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A Model for Heart Transplantation Sustainability

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Sustainability is a major challenge in multiple areas of the society; within the medicine it is necessary to promote it to develop ways to ensure resource allocation. Cardiovascular disease is one of the main death causes in the world and many resources are allocated to it. Heart transplantation is the only viable strategy for patients with terminal illness. The shortage of donors requires a process to ensure the appropriate selection of receivers. In Brazil there is a single list of candidates by chronological order of arrival and the use of a recipient's risk scores could dynamically allocate these patients. The objective of this study is to analyze the sustainability of a local heart transplantation program and the necessity for a novel process allocation. The Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score is a risk analysis model validated in other populations with the purpose of defining the risk of death of a transplantation candidate patient in the first year after the procedure. In total, 42 patients were analyzed. In this population, the IMPACT ≥ 6 was associated with a higher mortality risk. The allocation of patients according to their IMPACT score can facilitate the decision making about which candidate is allocated to a transplant and may optimize this scarce resource.

1. Introduction

Sustainability is a major challenge in multiple areas of the society; within the medicine it is necessary to promote it to develop ways to ensure the best resource allocation (Smits et al., 2013). Health is a vital sector of the world economy. Recent data from the World Health Organization (WHO) showed health expenses were 9.7 % of the Gross Domestic Product (GDP) in the world in 2007, an estimated expenditure of US$ 5.3 trillion. In the United States these expenses accounted for 15.7 % of GDP. In Brazil the cost is also quite significant representing the equivalent of 8.4 % (Ministério da Saúde, 2012). In addition to economic issues, health activities involve caring for individuals, which is extremely critical to the society. The care needs investments and health expenditures tend to gradually increase due to greater awareness and understanding of the individuals that they should receive better healthcare to greater availability of technological resources, to the increase in income, and to the increase in life expectancy. In this regard it should be noted that according to the latest data from the Brazilian Institute of Geography and Statistics (IBGE), the life expectancy at birth of a Brazilian was 73.2 y for both genders in 2009, an increased in more than ten years between 1980 and 2009 (MOH, 2012). Estimates of the same institute indicate a steady growth of the population over 60 y old, which represents a significant change in the Brazilian population age pyramid structure: the number of people above 60 should double in the next 20 y, becoming about 30 % of the total population in 2050. Consequently, healthcare costs tend to increase with time. In the United States, for example, some projections indicate that health costs can reach 20 % of the GDP in the coming years, which has led to important discussions about the sustainability of the US health system.
Some procedures in health impose a large social burden. One of those is the transplantation of any organ to save lives. The costs of each type of transplantation will vary depending on the situation. Each patient has a clinical situation of his own. It also depends on the insurance coverage for the type of transplant and the location of the transplant centre. Patients will also require lifetime medical assistance and financial demands for follow-up care and drugs (Aurora et al., 2010). Average costs for transplants and first-year

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expenses vary according to the type of transplant. The actual costs may be higher or lower than the figures listed here (in US$): Bone Marrow (autologous): $ 360,000; Bone Marrow (allogeneic): $ 800,000; Cornea: $ 25,000; Heart: $ 1 million; Intestine: $ 1.2M; Kidney: $ 260,000; Liver: $ 575,000; Lung: $ 550,000; Double Lung: $ 800,000; Pancreas: $ 290,000; Heart/Lung: $ 1.2M; Kidney; Pancreas: $ 475,000; Kidney/Heart: $ 1.3 M; and Liver/Kidney: $ 1 M (NFT, 2015). The total Brazilian cost of all transplants realized were $ 29 M in 1995 and grew to $ 100 M in 2003 (MOH, 2012). The sustainability of these models is complex because they represent a high burden for the society due to all the resources that are involved (human, technical, and financial). The results must be efficient to save the right person and allow a return of this person back to the society with quality of life. The saved person should be enabled to work or to do whatever his or her regular set of live activities are. The system needs an efficient triage method to treat even the sickest person and give him a better chance of a healthy life after the procedure.

