Received: 14 Nov 2022 | **Accepted:** 05 Dec 2022
DOI: 10.54005/geneltip.1203306

ORIGINAL ARTICLE

The Role of Plasmapheresis in Acute Rejection with Decompensated Heart Failure after Heart Transplantation

Kalp Nakli Sonrası Dekompanze Kalp Yetmezliğine Neden Olan Akut Rejeksiyonda Plazmaferezin Rolü

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How to cite ?

Karahan M. , Sert D. E. , Yılmaz A. , Yamac F. , Turgut S. , Demırkan B. , Güney T. , Dagdas S. , Kocabeyoğlu S. S. , Kucuker S. A. , Özatik M. , Çatav Z. , Sener E. The Role of Plasmapheresis in Acute Rejection with Decompensated Heart Failure after Heart Transplantation. Genel Tıp Dergisi. 2022; 32(6): 719-723.

ABSTRACT

Background: In this study, the results of patients who had orthotopic heart transplantation (OHT) in acute rejection who were admitted to our clinic with decompensated heart failure and could not undergo endomyocardial biopsy (EMB) were evaluated.
Methods: The study included 27 patients who underwent OHT in our clinic between December 1998 and November 2021, admitted with acute rejection causing decompensated heart failure during follow-up, and could not undergo EMB and administered IV pulse steroid plus plasmapheresis. Demographics of patients, peri-treatment left ventricular functions, survival rates and causes of mortality were analyzed.
Results: 19 (70.4%) were male and mean age was 28.7 ± 14.7 (range: 3-54). After OHT, overall survival rates were 92.6%, 77.6%, and 69.4% at 1st, 3rd and 5th year respectively. During the follow-up, the survival rates of patients who presented with decompensated heart failure and given pulse steroid plus plasmapheresis were 70.4%, 58.8%, and 53.4% at 1st, 3rd and 5th year respectively after plasmapheresis. Median rejection time after transplant was 19 months (range 0-113 months). Pre-, and post-treatment left ventricle ejection fractions were 25.11% ± 11.1%, and 52.14% ± 13.4% respectively ($p<0.05$). The leading causes of mortality were pneumonia causing sepsis (5/13 patients).
Conclusion: In acute rejection patients with decompensated heart failure in whom EMB is not possible, administration of plasmapheresis in addition to IV pulse steroid therapy may have a positive effect on survival in this patient group.

Keywords: graft rejection, heart transplantation, plasmapheresis

ÖZ

Amaç: Bu çalışmada ortotopik kalp nakli (OHT) yapılan, takip sırasında dekompanze kalp yetmezliğine neden olan akut rejeksiyon ile kliniğimize başvuran ve endomiyokardiyal biyopsi (EMB) yapılamayan hastaların sonuçları değerlendirildi.
Yöntemler: Çalışmaya Aralık 1998-Kasım 2021 tarihleri arasında kliniğimizde OHT yapılıp, takip sırasında dekompanze kalp yetmezliğine neden olan akut rejeksiyon ile başvuran ve EMB uygulanamayan, IV pulse steroid + plazmaferez uygulanan 27 hasta dahil edildi. Hastaların demografik özellikleri, tedavi öncesi sol ventrikül fonksiyonları, sağkalım oranları ve mortalite nedenleri analiz edildi.
Bulgular: Hastaların 19'u (%70.4) erkekti ve yaş ortalaması 28.7 ± 14.7 (3-54) idi. OHT sonrası genel sağkalım oranları 1., 3. ve 5. yılda sırasıyla %92.6, %77.6 ve %69.4 idi. İzlemde dekompanze kalp yetmezliği ile başvuran ve pulse steroid + plazmaferez uygulanan hastaların plazmaferez sonrası 1., 3. ve 5. yılda sağkalım oranları sırasıyla %70.4, %58.8 ve %53.4 idi. Nakil sonrası median rejeksiyon süresi 19 aydı (0-113 ay). Tedavi öncesi ve sonrası sol ventrikül ejeksiyon fraksiyonları sırasıyla %25.11±%11.1 ve %52.14±%13.4 idi ($p<0.05$). Mortalitenin önde gelen nedeni ise sepsise neden olan pnömoni (5/13 hasta) idi.
Sonuç: EMB'nin yapılmasının mümkün olmadığı dekompanze kalp yetmezliği olan akut rejeksiyon hastalarında, IV pulse steroid tedavisine ek olarak plazmaferez uygulanması sağkalımı olumlu etkileyebilir.

