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Original Research

Factors Affecting Adverse Effects after Kidney Transplantation

Necla Benlier[1], Hatice Güzel[2], Medet Korkmaz[2], Mehmet Fatih Yüzbaşıoğlu[3]

[1]Department of Medical Pharmacology, Sanko University School of Medicine, Gaziantep, Turkey

[2]Department of Nursing, Sanko University Institute of Health Sciences, Gaziantep, Turkey

[3]Department of General Surgery, Kahramanmaraş Sütçü Imam University School of Medicine, Kahramanmaraş, Turkey

ABSTRACT

Objective: The incidence of developing adverse effects in recipients after kidney transplantation (Tx) was analyzed.

Methods: A total of 206 patients (mean age was 41.40±11.88 years, 92.7% were between 46 and 59 years old, and 66.0% were men) who underwent Tx between 2011 and 2016 were evaluated retrospectively. Information regarding the sociodemographic characteristics of the patients was collected using the "Sociodemographic Characteristics Data Collection Form," which was created by the researcher.

Results: Various adverse effects were detected in 206 patients who participated in our study. The incidence of adverse effects was significantly higher in patients who had hypertension and chronic glomerulonephritis who underwent dialysis treatment during 0–12 months before Tx and who received a kidney transplant from a living donor (p=0.001). The incidence of adverse effects related to the immunosuppressive drugs used after transplantation was significantly higher in patients receiving mycophenolate mofetil (MMF)+steroid+tacrolimus and MMF+steroid+cyclosporine, and weight gain was higher in patients receiving the same group of drugs (p=0.001). There were no significant differences in terms of adverse effects that occurred in other drug combinations.

Conclusion: We found that many factors (e.g., immunosuppressive drugs) in Tx patients may be associated with the incidence of adverse effects.

Keywords: Kidney transplantation, immunosuppressive therapy, calcineurin inhibitors, side effects, dialysis

INTRODUCTION

Chronic renal failure (CRF) is an important public health problem in our country and worldwide due to its increased incidence and high treatment cost. Diabetes, hypertension, and glomerular diseases play important roles in the etiology of CRF. The most common causes of CRF in the world are these three chronic diseases (1). The options for renal replacement therapy (RRT) in patients diagnosed with end-stage renal disease (ESRD) are dialysis (hemodialysis or peritoneal dialysis) and kidney transplantation (Tx) (2, 3). RRT is a treatment that imposes a heavy burden on society and affects not only patients but also families due to its high treatment cost. In the United States in 2003, 360,000 people with ESRD were on RRT (4). Tx has been the most successful and most preferred method for patients with CRF thanks to the newly developed surgical methods and the introduction of immunosuppressive drugs (5). However, Tx has some disadvantages in addition to its advantages. Immunosuppressive drugs that are used to prevent rejection especially in patients who undergo Tx cause adverse effects (6). Giving adequate immunosuppressive therapy and providing immunity to protect infections that may occur in the recipient are proportional to the success of Tx and the survival rate of grafts (7). The immune system of the recipient after Tx should be suppressed by immunosuppressive drugs.

Sufficient immunosuppressive therapy is selected as a combination and is administered to patients (8). The age and gender of the patient, human leukocyte antigen compliance between recipient and donor, and the protocols of transplant centers are taken into account, and immunosuppressive therapy is then selected (9). The main goal in immunosuppressive therapy is to prevent the occurrence of rejection episodes (antigen recognition and costimulation proliferation) by creating a specific pharmacological tolerance against the graft with minimal adverse effects (10).

The selective properties of currently used immunosuppressive therapies are increasing. The combined use of different groups of medicines both provides a synergistic effect and avoids unwanted adverse effects by enabling dose reduction. Thus, it is possible to improve the optimal graft survival and the quality of life for transplant recipient (11).

Recently, classical triple immunosuppressive regimen started after Tx consists of mycophenolate mofetil (MMF), calcineurin

ORCID IDs of the authors: N.B. 0000-0002-9605-2387; H.G. 0000-0001-9388-5247 M.K. 0000-0002-9894-9331; M.F.Y. 0000-0002-0335-9524

Corresponding Author: Necla Benlier **E-mail:** nbenlier@hotmail.com

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inhibitors, and steroid hormone. MMF has been used since 1995 and is a reversible inhibitor of the enzyme inosine-5′-monophosphate dehydrogenase (12).

