

Original Article

Monitoring heart transplant recipients in order to investigate immunosuppressive drug absorption using pharmacokinetics parameters and its' correlation with nephrotoxicity

Zahra Tolou-Ghamari^{1*}, Mohsen MirMohammad Sadeghi², Hamid Mazdak¹

¹Isfahan Kidney Transplantation Research Center, Alzahra Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

²Department of Surgery, Isfahan Cardiovascular Research Center, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract. An appreciated and well-recognized treatment option for end stage heart failure verified as heart transplantation. Life-long immunosuppression suggested to be necessary due to the risk associated to rejection of transplanted heart by the recipient's body. This study aimed to monitor heart transplant recipients in terms of immunosuppressive drug absorption using pharmacokinetics parameters and its' correlation with nephrotoxicity. Heart transplanted recipients at Chamran Hospital Isfahan, Iran was studied. All data and factors that could affect immunosuppressive pharmacotherapy were noted in Excel and analyzed by SPSS. Available data resulted the study of 10 heart transplanted patients from 24 November 2013 to 24 August 2018. The study population was comprised of 8 male and 2 female, with a minimum of 24 and a maximum of 54 years, the mean age \pm SD was 38.7 ± 10.8 years old. Available data related to the hospital stay showed a minimum of 10, a maximum of 56 and a mean of 31 ± 14.9 days. Pharmacotherapy was based on cyclosporine, mycophenolate, acyclovir, prednisolone, valsartan, pantoprazole and others. Higher risk of infectious complications and malignancies after heart transplantation and a lower risk for acute or chronic rejection could be achieved by monitoring immunosuppressive drugs associated with nephrotoxicity or neurotoxicity based on well-structured program. Further studies in this direction seem to be advantageous.

Keywords: Heart, transplant, Isfahan, pharmacotherapy, rejection

Introduction

Transplantation of allogeneic organs and tissues signifies a lifesaving process for a range of patients affected with end-stage diseases. After heart transplantation (HTx) renal dysfunction occurs commonly with wide inter-individual variability [1-3]. Calcineurin inhibitors nephrotoxicity occur frequently and contributes expressively to late mortality after heart transplantation⁴. Immunosuppressive therapy prevents early acute rejection, but it is associated with nephrotoxicity and increased risks for infection and neoplasia³. One of the most complications in heart transplant recipients is rejection. Due to reduction in early graft loss, use of immunosuppressive drugs established in improving graft survival. Immunosuppressive therapy aim to prevent the proliferation and cytotoxic actions of T cells in addition to suppressing antibody production from B-Cells. The protocol for immunosuppressive therapy could be described as three phases of induction regimens, maintenance therapy and rejection treatment but there is increased risk of viral and bacterial infection. Most immunosuppressive drugs cause a

great range of adverse effects and increase the risk of cancer that donates to an important source of mortality in recipients [5-7]. Immunosuppressive drug monitoring based on dosage individualization, established in routine clinical practice for each individual of recipients. However the optimal point for monitoring immunosuppressive drug remains controversial but it is recommended based on trough level (C_0) or concentration at 2 hours (C_2) post taking drug [8-17]. Therefore the aim of this retrospective study was to monitor hearts transplant recipients based on available data noted in medical records, in terms of clinical history and correlation with toxicity and immunosuppressive drug regimen.

Materials and Methods

This study was conducted at Isfahan Kidney Transplantation Research Center (IKTRC) and approved by Ethics Committee via the code No. of 295127. Heart transplanted patients at Chamran Hospital Isfahan/Iran was studied associated with clinical, pharmacological and transplant outcomes. Electronic and paper records of all patients who

* Corresponding author: Prof. Zahra Tolou-Ghamari
(toloeghamari@pharm.mui.ac.ir)

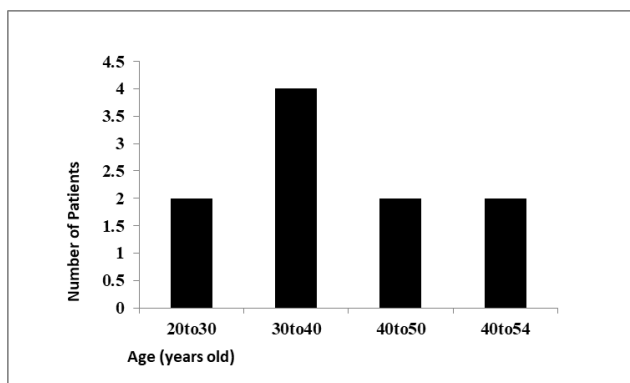


Figure 1 Age Distribution in Heart Transplanted Recipients

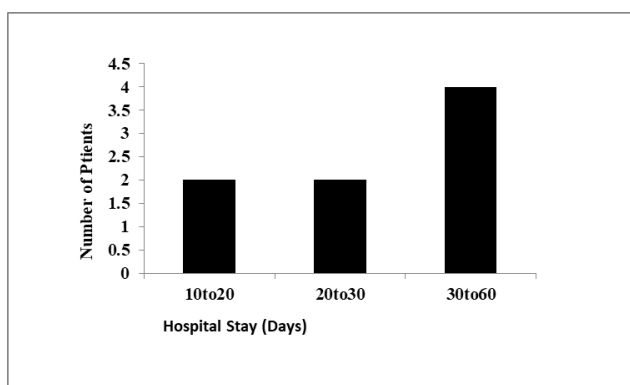


Figure 2 Hospital Stay in Heart Transplanted Recipients

had undergone heart transplantation were studied. All operations were performed by a team of academic staff including senior heart surgeons. Data on age, sex, hospital stay, immunosuppressive regimen were recorded in Excel.