Anahtar Kelimeler: greft rejeksiyonu, kalp nakli, plazmaferez

Introduction

Worldwide, approximately 6.000 heart transplants are performed annually and orthotopic heart transplantation (OHT) is the gold standard therapy in patients with end stage heart failure (1). Although different rates have been revealed in different studies, antibody-mediated rejection (AMR) can reach up to 85% after heart transplantation but clinically overt rejection is around 5%(2). AMR is also related with hemodynamic compromise up to 47%(3). After heart transplantation, organ rejection, including cellular, AMR, and mixed, can occur at any time. Despite AMR is a rare condition; it is severe condition due to the capillary vasculopathy caused by immune sentinel cells that attack to endothelial cells(4, 5).

Acute rejection should be diagnosed and treated as soon as possible, however, diagnosis and treatment may be delayed due to postponed endomyocardial biopsy (EMB) and its pathological evaluation, especially in patients presenting with decompensated heart failure clinic. Currently, treatment modalities for rejection episodes after heart transplantation have mostly been

developed for cellular response. Algorithms targeting B cells are not yet a part of standard treatment, and each center determines treatment strategies in the light of its own experience.

In this study, patients who developed decompensated heart failure due to acute rejection after heart transplantation and their treatment strategies are presented.

Materials – Methods

Since December 2000, all OHTs have been performed with bicaval technique in our center. While the protection solutions used during donor cardiectomy were St.Thomas cardioplegia solution before 2018, Custodiol cardioplegia was used for all donor cardiectomies after this date. In all patients, cold ischemia duration was under 4 hours. Our post-transplant maintenance immunosuppressive treatment regimen is a triple therapy consisting of cyclosporine or tacrolimus, mycophenolate mofetil (MMF) and steroids.

Endomyocardial biopsy (EMB)

EMB is performed routinely on the 10th, 15th and 30th days after the heart transplant, after patient discharge, EMB is repeated another three times until the end of the first year, for a total of six times. EMB is planned for every patient with heart failure symptoms or transthoracic echocardiographic findings suggestive of rejection. However, patients who could not undergo EMB due to hemodynamic instability and severity of rejection clinic, were included in our study.

Study population

All patients, who underwent OHT between December 1998 and November 2021, and had an episode of rejection leading hemodynamic with acute heart failure, and therefore did not have the opportunity to undergo EMB and were started on direct intravenous pulse steroid and plasmapheresis treatment, were included in the study.

Diagnosis and treatment

Diagnosis of acute rejection was performed with transthoracic echocardiographic evaluation and clinical manifestations of heart failure. IV pulse methylprednisolone (1000 mg/day for adults, 1.5 mg/kg/day for three days) was the treatment of choice for all symptomatic patients after admission. Plasmapheresis (ASTEC 204, Fresenius, Germany) was applied with 3 to 5 sessions of iv pulse steroid therapy every other day. Low-dose inotropic therapy was initiated in patients with low blood pressure and hemodynamic compromise.

Patient characteristics, left ventricle ejection fraction rates after transplant, before and after treatment, were evaluated. Survival rates, causes of mortality were also analyzed.

The local ethical committee approval (Ankara City Hospital, Ethical Committee, 23.02.2022 E1-22-2379) was obtained and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistics

Continuous variables were expressed as 'mean values ± standard deviation (SD)' and categorical variables were expressed as numbers and percentages. Demographic characteristics, pre and post-treatment variables were compared using "independent samples t-test" or "Mann-Whitney-U test" for continuous variables. Survival analysis was performed by the Kaplan–Meier method. p value < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS statistical software (SPSS for Windows 15.0, Inc., Chicago, IL, USA).