In this context cardiovascular disease is one of the main causes of death in the world and many resources are allocated to it. Heart transplantation is still a viable strategy for patients with a terminal illness (Jessup et al., 2009). A heart transplant is a surgery to remove a damaged or diseased heart and to replace it with a healthy donor heart. Finding a donor's heart can be difficult in all countries. The donated heart must be from someone who suffered brain death and that is still on life support. The donor's heart must be matched as closely as possible to tissue type of the recipient to reduce the chance that the recipient's body will reject it (Amarelli et al., 2012). A heart transplant is done in these circumstances: intractable angina pectoris that can no longer be treated with drugs or other surgeries; heart failure in terminal stages with symptoms at rest despite optimal medications and devices therapies; severe heart congenital defects that were present at birth and cannot be fixed with surgery; and life-threatening arrhythmias that do not respond to other treatments.

The transplant of organs and tissues in Brazil began in 1964 in Rio de Janeiro and in 1965 in São Paulo with the completion of the first two kidney transplants in the country. The first heart transplant was also in São Paulo in 1968 and it was conducted by the team of Dr. Euriclides de Jesus Zerbini. This occurred less than a year after the completion of the pioneering transplant by Dr. Christian Barnard in South Africa. From this initial period to the present day this activity had a tremendous development in terms of techniques, resulting in a variety of organ transplants and a growing number of procedures performed. To the extent that the majority of procedures performed was financed by public funds, a deep understanding that the organs were funded by "public goods" grew in the Brazilian society. The Brazilian Unified Health System's (SUS) managers and the transplant community desired to regulate the activity, to create a national coordination for a transplant system, and to establish clear criteria for a technically correct, socially acceptable, and fair allocation of organs to those in need of assistance.

On 30th June 1997, the National Transplant System (SNT) was created under the Ministry of Health (MOH), with the assigned mission of developing the process of collection and distribution of tissues, organs, and parts removed from the human body for purposes of therapeutic transplantation (MOH, 2001). Based on legal definitions, an intense work began in the MOH to implement the proposed measures, to organize the SNT, to deploy a receiver's single list, and to create the Central Transplantation system. In addition, the MOH took measures to regulate the activity, to register, and to authorize services and specialized teams, and to establish criteria for funding. These initiatives boosted the procedures and yet allowed the adoption of a series of measures necessary for the full operation of the system. All these activities, due to their complexity and scope, had natural difficulties of implementation. A transition period began, from the previous informal system of regulations to a new system of intense regulation and implementation of controls. The implementation of the SNT was a work-in-progress, in which in every single day additional difficulties and problems brought layers of organizational complexities, with new standards and improved mechanisms for control and management systems. At the end of this process, the SNT became a system respected by the Brazilian society, the patients, and the transplant community. The shortage of donors requires a process to ensure the appropriate selection of receivers. In Brazil there is a single list of candidates by chronological order of arrival. The existence of a risk score could allocate these patients dynamically and could permit the sustainability of the process. When a scarce resource is used efficiently, the right heart for the right patient with all risk factors analysed in the decision-making process permits a higher chance of success. In Brazil 227 heart transplants were carried out in 2012, with an estimated need of 1,145, according to DATASUS, the Brazilian MOH's data centre. In the state of Rio de Janeiro, 11 heart transplants were conducted in 2012, with a waiting list of at least ten more patients awaiting for an organ. Also, only two hospitals perform heart transplantation actually in Rio de Janeiro State: the National Institute of Cardiology and the Hospital Pró-Cardiaco. These two hospitals have already performed 34 transplants in total in the last three years. The cost of heart transplantation is increasing each year, as well as the public financing for the national transplantation system. According to

IPEA (2010), the Brazilian heart transplantation program spent US$ 106.51 million in 2003 and US$ 495.90 million in 2009.

The Brazilian guideline for heart transplantation edited by the Brazilian society of cardiology does not include the rules of allocation of patient waiting heart transplantation (Bocchi et al., 2012). The MOH assigns a single list for heart transplantation, according to the chronological order of admissions (MOH, 2001). It is expected under Brazilian rules, that patients refractory to venous inotropes or in mechanical circulatory support become a priority, as an urgency criteria. For these reasons, it is mandatory to have a score that incorporates the immediate risks of heart transplantation and that stratifies the recipient list in each situation. This strategy will line up the shortage of organs with the best choice of the recipient.

