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Thymoglobulin for induction therapy in heart transplantation in Mexico

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Abstract

Introduction: There is no consensus on induction therapy in heart transplantation, although interleukin-2 receptor blockers (basiliximab), thymoglobulin, and steroids are used. In Mexico, there is no experience in the use of thymoglobulin as an induction in heart transplantation. We compared thymoglobulin and basiliximab as inducers of immunosuppression in heart transplantation.

Material and methods: Retrospective study from January 2014 to January 2018 with patients undergoing heart transplantation, divided into two groups. Group A with thymoglobulin as an induction of immunosuppression at a dose of 0.5 mg/kg/day for 5 days and group B in which basiliximab was used. Infections, kidney injury, graft rejection and mortality were compared.

Results: Group A with 17 patients and group B with 43 patients. An increase in the number of infections was observed in group A compared to group B without statistical significance (23.5% vs 14%). There was no difference between the two groups in the percentage of renal failure, graft rejection and hemorrhage greater than usual (29.4, 0, 17.6% vs 32.6, 2.3, 14.6% respectively). Mortality in group A was 23.5% and in group B: 25.6%. An increase in hospital stay was observed in group A compared to group B (26.3 days vs. 14.8%) without statistical significance.

Conclusion: Thymoglobulin used as induction therapy had no significant difference compared to basiliximab, and may be an induction immunosuppressant in heart transplantation.

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Introduction

Since the beginning of Heart Transplantation (HT) in December 1967 performed by Barnard in South Africa [1], immunosuppression has been key to the success of this procedure. The evolution of immunosuppression has been difficult, at first the excessive use of it resulted in a higher number of infections and mortality. The advent of cyclosporine in the 1980s and other immunosuppressants (mycophenolate mofetil, sirolimus, everolimus) radically changed the course of transplants not only of the heart, but of other solid organs. Currently, the immunosuppressive regimen is threefold, based on steroids (prednisone), antimetabolites (mycophenolate mofetil), Calcineurin Inhibitors (CnI) such as tacrolimus or cyclosporine by up to 78%. Some prefer the use of mTor signaling inhibitors: sirolimus or everolimus (8.7%), especially in the presence of kidney injury [2].

Not only does chronic immunosuppression influence the successful outcome of solid organ transplants, but also Induction Immunosuppressive Therapy (IIT). This is performed with the aim of delaying the immediate immune response to the solid organ and prolonging the time to complete the triple immunosuppressive scheme, mainly delaying the onset of CnI (tacrolimus) because it is nephrotoxic [3], since it has been reported that postoperative CT patients present up to 50% of acute renal failure [4].

Only 47% of heart transplants receive IIT [5]. The drugs used are: Interleukin II-2 (BRIL-2) blockers, including the anti-CD2: basiliximab, or anti-CD25: daclizumab (already in disuse due to the increase in infection and mortality in the immediate period of the transplant and because it is out of the market), steroids (methylprednisolone, a steroid with a wide variety of immunosuppressive effects), monoclonal antibodies such as OKT3 and thymoglobulin: Human rabbit immunoglobulin antithymocyte [2,5].

The scheme used is the steroid plus some of the others. BRIL-2 is used preoperatively or transoperatively and a booster dose is given on the 4th day post-transplant. Thymoglobulin is used in the immediate postoperative period depending on hemodynamic stability and/or surgical bleeding.

The most common drug used, along with methylprednisolone, is basiliximab [2]. Thymoglobulin is used in selected recipients such as those who are previously sensitized, an Antibody Reactive Panel (ARP), greater than 25%, multiple organ transplantation, pregnancies, or previous sternotomy with sensitization to blood group. The dose of thymoglobulin for HT recipients ranges from 1.0 to 1.5 mg/kg every 24 h, with a maximum dose of 7.5 mg/kg. Higher doses are associated with higher infection rates [6].

In Mexico, there is no experience of the use of thymoglobulin in postoperative HT patients. It has only been used in kidney transplantation.

The aim of this study is to present our experience in of use of doses close to the ideal dose of thymoglobulin as IIT compared with basiliximab in HT.

Material and methods

Once approved by the Local Health Research Committee, a retrospective study was conducted in which patients undergoing HT scans were gathered from January 2014 to January 2018. They were divided into two groups: Group A: Received thymoglobulin as IIT at a dose of 0.5 mg/kg/day for 5 days and cumulative dose of 2.5 mg/kg/day, with an initial dose in the postoperative period once the patient's clinical stability was confirmed, and Group B received basiliximab as a TII at a preoperative dose of 20 mg and another dose of 20 mg on the fourth postoperative day. Demographic variables such as: Sex, height, weight and age were included: The study variables were: Duration of mechanical ventilation, presence of infections within the first month post-transplant, renal failure (creatinine elevation greater than 1.5 mg), hemorrhage greater than usual, ICU day stay, hospital stay and mortality.