Results

Between December 1998 and November 2021, 169 patients underwent OHT. Acute rejection accompanied by acute decompensated heart failure was detected in 27 of these patients, 19 (70.4%) were male and mean age was 28.7 ± 14.7 (range: 3-54). Mean body mass index was 23.5 ± 3.8 kg/m2. The etiology of heart failure was dilated cardiomyopathy in 18 (66.7%), and 19 (70.4%) patients had a history of left ventricle assist device implantation (Table 1).

After OHT, overall survival rates were 92.6%, 77.6%, and 69.4% at 1st, 3rd and 5th year respectively (Figure 1). During the follow-up, the survival rates of patients who presented with decompensated heart failure and given pulse steroid plus plasmapheresis were 70.4%, 58.8%, and 53.4% at 1st, 3rd and 5th year respectively after plasmapheresis (Figure 2). Median rejection time after transplant was 19 months (range 0-113 months). Pre-, and post-treatment left ventricle ejection fractions were 25.11% ± 11.1%, and 52.14% ± 13.4% respectively ($p<0.05$) (Figure 3). Extracorporeal membrane oxygenation was not required in any of the patients. There was no clinical improvement in only two patients and these patients died after treatment. In addition to plasmapheresis, rituximab was administered to nine (33%) patients.

The overall mortality rate was 48% (13/27 patients) and the leading causes of mortality were pneumonia causing sepsis (5/13 patients) and heart failure (5/13 patients). One patient died from acute renal failure, one patient from cerebrovascular accident, and one patient from sudden cardiac death (Table 2). Mean mortality time was 1390±255 days after transplantation.

In our heart transplant cohort, acute cellular rejection was seen in 23 (13%) of the patients, acute humoral rejection in 17 (10%) and mixed rejection in 5 (2%).

Table 1. Demographics of the patients

		n=27
Age (years)		28.7±14.7 (range: 3-54)
Male gender		19 (70.4%)
Body mass index (kg/m2)		23.5±3.8
Etiology		
	Dilated CMP	18 (66.7%)
	Ischemic CMP	3 (11.1%)
	Hypertrophic CMP	3 (11.1%)
	Restricted CMP	3 (11.1%)
Previous LVAD implantation		19 (70.4%)

CMP: Cardiomyopathy

Table 2. Reason of death

	Reason of Death
Patient 1	Endomyocardial fibrosis (primer disease recurrence), Right heart failure
Patient 2	Acute renal failure
Patient 3	Pneumonia, sepsis
Patient 4	Surgery for ascending aortic pseudoaneurysm, cerebrovascular accident after operation
Patient 5	Right heart failure
Patient 6	Heart failure
Patient 7	Heart failure
Patient 8	Pneumonia, sepsis
Patient 9	Sudden cardiac death (relatives were COVID19 positive)
Patient 10	Pneumonia, sepsis
Patient 11	Heart failure
Patient 12	Pneumonia, sepsis
Patient 13	Pneumonia, sepsis

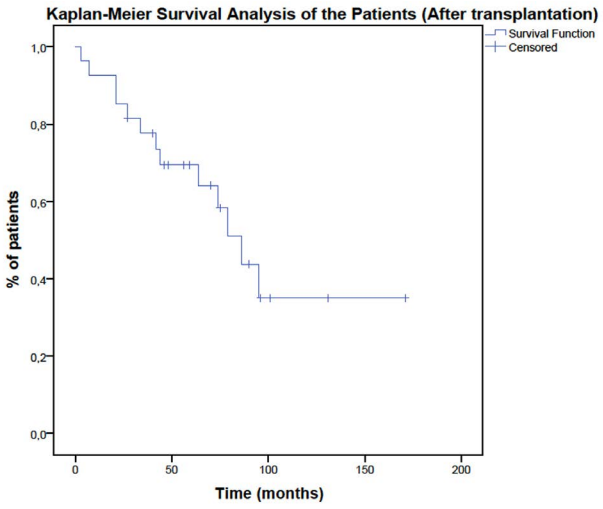

Figure 1. Kaplan-Meier survival analysis of the patients after transplantation.

