INDUCTION THERAPY WITH MESENCHYMAL STEM CELLS USED FOR THE TRANSPLANTATION OF KIDNEYS AMONG THE POPULATION OF KARACHI, RANDOMIZED CONTROL TRIAL

[1]Dr. Qurat ul Ain Khan, [2]Dr. Fareena Zaheer, [3]Dr. Amrat Ijaz, [4]Dr. Rabia Haider, [5]Dr. Mubeena Abdul Quyyum, [6]Dr. Hamna Faryad

[1] Dr. Qurat ul Ain
Senior Lecturer, Department of Anatomy, Sir Syed Medical College of Medical Sciences for girls, Karachi, Pakistan.

[2] Dr. Fareena Zaheer
Associate Professor, Department of Physiology, Sir Syed College of Medical Sciences for girls Karachi, Pakistan.

[3]Dr. Amrat Ijaz
Assistant Professor, Department of Anatomy, Azra Naheed Dental College Lahore, Pakistan.

[4] Dr. Rabia Haider
Senior Lecturer, Department of Anatomy, CMH Kharain Medical College, Pakistan.

[5]Dr. Mubeena Abdul Quyyum
Lecturer, Department of Anatomy, Ameer-ud-din Medical College, Lahore, Pakistan.

[6]Dr. Hamna Faryad
Lecturer, Department of Anatomy, Ameer-ud-din Medical College, Lahore, Pakistan.

Author's Contribution:

Q.A. and F.Z. designed the model and the computational framework and analyzed the data. A.I. and R.H. carried out the implementation. M.A.Q. performed the calculations. H.F. and F.Z. wrote the manuscript with input from all authors. A.I. and R.H. conceived the study and were in charge of overall direction and planning.

Corresponding Author:

Dr. Qurat ul Ain
Senior Lecturer, Department of Anatomy, Sir Syed Medical College of Medical Sciences for girls, Karachi, Pakistan

ABSTRACT:

Background:

With the passage of time and advancements in the field of medicine, mesenchymal stem cells have played a significant role in the transplantation of kidneys.

Aims and objectives:

To assess the induction therapy of mesenchymal stem cells used for the transplantation of kidneys among the population of Karachi.

Methodology:

In the study, thirty patients were randomly selected in three groups from one of the public hospitals of Karachi, Pakistan from March 2021 to June 2022. Out of these ten patients from group A received a regular dosage, eight patients from group B received a low dosage of immunosuppressive drugs along with mesenchymal cells and seven patients from group C received anti-interleukin-2 receptor antibodies with regular dosages of immunosuppressive drugs.

Results:

The results of the study revealed that the group of patients treated with mesenchymal stem cells showed elevated eGFR values within the first month followed by surgery, and their renal function improved more quickly than that of the control group. Those patients who received a regular dosage of immunosuppressive drugs with mesenchymal stem cells had a mean difference of 5.2 mL/min per 1.73 m^2 (95% CI, 0.3-10.8; P=.03) and on the contrary, the group of patients who received a low dosage of immunosuppressive drugs with mesenchymal stem cells was 9 mL/min per 1.73 m^2 (95% CI, 3.9-15.8; P=.002).

Conclusions:

The study concluded that the use of mesenchymal cells among those patients who are going for kidney transplantation would reduce the chances of acute rejection along with low chances of infection with a better glomerular filtration rate within a year.

Keywords: Induction therapy, kidney, mesenchymal cells, transplantation

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INTRODUCTION:

When a person reaches the last stage of kidney disease, the most appropriate form of renal replacement therapy is the transplantation of the kidney. Since the last few decades, the effect of long-term allograft has not changed, although many innovations have been introduced in immunosuppressive therapy, still there are a few adverse effects of immunosuppressive drugs on transplantation leading to various infections (1).