Despite the existence of several risk scores in cardiac surgery, there is not a validated risk score related only to the recipient of heart in transplantation. The risk-based approach is used in many fields and it should be incorporated into the healthcare system to help the decision-making process (Glavan and Palaneeswaran, 2015). A score was recently published by an American research group: the Index for Mortality Prediction After Cardiac Transplantation (IMPACT). This risk score uses a scale of 50 points draw from 12 variables of relative preoperative risk related to the postoperative mortality in the first year after surgery (Kilic et al., 2013). Each score point increases by 14 % the risk of death in one year. Patients scoring more than 14 points in the original population have a survival rate of 60 % in one year. Those with scores lower than 14 points have a 92.5 % chance of survival after one year (Weiss et al., 2011).

2. Objective and methodology

The aim of this study is to review the sustainability of a local heart transplantation program and the necessity for a novel process allocation. This is a prospective observational study of the transplanted patient cohort in the public healthcare system of Rio de Janeiro State (Brazil). The patients were all transplanted in the National Institute of Cardiology between 2008 and 2013. Patients transplanted in the private healthcare system were not included. The criteria for inclusion was patients' age of 17 yrs. or older and transplanted for the first time. Characterization variables were collected from patient general files, including laboratory results obtained and summaries of pre-transplant variables filed during hospitalization. The following variables were collected from the summary of pre-transplant for each patient: colour (white or black); beta-blocked; hypertension; diabetes mellitus; dyslipidemia; smoking status; alcoholism; and previous cardiac surgery. Quantitative variables were collected from patients' records: weight, clearance of creatinine, and total bilirubin. The IMPACT score was calculated for each patient using the methods published by Killic (2013). The variables were tested for normality with the Shapiro-Wilks test, a basic statistical assumption to model the relationship between clinical and laboratory variables with mortality after surgery. A logistic regression analysis was performed to evaluate the simultaneous influence of the predictor variables on mortality after surgery. All explanatory variables were included in the multivariate analysis. An exploratory analysis was conducted to determine the existence of a cut-off point on the IMPACT score with prognosis significance for the selected cohort of patients, due to the failure to find any evidence in previous analyses. The criterion for statistical significance of hypothesis tests was 5 %. The statistical analyses were performed using SAS ® version 6.11 (SAS Institute, Inc., Cary, North Carolina). Data from the Brazilian Government were taken from the official site in the DataSus webpage. This project was approved by the Research Ethics Committee of the Brazilian National Institute of Cardiology (INC) in compliance with the legislation and rules governed by the Resolution 466/2012 of the Brazilian National Health Council. The Research Ethics Committee granted the consent form authorizing the research. This is a retrospective observational study with data extracted from medical patient records only.

3. Results

All 42 patients transplanted in the period of the study, according to the INC records were included in the cohort. There were no patients excluded and no missing data from these patients. The cohort is comprised mostly of white men classified in functional class III. The main etiology of heart failure was defined as not ischemic or idiopathic diseases and it was of a valvular origin. On the traditional risk factors, we have a population with a low prevalence of hypertension, diabetes, dyslipidemia, obese, smokers or that have had previous cardiac surgery. This cohort has an average body mass index of 23; a mean creatinine clearance of 60, an average total bilirubin of 2.23, and an average IMPACT score of 4.48. The average survival of these patients evaluated in the study was 635 days with 19 deaths during the study period. There was no statistical significance in any numeric variable for postoperative mortality. No statistically significant relationship was observed for categorical variables and postoperative mortality. The logistic regression analysis was performed to evaluate the simultaneous influence of the predictor variables on mortality after surgery. The variable selection process was the forward stepwise at 5 %, which selects the smallest subset of independent variables that best explains (or predicts) mortality after surgery. Although the univariate and multivariate analysis of numeric variables failed to detect statistically significant effect of criterion variables on post-operative mortality, the inclusion of categorical variables in the model resulted in statistically significant results at a 95 % confidence interval. The IMPACT score has a normal distribution, with a mean value of 4.5 +/- 2.4 standard deviations; a median of 4 and a range of 1 to 10. Several cut-off points for the IMPACT score were calculated. The cut-off point dividing the population in two groups with the score of more or less than 6 shows that the subgroup with score ≥ 6 points (42.1 %) had a significantly higher mortality ($p = 0.014$). Thus, the logistic regression was performed including only the IMPACT score equal or above 6 points. It was observed that only the IMPACT score ≥ 6 ($p = 0.020$) was an independent predictor of mortality after surgery. The overall survival of this population was 50 % in 900 d. The analysis of the survival of the population stratified by the IMPACT score ≥ 6 points revealed statistical significance for a survival curve. The population of curves with a score> 6 and <6 were compared with the log-rank statistic that showed a significant difference in survival between the two subgroups of the IMPACT score ($p = 0.004$).