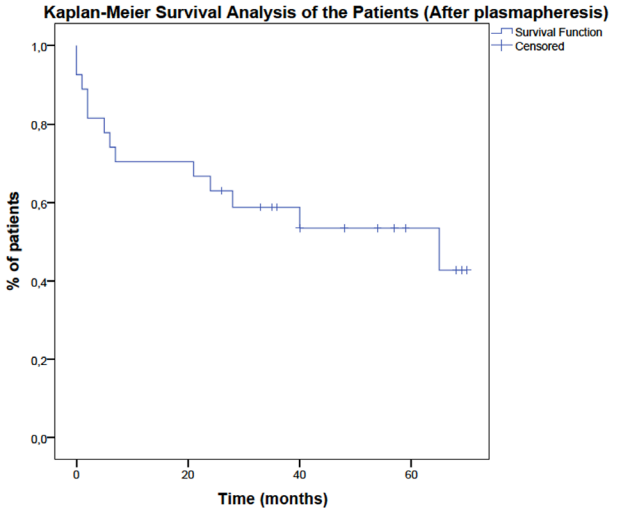

Figure 2. Kaplan-Meier survival analysis of the patients after treatment.

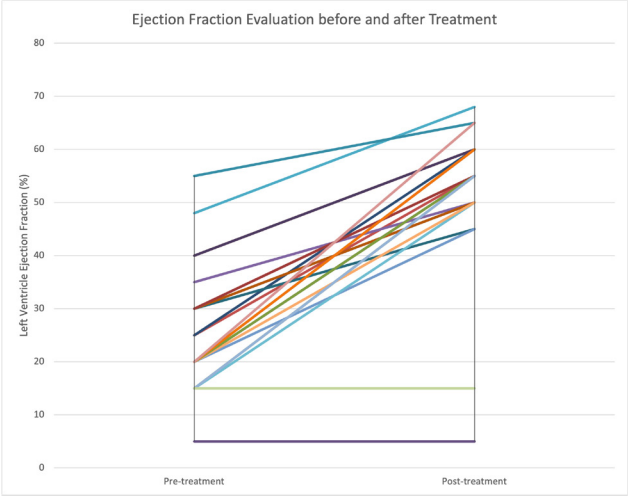

Figure 3. For each patients, left ventricle ejection fraction changing before (25.11±11.1%) and after (52.14±13.4%) treatment (p<0.05)

Discussion

Acute rejection after heart transplantation could be cellular, humoral or mixed type. Especially in cases with dominant decompensated heart failure clinic, it is important to start treatment as soon as possible and to eliminate the adverse events that may be caused by rejection. Acute rejection may be of the cellular type, or the humoral type may accompany this condition, especially in cases that seriously affect cardiac functions(6). AMR is defined as the accumulation of immunoglobulin and complement deposits in myocardial capillaries regulated by donor-specific antibodies (3). AMR was first shown in 1987 as a arteriolar vasculitis (7). In later studies, it was stated that vascular rejection is actually related to antibody accumulation and complement activation (8). The incidence of AMR is shown between 10% and 20% in different studies, and risk factors are female gender, young age, positive donor specific cross-match, cytomegalovirus infection, pre-transplant ventricular assist device implantation, and high panel-reactive

antibody (PRA) levels (9-13). Although AMR was thought of as an acute condition in previous years, the opinion that it is a phenomenon that affects a longer period has gained weight as a result of studies (8, 9, 14-17). In our study, there were early and late rejections, and these results were similar to the literature. However, post-treatment survival of heart transplant patients presenting with decompensated heart failure was higher. The reason for this survival advantage could be that the use of plasmapheresis in cases of AMR or mixed rejection provides treatment advantage in cases of undetected rejection.

In our center, EMB is routinely performed on 10th day, 15th day, 1st month, 3rd month, 6th month and 1st year postoperatively and we found severe cellular rejection (Grade 2R or 3R) rate of 8%(18). In routine scans, pulse steroid and plasmapheresis are administered in patients with AMR after EMB. However, since EMB and biopsy results were delayed in patients presenting with hemodynamic compromise, we routinely applied this treatment in such patients, as patients may need pulse steroids and plasmapheresis. The degree of microvascular inflammation caused by AMR correlated with clinical outcomes; high-intensity inflammation has been associated with acute organ dysfunction(19). Accordingly, plasmapheresis should be kept in mind, especially in hemodynamic compromise patients who do not have the opportunity to undergo EMB.