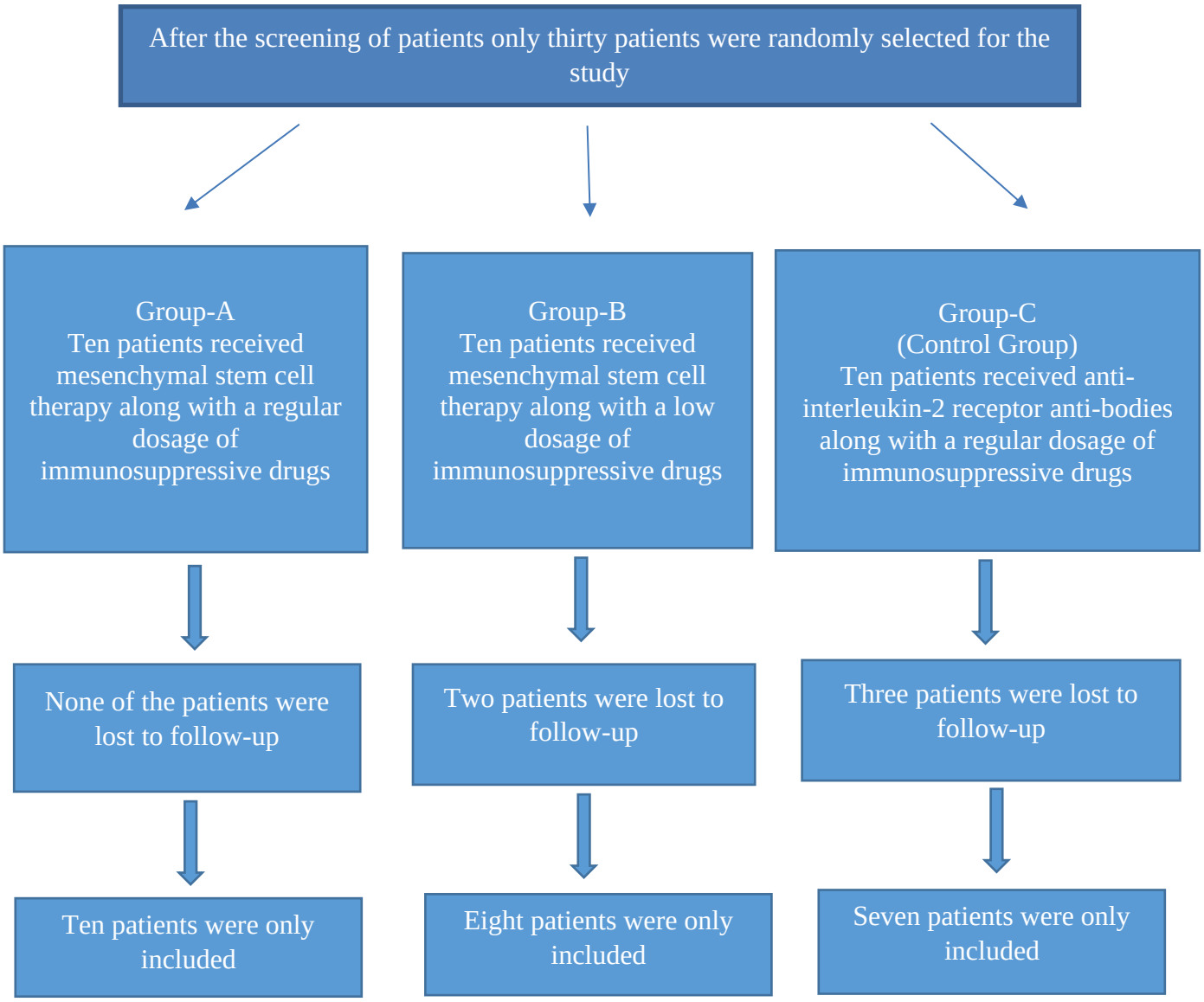
The main goal of clinical transplantation continues to be the induction of recipient immune manipulation donor-specific immunologic tolerance. Each year, there are more people diagnosed with various kidney diseases. Hence, long-term treatment for kidney diseases is the transplantation of the kidney, with a high risk of post-transplant rejection. The risk of acute renal post-transplant rejection has been decreased due to advancements in tissue type matching along with the use of immunosuppressive drugs, but the risks for long-term graft survival have remained constant (2). In organ transplant procedures such as induction therapies, biological drugs play a vital role in inhibiting early immune activation which is commonly used (3). After renal transplantation, the incidence of acute rejection delayed graft function, and graft loss has been decreased with the help of anti-thymocyte globulin induction therapy (4). The acute rejection events in the kidney can be reduced by using a combination technique in which conventional immunosuppressive drugs, target the interleukin-2 receptor chain which is activated on T cells. The main reason for adopting innovative immunosuppressive induction techniques was to avail their higher efficacy along with minimum side effects (5). Mesenchymal stem cells are produced from bone marrow which further develops into mesenchymal tissues, they are appealing because of their immune-regulatory abilities and antifibrotic properties, as they may indirectly enhance renal function by lowering fibrosis and inflammation which is usually caused by illness (6). The capacity of mesenchymal stem cells to reduce inflammation appears to be influenced by both released substances and close interaction with inflammatory cells (7). Hence, T-cell proliferation, monocyte development into dendritic cells, and cytotoxic effects of natural killer cells are reduced as they modify B-cell activities (8, 9). The results of the studies conducted in vitro have revealed that mesenchymal stem cells can preserve renal function by creating growth factors, cytokines, and anti-inflammatory mediators (10). Mesenchymal stem cells have been shown to have immunomodulatory effects, which include reducing the generation of cytokines and lymphocyte proliferation, dendritic cell activity, and interferon by natural killer cells (11). Hence it is assumed that using mesenchymal stem cells in the