It was a retrospective, longitudinal, descriptive study, with measures of central tendency and dispersion (median, standard deviation) and for comparison between groups: Chi-square, Student's T-test and Mann-Whitney U. A p-value<0.05 was considered significant.

Table 1: Demographics of transplant patients.

	Thymoglobuline 17 patients	Basiliximab 43 patients	(p<0.05)
Age (years)	44.29	47.77	0.27
Size (m)	1.6	1.65	0.1
Weight (kg)	60	64	0.09
BMI (kgm^2)	23.39	23.85	0.2
SC (m^2)	1.65	1.7	0.09
Isquemia Total (min)	260.82	228.63	0.38
Pinching (min)	90.06	88.81	0.31
DCP (min)	191.53	143.65	0.35
Gender			
Male	12 (70.6%)	32 (74.4%)	0.44
Female	5 (29.4%)	11 (25.6%)	
NYHA			
III	2 (11.8%)	28 (65.1%)	0.001 *
IV	15 (88.2%)	15 (34.9%)	
Kidney Injury			
Yes	5 (29.4%)	14 (32.6%)	0.81
No	12 (70.6%)	29 (67.4%)	
Rejection			
Yes	0	1 (2.3%)	0.52
No	17 (100%)	42 (97.7%)	
Major bleeding			
Yes	3 (17.6%)	6 (14%)	0.71
No	14 (82.4%)	37 (86%)	
Infection			
Yes	4 (23.5%)	6 (14%)	0.37
No	13 (76.5%)	37 (86%)	
Primary Infection			
No	13 (76.5%)	37 (86%)	0.07
Pneumonia	2 (11.8%)	6 (14%)	
Surgical Wound	2 (11.8%)	0 (0%)	
Mortality			
Yes	4 (23.5%)	11 (25.6%)	0.86
No	13 (76.5%)	32 (74.4%)	
Cause of Mortality			
Living Patient	13 (76.5%)	32 (74.4%)	0.83
Rejection	0 (0%)	1 (2.3%)	
Primary Graft Failure	1 (5.9%)	1 (2.3%)	
Infection	3 (17.6%)	5 (11.6%)	
Pulmonary embolism	0 (0%)	1 (2.3%)	
Sudden death	0 (0%)	2 (4.7%)	
ARI	0 (0%)	1 (2.3%)	
Time to Extubation (days)	5.8	3.6	0.06
Time in ICU	11.4	10	0.16
Time to Hospitalization	26.31	14.79	0.15

NYHA: New York Heart Association, ARI: Acute Renal Injury.

Results

During the study period from January 2014 to January 2018, 60 patients were found, 16 female (26.7%), 44 male (73.3%), with a mean age of 46.78±12.27 years (range of 20 to 66 years). The distribution by group was as follows: group A consisted of 17 transplant recipients, 5 women (29.4%) and 12 men (70.6%), with mean age 44.29 years, mean total ischemia 260.82 min, Body Mass Index (BMI), mean 23.39 kg/m^2, body surface area (BS), 1.65 m^2. In group B: 43 transplant recipients, 11 female (25.6%) and 32 male (74.4%), mean age 47.7 years, mean total ischemia 228.63 min, mean BMI 23.85 kg/m2, CS; 1.7 m^2 (Table 1).

The most frequent complications that occurred were: renal injury in 19 patients (31%), of which 5 patients (29.4%) were in group A and 14 patients (32.6%) in group B 14, p=0.81; infections in 10 patients (16.6%), hemorrhage greater than usual in 9 patients (15%). The period of withdrawal from mechanical ventilation in group A was 5.8 days and group B 3.6 days with a non-significant p. The ICU stay in group A was 11.4 days and group B was 10 days. Hospital stay until discharge in Group A was 26.31 days and Group B: 14.79 days with a p=0.15. The distribution of these variables by group and the level of significance of the comparisons are presented in Table 1 and it should only be noted that there was a greater number of patients in functional class III in group B and a difference was observed in the number of infections (slightly higher in group B) and extubation time (longer in group A). without statistical significance.