4. Discussion

Heart transplantation is inserted into the reality that involves high costs to the society associated with a limitation of donors. This setting prevents the transplant from being used as a solution for all patients with severe heart failure. The identification of risk factors related to post-transplantation mortality is essential in this context to justify the cost to the society, the patients, and the funding bodies and the allocation of resources. While we know that characteristics of the donor and the institution influence these results, much attention has been highlighted in the selection of patients.

In the population of 42 patients transplanted in the INC in the period of the study, it was observed that there was no significant difference at the level of 5 % in the analysed variables related to the recipient characteristics (the clinical variables, the laboratory, and the IMPACT score) based on univariate analysis. However, we can confidently say that the subgroup of deceased patients presented clearance of creatinine ($p = 0.059$) and lower bilirubin ($p = 0.059$) than the group who survived surgery. Another finding would be the tendency of the subgroup who died to have a higher proportion of blacks ($p = 0.068$) when compared to the group who survived surgery. These results are different from those described by the International Society for Heart & Lung Transplantation (Weiss et al., 2011), probably due to the small size of our population, which does not allow for the differentiation of these factors significantly. Furthermore, there were no disclosures of additional risk factors such as dialysis or mechanical support, which cannot be analysed in our population since these methods were not used during the study period in these patients. Despite these results, the IMPACT score could still be used to differentiate the risk of death. As the IMPACT score has a normal distribution in this population, the IMPACT score was tested in an exploratory way, point to point. The hypothesis was whether there was a cut-off point statistically related to the postoperative mortality. It was observed that the subgroup that had died had an IMPACT score equal or above 6 points, which was significantly different than the score for the group of survivors ($p = 0.014$). Therefore, the logistic regression was calculated including the IMPACT categorized score (≥ 6 points) and it was observed that only the IMPACT score ≥ 6 ($p = 0.020$) was an independent predictor of mortality after surgery. Despite this strong significance in the groups with more than 6 point in this score, in this population all the traditional variables showed no independent contribution at the 5 % statistical significance level.

In relation to the literature in the original study, which scored an average of 6.1 in a 0-33 range (Weiss et al., 2011), our population had an average of 4.5 in a range of 1 to 10. Among patients with the IMPACT score of six or more, 79% deceased in the first-year post-transplantation. Therefore, we can suggest this score as the cut-off point for the feasibility of this procedure. Furthermore, we know from studies of the original population of the IMPACT score that each additional point in the score increases mortality. These figures indicate that we are transplanting patients with fewer severity criteria than those reported in the literature. In the original study of the IMPACT score, which was validated with a larger sample than ours, a surgical feasibility cut-off point of 14 was proposed. This higher cut-off point might be indicative of the differences between the study population and the environment, in which the study was conducted. Also, our program might still be experiencing a learning curve. Another important point related to this mortality is the volume of procedures performed by the centre. Our service conducts around ten procedures a year, which the literature suggests can be related to a higher mortality after the procedure.

Currently, the allocation system of the heart transplantation list in Brazil is based on two possibilities, queue time and urgency state; with the inclusion of a risk score related to receiver factors, this scenario could be changed. Patients in urgent need today are prioritized over others. This is also the reality in many parts of the world that have long waiting lists and most of those transplant patients in an emergency state. As a result, we may be selecting only the most serious patients, who are less likely to get better results in these procedures. In practice, perhaps we are not optimizing the scarce resources we have. Systems with limited resources require a careful selection of the use of time scale and urgency criteria. Therefore, the use of standard scores in the various centres involved in each transplant program would ensure an ethical and optimal allocation of resources. The use of a single score would standardize the receiver classification, also indicating that centres with higher volume would have better results for patients with higher risks. Another important topic is the use of a risk score as a potential to facilitate discussions with families and to make it in a more objective way. For example, to show these risks to the patient in a transplant setting or in a no transplant scenario or to compare the possibility of transplantation with the implantation of a mechanical support, as well as a drug therapy. Furthermore, the use of the score could help in allocating marginal organs and it could also usefully serve in a situation in which there is increased mechanical support of information as target therapy.