Bibliographic data from our previous studies and experiences plus Directory of Open Access Journals (DOAJ), Google Scholar, PubMed (NLM), Library, Information Science and Technology Abstracts (LISTA, EBSCO publishing) and Web of Science with key words relevant to "Heart, Transplantation, Pharmacokinetics, Monitoring, Toxicity, Immunosuppressive, Pharmacotherapy". All data were noted in d-base and analyzed by SPSS.

Results

Based on available information, there were 10 heart transplanted patients from 24 November 2013 to 24 August 2018. The study population was comprised of 8 male and 2 female. Figure 1 shows distribution of age in population studied. With a minimum of 24 and a maximum of 54 the mean \pm SD was 38.7 ± 10.8 years old. Figure 2 shows hospital stay in heart transplanted recipients. Available data showed that with a minimum of 10, a maximum of 56 the mean \pm SD for hospital stay was 31 ± 14.9 days.

Study of individual heart transplanted recipients confirmed that immunosuppressive such as cyclosporine was used for most patients.

A 26 years old lady was heart transplanted. The cardiac heart failure was diagnosed 3 years before and the time between diagnosis and heart transplantation was around 2 years. A year after transplant she was admitted to hospital with clinical presentation associated to apnea that from the night before symptoms was increase. Her drug history was reported as; cyclosporine, mycophenolate, acyclovir, prednisolone, valsartan, pantoprazole. Another 34 years old man underwent for heart transplant showed acute rejection 5 days after transplant surgery. Pharmacotherapy was based on cyclosporine as the main immunosuppressive drug regimen. In these patients stimulated T-Cell receptor resulted calcineurin activation that cyclosporine could not inhibited this activation and resulted to rejection.

Discussion

In 1967 Christian Bernard performed the first successful heart transplantation in Cape Town, South Africa [18]. The introduction of cyclosporine revolutionized the outcome associated to heart transplantation. Now a day's heart transplantation has been the definite treatment for severe heart failure. The first successful heart transplantation in Isfahan was performed in Chamran Hospital affiliated to Isfahan University of Medical Sciences in 2002. Since then, this hospital has been the major site of heart transplantation in Isfahan Province as the third biggest province of Iran. Due to improving in surgical techniques and skills of transplanted surgeons, outcome seems to be more improved in Isfahan, Iran.

In agreement with heart transplant centers all over the world, the aim of our center in Chamarn Hospital Isfahan/Iran is improving first year survival. There, some difficulties associated with heart transplantation as lack of legal support, rules or nonexistence of a centralized recipient-donor filling and matching system. In 2002, Isfahan University Cardiac surgery team under the leadership of Professor Mohsen MirMohammad Sadeghi took the risk of the first heart transplantation in Isfahan and accomplished it in Chamran Hospital.

Previous published article confirmed that post-transplant survival from a median of 8 years in the 1980s has improved to over 12 years in 2016 [16]. Cardiac allograft vasculopathy mentioned as the third most common cause of death after heart transplant that is observed in 30-45% of recipients by 5 years and in 50-65% by 10 years [17].

In this study the mean age of heart transplanted recipients was 38.7 ± 10.8 years old.

Previous publication reported that heart transplanted recipients of older age group had a higher preoperative left ventricular ejection fraction ($P = .02$) and cardiac index ($P = .04$) than the younger group. Another study in 1262 heart transplant recipients found that advanced recipient age (≥ 55 years) was associated with increased early death and reduced long-term survival [18-20]. In this study recipients received comparable immunosuppressive regimens, based on initial triple-drug therapy with cyclosporine A, mycophenolic acid, and steroids. Long-term immunosuppressive therapy consisted of cyclosporine A

and mycophenolic.

Previous publications mentioned that steroid upkeep should be rather dodged. In case of significant rejection, defined by International Society of Heart and Lung Transplantation (ISHLT), as grade 3A or higher rejection, pulsed steroids with methylprednisolone were given for 3 days. If more than three episodes of ongoing rejection occurred, prednisone was given orally and then tapered slowly [20].

In conclusion, our data support the outlook associated to heart transplantation in Isfahan/Iran. The decision to offer successful heart transplantation to recipients should be considered cautiously in view of the problems associated with; inter and intra individual variations, therapeutic drug monitoring based on pharmacokinetics data of immunosuppressive drugs and recording all clinical and pharmacotherapy data.

Acknowledgments

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Conflict of Interest

The authors declare no conflicts of interest.

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