transplantation of a kidney will not only reduce the number of immunosuppressive drugs which are usually required by the patient but in fact, it will also improve renal function and long-term survival of a patient (12). For the management of renal diseases, mesenchymal stem cells have been suggested as a novel therapy option. In the study, the induction therapy of mesenchymal stem cells has been acknowledged.

MATERIAL AND METHODS:

A single-centered study was conducted among thirty patients which were recruited from one of the public hospitals of Karachi. Patients were randomized to assess the risk-benefit ratio of mesenchymal stem cells against the induction of anti-Interleukin-2 receptor for the transplantation of the kidney. The study included the patients based on specific criteria that donors should have blood relation with the recipients and those patients were excluded from the study who had systemic infections. Informed consent was taken from the patients. Prior, to surgery patients were screened properly so that are they able to withstand surgery along with immunosuppressive drugs. Technetium-99m diethylenetriaminepentaacetic acid plasma clearance was used to detect the kidney functioning of the donor. Hence no blood transfusion was done before and after kidney transplants. The data was collected by trained data collectors under the supervision of the principal investigator. The study was approved by the ethical review committee of the hospital. All the recruited participants were randomly assigned to three groups such as A, B, and C. Hence, corticosteroids were given to all groups. In the study, group-A received mesenchymal stem cell therapy along with a regular dose of an immunosuppressive drug such as cyclosporine, group B received mesenchymal stem cell therapy along with a low dosage of immunosuppressive drug; and group C, which was ultimately the control group, received anti–interleukin-2 receptor antibody along with the regular dose of an immunosuppressive drug. Hence, data Statistical analysis was performed using SPSS version 21. With 10 patients in each group and three independent proportions, tests of independence showed sufficient power to identify this difference (type I error, 0.05; 80% power). Continuous pre-transplant measurements were compared using a one-way analysis of variance within three groups. The linear mixed-model regression method was used to assess repeated measurements of the eGFR. For a two-sided test, only P values of 0.05 were considered statistically significant.