The most common adverse effects of MMF use are leukopenia, diarrhea, and gastrointestinal irritation. When used at higher doses, there has been an increase in invasive cytomegalovirus disease (13). Calcineurin inhibitors, such as tacrolimus and cyclosporine, are important immunosuppressive drugs used after Tx and have been found to cause adverse effects, such as hypertension and diabetes (14). Sirolimus, which is another immunosuppressive drug used after Tx, is an antibiotic with immunosuppressive properties. It inhibits the development of T cells and provides a powerful control mechanism on these cells when used with cyclosporine (15). However, it has dose-dependent adverse effects, such as hyperlipidemia, diabetes, anemia, thrombocytopenia, proteinuria, edema, impaired wound healing, and mouth ulcers (16). Corticosteroids, such as prednisolone, are drugs that have been used for many years in order to prevent rejection (17). Immediately after starting immunosuppressive drugs in all transplant patients, blood drug levels should be monitored closely. Many studies have provedn that nephrotoxicity and kidney failure rates are increased when drug levels are not adjusted well (18). In light of these data, we attempted to determine the rates of adverse effects in 206 transplant patients and the role of immunosuppressive drugs in these adverse effects.

METHODS

A total of 206 patients who underwent Tx between 2011 and 2016 were evaluated retrospectively. The mean age of the patients was 41.40±11.88 years, 92.7% were between 46 and 59 years old, and 66.0% were men. Inclusion criteria for our study were as follows: being a volunteer, receiving a kidney transplant from either a living or a deceased donor, being >18 years old, receiving immunosuppressive drugs, having no mental health illness, lack of inappropriate self-expression, and having completed at least the second month after Tx. A total of 206 patients who met the criteria were included in the study. The patients were informed about the study by the researcher. Verbal and written informed consents were obtained. Data of the study were collected by the face-to-face interview technique. The data collection period lasted 15–20 min for each individual.

The questions in the questionnaire were read out loudly and clearly by the researcher, and the answers given by the patient were marked on the forms by the researcher. The "Sociodemographic Characteristics Data Collection Form" was prepared by the researcher in order to obtain information about the characteristics of the sample patients. This form included the demographic variables, such as age, gender, marital status, educational level, family type, occupation, whether or not the patient has been informed about the use of immunosuppressive drugs related to the organ transplantation process by the health personnel, employment status after transplantation, working status, and income level, and the variables related to the disease, such as the cause of kidney failure, how many years the patient has had chronic kidney failure, whether or not the patient underwent dialysis treatment, what type of dialysis treatment the patient received, date of transplantation, donor type, whether or not the patient knew the discomforts that may occur after transplantation, immunosuppressive drugs the patient received, whether or not adverse effects occurred, what the patient did when the adverse effects occurred, whether or not the patient had rejection, and the priority ranking of drugs in the patient's life. Ethics committee approval was obtained the study Sanko University (decision no: 5, date:21.10.2016).

Statistical Analysis

Statistical analysis of the data was performed using the IBM Statistical Package for the Social Sciences Statistics version 23.0 software package (SPSS IBM Corp.; Armonk, NY, USA). The 95% confidence interval was used. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 41.40±11.88 (18–71) years. Of the study population, 92.7% were aged 46–59 years. When the distribution of the patients according to their genders was examined, 66.0% were men. Of the patients, 79.1% were married, 45.2% were literate or primary school graduates, 68.4% were core family members, and 26.7% were retired. Of these patients, 53.5% did not continue to work after transplantation, and 70.7% did not continue to work because they were retired. Among them, 48.5% had a balance between their income and expenses. Table 1 shows the distribution of patients according to their sociodemographic characteristics.

Of the patients who participated in our study, 99% were informed by the health personnel, 92.2% deemed that this informing was sufficient, 35.9% did not know the cause of chronic kidney failure, and 30.6% argued that the cause of chronic kidney failure was hypertension. The duration of CRF in 39.3% of the patients was ≥121 months. Of the transplant patients, 88.3% underwent dialysis treatment, and 29.1% had been treated for at least 10 years. Of the patients undergoing dialysis treatment, 85.7% underwent hemodialysis treatment. Of the patients, 52.4% were between the range of "12–60 months" after transplantation, and 54.4% received a kidney transplant from a living donor.