Discussion

Immunosuppression is essential for the preservation and avoidance of cardiac graft rejection. This has been divided into two stages: IIT and chronic immunosuppression [7]. In chronic immunosuppression, immunosuppressants such as calcineurin inhibitors (tacrolimus and cyclosporine) are used, which are nephrotoxic, and in patients undergoing HT with pre-existing kidney damage, the risk of further compromise of function increases [8], since most heart transplant recipients already have kidney injury secondary to chronic heart failure and drugs that influence kidney function itself, such as antihypertensive drugs (ACE inhibitors, ARBs), in addition to the risk of acute kidney injury in the postoperative period of CT, which occurs in up to 40% [4]. IIT is used to slow the body's immune response to the antigen (heart graft) and to delay the initiation of the calcineurin inhibitor until kidney function recovers. Approximately 54% of hospitals do not use IIT, especially in European centers. The drugs used in IIT are BRIL-2, such as basiliximab, which is an antiCd20, and daclizumab, an antiCd25, rabbit globulin, human antithymocyte (thymoglobulin) [5]. The most widely used of the two groups is BRIL-2, and of these only basiliximab is used, since daclizumab is in disuse due to the cessation of production since 2010 by the pharmaceutical industry that manufactured it, but the efficacy to avoid acute postoperative rejection is very similar to basiliximab [9].

Thymoglobulin is a globulin from rabbit with action against the human thymocyte, which acts by blocking the series of T lymphocytes and B lymphocytes, the natural killer lymphocytes, plasma cells, that is, action on the cellular and humoral immune response; causing depletion not only of leukocytes but also of antibodies. In addition, it causes a decrease in the production of the medullary red series and megakaryocytes, causing anemia and thrombocytopenia [6].

The use of thymoglobulin as a IIT in HT is rare. It is recommended to use it in cases where there is sensitization, with elevated ARP, multi-organ transplantation, a history of pregnancy, and with a certain reserve in those with ventricular supports [10].

Patients with end-stage heart failure awaiting HT scans present with multifactorial kidney injury, some due to diabetes mellitus and the use of nephrotoxic drugs. In the postoperative HT period, up to 30-40% [4] have acute renal injury, which makes it impossible for the calcineurin inhibitor to be useful because it is nephrotoxic. Thymoglobulin, used as a IIT, delays the initiation of the calcineurin inhibitor, which should be initiated until renal function is restored [11].

The dose of thymoglobulin as IIT in HT is not well established, ranging from 1.5 to 3.0 mg/kg/day for up to 7 days. The initiation of the drug is after surgery and will depend on the postoperative hemodynamic stability, the presence of hemorrhage greater than usual. The higher the dose, the greater the risk of hematological, infectious, and anaphylaxis adverse reactions [6].

In Mexico, there is no experience in the use of thymoglobulin as a IIT in heart transplantation. We performed this study with thymoglobulin as IIT in HT and compared it with those TCs in which basiliximab was used as TTI. With the exception of BMI, demographic variables did not differ statistically significantly. Complications such as kidney injury, infections, and hemorrhage greater than usual were also not statistically significant. Rejection was practically non-existent in both groups at the first 3-month follow-up. In other studies, thymoglobulin showed fewer rejection episodes at six months compared to patients in whom basiliximab was used, and an extra benefit in renal function was also evidenced in patients who were used thymoglobulin [12,13] tags. The length of stay at hospital discharge was even shorter in group B than in group A.

The incidence of rejection 2 R or greater was similar. Authors with fewer than 50 patients have observed lower incidence and severity with the use of thymoglobulin compared to BRIL-2 in standard-risk populations [14].

It is important to mention that the dose used in this study was 0.5-1.0 mg/kg/day in central catheter infusion for 24 hours for 5 days, and the cumulative dose of 2.5 mg/kg/day is undoubtedly lower than the stipulated (1.5 mg/kg/day), and even in African-Americans up to 3.0 mg/kg/day have been used. and it is possible that the results obtained could be attributed to the idiosyncrasy, somatometrics of the Mexican population.

Some authors have used the combination of thymoglobulin and basiliximab as a TII in kidney transplantation, with doses of 20 mg basiliximab on days 0 and 4, followed by thymoglobulin at a maximum dose of 200 mg total in 3 days, in addition to steroids. Maintenance therapy was with tacrolimus, mycophenolate mofetil and steroid at therapeutic doses, with no impact on rejection rates, infections and graft survival [15], trying to minimize side effects.

The mortality reported in our study was slightly lower in group A. Bellumkonda et al. reported their study in which thymoglobulin had zero mortality as a TII compared to basiliximab [16].

There is little information about the use of thymoglobulin with IIT in paediatric HT scans. Parisi et al. [17] reported its use

in 31 pediatric transplants: the dose used ranged from 1.5 to 2.5 mg/kg/day for 7 days based on the age of the recipient, and its follow-up was through the total lymphocyte count, and based on their results they confirm the usefulness of thymoglobulin in these patients.