Standard immunosuppressive and rejection therapy is designed according to the immune response of T cells. Recently, many large transplant centers define different treatment protocols in the light of their experience. The first-line treatment in many centers is IV pulse steroid and concomitant plasmapheresis in AMR. Cyclophosphamide (0.5 to 1 gm/m2, every 3 weeks for 4 to 6 months) can be added to treatment protocol. For removal of B-cell memory after plasmapheresis, rituximab (375 mg/m2, once a week, four dose infusion) can be added to the treatment (17).

Plasmapheresis is fundamental in AMR. The circulating immunoglobulins are eliminated nonselectively, and this is achieved using the exchange and double filtration technique. If more specifically antibody removal is desired, immunoadsorption plasmapheresis is another technique option. The adverse events of plasmapheresis are infection, hypovolemia, exposure to fresh frozen plasma and adsorption membrane (5, 20). In our series, both early and late-onset pneumonia was the leading cause of mortality. Plasmapheresis cannot suppress all antibodies continuously, thus there is always a possibility of AMR recurrence. In this view, to prevent recurrence and to treat effectively, other therapies are also needed. In our series, we observed a significant increase in EF and good long-term survival after plasmapheresis treatment in heart transplant patients who presented with decompensated heart failure.

Although plasmapheresis has a very important place among the treatment options of AMR(21), there is no consensus regarding the duration and frequency of this treatment. It is recommended to apply 3 to 5 seasons every other day. Although it is recommended to apply 3 to 5 seasons every other day, there are also studies in which the treatment continues until clinical improvement is observed(15). In our clinical practice, plasmapheresis is performed as 3 sessions every other day, if there was no clinical improvement, there were treatments that we extended up to 5 seasons. Cytolytic therapy would be useful especially for those who need inotropic or mechanical circulatory support(9, 22). In addition to immunoglobulin removal, cytotoxic therapy and antithymocyte globulin can be used to suppress B cell activation and functions (23, 24). It was shown that cyclophosphamide can suppress B-cells more potently than azathioprine (25). In a study comparing the combination of high-dose IVIG and plasmapheresis/IVIG/anti CD20; at the end of 36 months, graft survival rates were 50% vs 91.7%, respectively(26). In addition, there was fewer rejection episodes in the combined therapy patients. Tacrolimus with sirolimus or MMF combination has been shown to be more effective than cyclosporine/MMF in treatment of either cellular rejection and AMR(27). Some centers reported that they switched to tacrolimus instead of cyclosporine in case of AMR(5). CD20 protein is a molecule present on the surface of B lymphocytes. Rituximab is a chimeric monoclonal antibody that binds to the CD20 antigen on B lymphocytes. The addition of rituximab to standard therapy has been shown to yield better outcomes in AMR (28-30). We preferred rituximab with plasmapheresis in nine (33%) patients. The reason of use of rituximab was that these patients had a previous history of humoral rejection and severe myocardial edema on echocardiographic images.

It is critical to start the treatment process as soon as possible in heart transplant patients who present with decompensated heart failure clinic. Possible mixed or AMR conditions may be found in these patients, and performing EMB and waiting for the results may delay the treatment of patients whose clinical condition is already poor and worsen the outcomes. Therefore, the performing of plasmapheresis in such patients without waiting for EMB results may improve clinical outcomes.

Limitations

First, this study was designed as retrospective cohort. Second, although this treatment has been applied to all heart transplant patients presenting with decompensated heart failure, the gold standard treatment method is to observe the results of EMB and plan accordingly.

Conclusions

Although cellular rejections responding to "pulse steroid" may be more obvious, each transplant team now need to keep in mind that there is one more clinical entity in case of hemodynamic compromise cases; "humoral rejection". Although, AMR has a very high mortality in short term, patients can be treated as easily

as cellular rejection with early diagnosis and treatment. In particular, even though the immunohistochemical staining is negative, plasmapheresis surely should be considered in the treatment of rejection in patients with decompensated heart failure. We believe, algorithms regarding the diagnosis and treatment of rejection would change to include humoral rejection in the coming years.

Conflict of interest: None

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