Among the patients, 61.2% knew the discomforts that can develop after organ transplantation. Table 2 shows the distribution of the patients according to the characteristics of their disease.

Of the patients, 93.1% received MMF+steroid+tacrolimus as immunosuppressive drug after transplantation. Moreover, 18% received antiviral agents, 18.4% received antifungal agents, 55.3% received antihypertensive drugs, and 14.1% received antidiabetic drugs. Among the patients, 54.9% developed adverse effects, 72% of those experiencing adverse effects gave their doctor information, 2.9% developed rejection due to incompatibility, and 94.6% reported that drugs ranked first in their life. Table 3 shows the distribution of the properties of immunosuppressive drugs used after transplantation.

Table 1. Distribution of patients according to their sociodemographic characteristics

Sociodemographic characteristics		n	%
*Age (min-max $\bar{x}$±SD), years	18-71 (41.40±11.88) years		
Gender	Male	136	66.0
	Female	70	34.0
	Total	206	100.0
Marital status	Married	163	79.1
	Single	43	20.9
	Total	206	100.0
Educational level	Illiterate	11	5.3
	Literate-primary school	93	45.2
	Secondary school-high school	82	39.8
	University and above	20	9.7
	Total	206	100.0
Family type	Core family	141	68.4
	Extended family	65	31.6
	Total	206	100.0
Occupation	Housewife	52	25.2
	Retired	55	26.7
	Self-employment	42	20.4
	Worker-officer	57	27.7
	Total	206	100.0
Employment status after transplantation	Yes	87	46.5
	No	100	53.5
	Total	187	100.0
Reason for leaving work	Changing work	2	2.5
	Leave work	22	26.8
	Being retired	58	70.7
	Total	82	100.0
Income level	High	8	3.9
	Balanced	100	48.5
	Low	98	47.6
	Total	206	100.0

n: no. of individuals
*Student's t-test was used for the analysis
Data were expressed as mean±standard deviation

Table 2. Distribution of patients according to the characteristics of their disease

Characteristics related to the disease		n	%
Informing the patients about organ transplantation	Yes	204	99.0
	No	2	1.0
	Total	206	100.0
Informing the patients sufficiently	Yes	190	92.2
	No	16	7.8
	Total	206	100.0
Cause of CRF	Hypertension	63	30.6
	Diabetes	10	4.9
	Chronic glomerulonephritis	25	12.2
	Polycystic kidney disease	4	1.9
	Chronic pyelonephritis	4	1.9
	Infections	19	9.2
	Nephrotic syndrome	1	0.5
	I do not know	74	35.9
	Hypertension and diabetes	6	2.9
	Total	206	100.0
Duration of CRF	0-12 months	30	14.6
	13-60 months	29	14.1
	61-120 months	66	32.0
	≥121 months	81	39.3
	Total	206	100.0
Dialysis status	Yes	182	88.3
	No	24	11.7
	Total	206	100.0
Duration of dialysis treatment	0-12 months	43	23.6
	13-60 months	39	21.5
	61-120 months	47	25.8
	≥121 months	53	29.1
	Total	182	100.0
Type of dialysis	Hemodialysis	156	85.7
	Peritoneal dialysis	8	4.4
	Hemodialysis-peritoneal dialysis	18	9.9
	Total	182	100.0
Time after Tx	2-12 months	57	27.7
	13-60 months	108	52.4
	61-120 months	41	19.9
	Total	206	100.0
Donor type	Living donor	112	54.4
	Cadaveric donor	94	45.6
	Total	206	100.0
Knowing the problems that can develop after Tx	Yes	126	61.2
	No	80	38.8
	Total	206	100.0

n: no. of individuals; CRF: chronic renal failure

Table 3. Distribution of properties of immunosuppressive drugs used after transplantation