We can conclude that thymoglobulin compared to basiliximab is useful as an induction immunosuppressive therapy in patients undergoing heart transplantation.

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References

1. Swanevelder J, Gordon P, Brink J, Gutsche J. Fifty years: Reflections since the first successful heart transplant. J Cardiothorac Vasc Anesth. 2018; 32(1): 14-18. doi: 10.1053/j.jvca.2017.10.028.
2. Khush K, Cherikh W, Chambers D, Harhay M, Hayes D, et al. International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirtysixth adult heart transplantation report- 2019; focus theme: Donor and recipient size match. J Heart Lung Transplant. 2019; 38(10): 1056-1066. doi:10.1016/j.healun.2019.08.004.
3. Cantarovich M, Giannetti N, Barkun J, Cecere R. Antithymocyte globulin induction allows a prolonged delay in the initiation of cyclosporine in heart transplant patients with postoperative renal dysfunction. Transplantation. 2004; 78(5): 779-781.
4. Hamour IM, Omar F, Lyster HS, Palmer A, Banner NR. Chronic kidney disease after heart transplantation. Nephrol Dial Transplant. 2009; 24(5): 1655-1662.
5. Stehlik J, Edwards L, Kucheryavaya A, Benden C, Christie J, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th Official Adult Heart Transplant Report-2012. J Heart Lung Transplant. 2012; 31(19): 1052-1064.
6. Gaber AO, Monaco AP, Russell JA, Lebranchu Y, Mohty M. Rabbit antithymocyte globulin (thymoglobulin): 25 years and new frontiers in solid organ transplantation and haematology. Drugs. 2010; 70(6): 691-732.
7. Zetina-Tun H. Chapter 11. Preoperative and postoperative management of heart transplantation. In: Careaga-Reyna G, Zetina-Tun H. Thoracic organ transplantation in Mexico. 1st Edition. Editorial El Manual Moderno. Mexico. 2014; 163-174.
8. Sikma M, Van Maarseveen. E, Van de Graaf E, Kirkels J, Verhaar M, Donker D, et al. Pharmacokinetics and toxicity of tacrolimus early after heart and lung transplantation. Am J Transplant. 2015; 15(9): 2301-2313. doi: 10.1111/ajt.13309.
9. Martin S, Kato T, Farr M, McKeen J, Cheema F, et al. Similar survival in patients following heart transplantation receiving induction therapy using daclizumab vs. basiliximab. Circ J. 2015; 79(2): 368-374. doi:10.1253/circj. CJ-14-0718.
10. Loupy A, Lefaucheur C, Vernerey D, Prugger C, van Huyen JPD, et al. Complement-binding anti-HLA antibodies and kidney-allograft survival. N Engl J Med. 2013; 369(13): 1215-1226.
11. Taylor D, Barr M, Meiser B, Pham S, Mentzer R, et al. suggested guidelines for the use of tacrolimus in cardiac transplant recipients. J Heart Lung Transplant. 2001; 20(7): 734-738. doi: 10.1016/s1053-2498(00)00222-9.
12. Higgins R, Kirklin J, Brown R, Rayburn B, Wagoner L, et al. Cardiac Transplant Research Database (CTRD). To induce or not to induce: do patients at greatest risk for fatal rejection benefit from cytolytic induction therapy? J Heart Lung Transplant. 2005; 24(4): 392-400. doi: 10.1016/j.healun.2004.01.002.
13. Beniaminovitz A, Itescu S, Lietz K, Donovan M, Burke E, et al. Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. N Engl J Med. 2000; 342(9): 613-619.
14. Carlsen J, Johansen M, Boesgaard S, Andersen CV, Arendrup H, et al. Induction therapy after cardiac transplantation: a comparison of anti-thymocyte globulin and daclizumab in the prevention of acute rejection. J Heart Lung Transplant. 2005; 24(3): 296-302.
15. Spagnoletti G, Salerno MP, Calia R, Romagnoli J, Citterio F. Thymoglobuline plus basiliximab a mixed cocktail to start? Transpl Immunol. 2017; 43-44: 1-2. doi: 10.1016/j.trim.2017.06.005.
16. Bellumkonda L, Oikonomou EK, Hsueh C, Christopher Maulion C, Testani J, et al. The impact of induction therapy on mortality and treated rejection in cardiac transplantation: a retrospective study. J Heart Lung Transplant 2022; 41(4): 482-491. doi: 10.1016/j.healun.2022.01.008.
17. Parisi F, Danesi H, Squitieri C, Di Chiara L, Ravà L, et al. Thymoglobuline use in pediatric heart transplantation. J Heart Lung Transplant. 2003; 22(5): 591-593. doi: 10.1016/s1053-2498(02)00813-6.