable consequences for the organism as a whole. In addition, if not removed by photopheresis already formed autoantibodies, which makes this procedure defective.

Therefore, the safest and easiest method elementary counterwork of autoimmune reactions in transplantation remains normal nonselective plasmapheresis outputting gradually formed autoantibodies.

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