Figure-1 Flow chart for patient randomization



RESULTS:

The results of the study revealed that thirty patients were included in the study. The patients who had kidney transplantation belong to the age group ranging from (20-60), whereas the mean age was 36 years with a mean BMI of 20 ranging from (16-32). The patients were grouped into A, B, and C. In group A, none of the patients was lost to follow-up when the patients were taking a regular dosage of immunosuppressive drugs, in group B two patients were lost to follow-up when they were taking a low dosage of immunosuppressive drugs, and in group C three patients

were lost to follow up when they were taking anti-interleukin-2 receptor anti-bodies along with a regular dosage of immunosuppressive drugs. The levels of eGFR at a different period during a follow-up of one year can be seen in table-1. Hence, eGFR was immediately increased after transplantation as seen in table-1 & 2. After a follow-up of one year, estimated from linear mixed-model regression comparing overall eGFR values between groups showed significantly higher levels among those in the mesenchymal stem cells along with a regular dosage than those in the control group, with a mean difference of 9.2 mL/min per 1.73 m^2 (95% CI, 1.7-16.3; P=.02) as shown in table-2.

Table 1- After transplantation the level of eGFR at different time points

After transplantation The level of eGFR, mean (95% CI), mL/min per 1.73 m^2	**Regular-dosage (n=10)**	**Low-dosage (n=8)**	**Control group (n=7)**	**p-value**
0 day	5.9(4.2-7.9)	5.1(2.9-1.3)	5.4(2.9-8.1)	.56
14 days	91.9(72.1-90.1)	71.9(61.0-91.0)	59.0(52.0-90.1)	.07
6 months	89.1(91.2-61.1)	90.1(71-98.1)	89.2(91.0-0.49)	.62
12 months	91.2(96.2-99.2)	92.1(78.1-91.0)	91.3(78.2-02.0)	.40
Acute rejection after 6 months Confirmation of biopsy	3(6.9)[0.3-13.7]	3(6.1)[0.6-13.9]	10(20.4)[9.4-31.4]	.01
Corticosteroids	0	0	3(6.7)[0.5-13.0]	.02
Acute rejection after 12 months Confirmation of biopsy	7(14.1)[4.1-23.5]	9(16.2)[6.5-26.3]	13(25.5)[13.8-37.2]	.37
Corticosteroids	0	1 (2.0)[0-5.0]	3 (8.3)[0.5-16.0]	.03

eGFR=estimated glomerular filtration rate

Table 2- Differences in the level of eGFR between the groups

Average period	**Differences in the level of eGFR (Mesenchymal stem cells + Regular-Dose of immunosuppressive drugs vs Control Group**	**p-value**
7 to 30 days	5.2(0.3 to 10.8)	.03
0 to 360 days	9.2(1.7 to 16.3)	.02
Average period	**Differences in the level of eGFR (Mesenchymal stem cells + Low-Dosage of immunosuppressive drugs vs Control Group**	**p-value**
7 to 30 days	9(3.9 to 15.8)	.002
0 to 360 days	3.9(-1.9 to 11)	23
Average period	**Differences in the level of eGFR (Mesenchymal stem cells + Regular-Dosage vs Low-Dose immunosuppressive drugs)**	**p-value**
7 to 30 days	-2.9(-0.3 to 1.8)	.19
0 to 360 days	4.9(-1.8 to 10.0)	.15

Table 3- Consequences of mesenchymal stem cells observed within a follow-up of one year