Properties of immunosuppressive drugs		n	%
Immunosuppressive drugs used after transplantation	MMF+steroid+tacrolimus	192	93.1
	MMF+steroid+cyclosporine	8	3.9
	MMF+steroid+sirolimus	3	1.5
	MMF+tacrolimus	3	1.5
	Total	206	100.0
Antiviral agents used persistently	Use	37	18.0
	Not use	169	82.0
	Total	206	100.0
Antifungal agents used persistently	Use	38	18.4
	Not use	168	81.6
	Total	206	100.0
Antihypertensive drugs used persistently	Use	114	55.3
	Not use	92	44.7
	Total	206	100.0
Antidiabetic drugs used persistently	Use	29	14.1
	Not use	177	85.9
	Total	206	100.0
Development of adverse effects related to drugs	Yes	113	54.9
	No	93	45.1
	Total	206	100.0
Type of processes performed after the development of adverse effects	I stopped using the drug or I reduced its dose	5	5.4
	I called my doctor	67	72.0
	I did not do anything	21	22.6
	Total	93	100.0
Presence of rejection due to incompatibility	Yes	6	2.9
	No	200	97.1
	Total	206	100.0
Priority ranking of drugs in the patient's life	First	195	94.6
	Second	9	4.4
	Third	2	1.0
	Total	206	100.0

n: no. of individuals; MMF: mycophenolate mofetil

Various adverse effects were detected in 206 patients who participated in our study. These adverse effects were weight gain (20.08%), acne (4.9%), tremor (4.4%), diabetes (4.4%), hair loss (2.4%), fatigue (1.9%), itching (1.5%), irritability (1%), palpitation (1%), stomach pain (1%), osteoporosis (1%), eye complaints (1%), shingles (1%), nausea and vomiting (1%), hairing (0.5%), headache (0.5%), nail fungus (0.5%), lung infection (0.5%), insomnia (0.5%), drowsiness (0.5%), urinary infection (0.5%), weight loss (0.5%), ecchymosis in the skin (0.5%), blockage of the brain vessels (0.5%), tinnitus and numbness in the ear (0.5%), and redness in the body (0.5%), respectively. Table 4 shows the distribution of adverse effects after Tx according to their incidence. The incidence of adverse effects after Tx was significantly higher in patients who had hypertension and chronic glomerulonephritis (p=0.001).

Table 4. Distribution of adverse effects after Tx according to their incidence

Adverse effects	n	%
Weight gain	49	20.8
Acne	10	4.9
Tremor	9	4.4
Diabetes	9	4.4
Hair loss	5	2.4
Fatigue	4	1.9
Itching	3	1.5
Irritability	2	1
Palpitation	2	1
Stomach pain	2	1
Osteoporosis	2	1
Eye complaints	2	1
Shingles	2	1
Nausea and vomiting	2	1
Hairing	1	0.5
Headache	1	0.5
Nail fungus	1	0.5
Lung infection	1	0.5
Insomnia	1	0.5
Drowsiness	1	0.5
Urinary infection	1	0.5
Weight loss	1	0.5
Ecchymosis in the skin	1	0.5
Blockage of the brain vessels	1	0.5
Tinnitus and numbness in the ear	1	0.5
Redness in the body	1	0.5

n: no. of individuals

When the incidence of adverse effects after Tx was compared with the dialysis duration before Tx, the incidence of adverse effects (especially weight gain) was significantly higher in patients who underwent dialysis treatment for 0–12 months (p=0.001).

The incidence of adverse effects after Tx was significantly higher in patients who received a kidney transplant from a living donor than in those who received a kidney transplant from a deceased donor (p=0.001). The incidence of adverse effects related to the immunosuppressive drugs used after Tx was significantly higher in patients receiving MMF+steroid+tacrolimus and MMF+steroid+cyclosporine, and weight gain was higher in patients receiving the same group of drugs (p=0.001 and p=0.001). There were no significant differences in terms of adverse effects that occurred in other drug combinations.

DISCUSSION

Several adverse effects occurred after Tx in the patients included in the study, and that these adverse effects were mostly compatible with previous studies (19). In our study, when the incidence of adverse effects after Tx and the causes of CRF were examined, there was a significant relationship especially in patients with hypertension and chronic glomerulonephritis (p=0.001). This can be attributed to the larger number of patients with hypertension and chronic glomerulonephritis.