With a cost of 7,000 dollar for each heart transplantation procedure, which is much less than the American cost that was calculated as a total cost in one million in the first year for each procedure, we have poor results in terms of mortality. As shown, in this population, 50 % of our patients are alive at the end of one year. In the USA 75 % of the patients are alive at the end of the first year. Maybe in improving our selection criteria, we may achieve better results. Another point of action is the post-procedure care. In this study, we did not analyse those details, but just the hard results; this is an important process point related with the mortality. The post-procedure time may be divided into two moments. The first is the immediate post-procedure time in which the mortality is related to haemorrhage an infection inside the hospital. The second post-procedure time is related to rejection and others kinds of infection related to immunosuppression. Another study is necessary and should be designed to analyse post-procedure care.

In this context of high complexity, we are faced with a decision making that requires formal analyses. This decision is different from some soft decisions, which are widely used in simple situations. In some simple situations, there are many repetitions and few alternatives to consider and an instinctive decision can be made. In the case of heart transplantation, although one is at the front of some factors that are difficult to compare, doctors end up making an instinctive decision based on their previous experiences. Several factors affect this, among which the urgency of the decision making, the difficulty of comparisons, and because it is a decentralized decision rested on the Head of the transplant team. Incorporating a single list for the heart transplantation allocation of patients according to their IMPACT score would simplify decision making. In this case, we would have a dynamic list that will allocate the patients for each situation of possible heart transplantation, according to their risk of death after transplantation. Sometimes, due to various logistical problems, we ended up having a marginal organ or sub-optimal one for transplantation. In this case, we do not need to discard the opportunity and evaluate the implant as compassionate therapy in patients with high risk of mortality. By doing these types of alignments, we are offering ethically objective parameters of viable organs for the most viable patients. For those patients outside these possibilities, we would still offer other options. This change in the allocation paradigm would make the decision-making process a softer decision. These analyses would become simple according to a single parameter of gravity provided by scores, reducing the interference of the intuitive analysis of several independent factors, including mortality risk factors. This model is already in use for liver transplantation. In such cases, patients are allocated to the single list according to the transplant Model End-Stage Liver Disease (MELD) scale. Thus, with the existence of a body, patients are transplanted according to their risks of mortality and this model is governed by the laws in Brazil (Boin et al., 2008).

A limitation of this study was the small number of participants, although we have included all transplant patients in the INC. This centre also conducts around ten transplants per year. A study from a single centre is also a limitation factor, in this case. A sample of the many centres that perform transplantation would be more emblematic of the Brazilian reality, allowing more robust results. Another limitation was that some basic features such as diabetes, hypertension, and recent infections were based on the clinical opinion described in the pre-transplant report alone. Another important point was the inclusion of pulmonary vascular resistance and the antibody reactivity panels as risk factors in the analysis; these two variables are known to be related to mortality in other studies. However, as they were not part of the IMPACT score variables, we did not include them in our analysis.

5. Conclusions

It is possible, to implement the IMPACT score as a criterion for allocation of candidates to heart transplantation, based on studies with large samples. The proposed transplantation list would be updated based on the post-transplantation risk to patients, for each candidate. In this manner, the allocation in the presence of a donor would have a priority order in a comparable and reproducible manner. This means that the constantly updated list will be a real photograph of our patients. If these procedures were followed systematically, we would be contemplating the dynamics of the complex patients eligible for cardiac transplantation. It is important to notice in this context, the magnitude of the complexity of a healthcare system that requires for each individual patient, an analysis that includes in the physician's decision making the best options for all the stakeholders for each individual patient. This means that the decision-making process includes the recipient patient, the analysis of the other patients that will not receive the organ, the efficient resource usage, and the financial aspect involved in all these issues. When it is made correctly, it creates a value stream for all the society enabling the sustainability of the heart transplantation process. More extensive and detailed studies are needed to assess the efficiency of this model.

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