Adverse consequences	**Regular-dosage (n=10)**	**Low-dosage (n=8)**	**Control group (n=7)**	**p-value**
All infections	27(52.0)[39.2-65.3]	19(37.5)[25.1-51.2]	42(83.3)[73.9-94.0]	.01
Candida	1(2.8)[0-8.0]	1(1.7)[0-5.3]	2(4.9)[0-11.3]	.03
cytomegalovirus	1(2.8)[0-8.0]	1(1.7)[0-5.3]	2(4.9)[0-11.3]	
EB virus	2(4.9)[0-10.0]	1(1.7)[0-5.3]	5(0.2)[1.7-16.2]	
Herpes simplex virus	2(4.9)[0-10.0]	1(2.90[0-8.0]	4(7.2)[0.3-14.7]	
Nasopharyngitis	6(10.1)[1.0-19.0]	3(6.7)[0.2-12.0]	3(10.0)[2.4-19.0]	.85
Pneumonia	4(7.1)[0.2-13.1]	2(3.1)[0-8.0]	3(6.8)[0.3-14.1]	
Urinary tract infections	5(0.3)[1.4-16.2]	5910.2)[2.0-19.1]	3(6.8)[0.3-14.1]	

DISCUSSION:

With time, significant advancement is observed in the field of medicine. The procedure of kidney transplantation is one of them as a result of which the rate of patient survival has increased (13). Recently, more emphasis is given to creative therapies that would increase graft and patient survival (14-16). Mesenchymal stem cells have been considered efficient because of their potential use in the induction phase of transplant immunosuppression. Hence, in a pre-clinical model usually, mesenchymal stem cell injection speeds up the process of histo-incompatible skin graft rejection (17). Various studies conducted globally have revealed that the use of mesenchymal stem cells whether they are derived from the donor, bone marrow, or adipose tissue has been proven effective in the management of acute graft vs. host disease (18). The results of the study revealed that after a follow-up of one year when eGFR values were compared among all the groups. It showed significantly higher levels among those patients who were treated with mesenchymal stem cells along with a regular dosage than those in the control group. A similar study was conducted by tan et al, in which 159 patients received living-related donor kidney transplants. Three equal groups of patients were randomly assigned to receive either autologous mesenchymal stem cells with standard or low-dose calcineurin inhibitors or anti-interleukin-2 receptor antibodies with a standard dose of calcineurin inhibitors. Although, steroids were administered to all the patients of three groups at the same dose. The authors concluded that using autologous mesenchymal stem cells was associated with decreased chances of acute rejection and infections along with improved eGFR (19). Further, the results of the study revealed that additionally, combined analysis of the groups treated with mesenchymal stem cells during the period of 1-year follow-up revealed that the patients had significantly lower chances of infections than the control group which is similar to a study conducted in New Delhi by Chetan Mudrabettu et al., which also revealed that with an infusion of mesenchymal stem cells, the patients didn't experience any health-related issues. All of the patients had a great experience with graft function and none of the patients experienced graft dysfunction (20).

Hence, certain factors allow the transplantation of solid organs with the use of mesenchymal stem cells due to the requirement of identifying and expanding the number of cells in the desired amount before the transplant, which would be challenging to get from allogeneic cadaveric organ donors (21). Many studies conducted in various parts of the world have revealed the clinical efficacy of autologous mesenchymal stem cells and their extensive application for the management of incurable diseases. Nowadays, mesenchymal stem cells have been generated

from many sources and are willingly used in modern therapy procedures (22). Researchers are becoming more knowledgeable about mesenchymal stem cells' characteristics and potential applications. Mesenchymal stem cells have emerged as a promising tool for creating an effective future treatment plan due to their qualities, particularly their capacity to self-regenerate (23). The main limitation of this study was its small sample size and it was confined to only one hospital. More work should be done by researchers to evaluate the induction therapy with mesenchymal stem cells for the transplantation of kidneys.

CONCLUSION:

This study discusses the efficacy of mesenchymal stem cells in detail. A lower incidence of acute rejection, a lower risk of opportunistic infection, and improved estimated renal function at one year were observed among patients receiving kidney transplants by using mesenchymal stem cells instead of anti-InterLeukin-2 receptor-induction medication. Significantly, mesenchymal stem cells did not cause adverse effects on the patients or affect the success rate of kidney transplantation. Hence, the long-term effects, survival rate, and efficacy can be evaluated through continued monitoring of research participants.

CONFLICTS OF INTEREST:

The authors reflect no conflict of interest.

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