When the incidence of adverse effects after Tx was compared with the dialysis duration before Tx, the incidence of adverse effects was significantly higher in patients who underwent dialysis treatment for 0–12 months (p=0.001). A previous study reported that an increased dialysis duration before transplantation in patients undergoing liver transplantation affected long-term outcomes after transplantation negatively and was an independent risk factor for increased mortality (20). The results of that study are significantly different when compared with our results. This may suggest that adverse effects and negative situations that may be seen after different organ transplantations may be different. Diabetes mellitus (DM), which is present before or develops newly after Tx, increases the frequency of infection, disrupts graft function, and increases the frequency of cardiovascular diseases, which are the most important causes of mortality in transplant patients (21). Preventable risk factors, such as hepatitis C and obesity, as well as uncorrectable risk factors, such as age and family history, of newly developed DM after transplantation are gaining importance (22). Particularly, calcineurin inhibitors and corticosteroids from immunosuppressive drugs used after Tx are among the factors that facilitate the occurrence of DM after transplantation (23). Close monitoring of patients after Tx, identification of the possible risk factors, and early detection of glucose intolerance are important for preventing the development of DM and complications. Of the 206 patients included in our group, 9 (4.4%) developed DM. Since DM is a well-known risk factor, patients with DM especially in close relatives should be determined. These patients should be monitored more carefully in terms of the development of DM after transplantation, and treatments should be planned accordingly. In all solitary organ transplantations including Tx, infections are encountered especially during the first 3 months after Tx in recipients (24). Studies have shown that infections occur especially in the urinary tract, abdominal area, and chest region (25). In our study, nail fungus, lung infection, and urinary tract infection were observed in 0.5% of the 206 patients (Table 4).

In a study of the majority of Tx patients, no organ transplant rejection was found (26). In our study, 2.9% of the patients had organ rejection. In this respect, our findings are similar to the literature. Tx patients need immunosuppressive treatment throughout their lifetime. Immunosuppressive regimens used currently for this purpose are administered in combination. The majority of the Tx patients included in our study received a combined therapy of MMF+steroid+tacrolimus. Our findings are similar to the literature (27). This can be attributed to that the combination of MMF+steroid+tacrolimus is the most effective combination for immunosuppression.

When what the participants did after the development of adverse effects related to drugs was examined, it was found that the vast majority of them called their doctor. When the literature was examined, no data were found about this finding. Although it is known that immunosuppressive drugs have many adverse effects, the impacts of immunosuppressive drugs on weight gain are still unclear (28). Some studies show that there is no significant difference between them, but there are publications in the literature that report an opposite opinion (29). Many factors, such as the presence of weight gain before transplantation, sedentary life and nutritional recovery after transplantation, and immunosuppressive drugs, are thought to play a role in the development of obesity (14).

In our study, when the incidence of adverse effects related to immunosuppressive drugs was examined, adverse effects were significantly higher in patients receiving a combined therapy of steroid and tacrolimus, and weight gain was also significantly higher in the same patient group (p=0.001). Immunosuppressive drugs cause many adverse effects in the gastrointestinal tract. In a previous study, approximately 68% of the Tx patients were found to have severe gastrointestinal complaints in the first year (29).

Adverse effects, such as nausea, vomiting, and diarrhea, were frequently observed especially in patients treated with MMF (13). Studies have shown that calcineurin inhibitors, such as tacrolimus and cyclosporine, led to gastrointestinal adverse effects (14). In our study, a small proportion of Tx patients were observed with gastrointestinal adverse effects, such as nausea and vomiting. We found that the incidence of side effects was significantly higher in patients who had a living donor Tx than in those who used a cadaver donor (p=0.001). However, in literature studies, side effects occurring in recipients of cadaver and, consequently, more costs of treatment are found (30). This shows that cadaver transplantation is more effective, and that the idea is more suitable in terms of cost.

The most important limitation of the study is that it was conducted at a single center. Since the study was conducted at an organ transplant center located within a private hospital, low-income patients who need to pay extra money could not be referred to this center. Therefore, the present study cannot be generalized to all transplant patients in Turkey.

CONCLUSION

We found that many factors in Tx patients may be associated with the incidence of adverse effects.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Sanko University (decision no: 5, date:21.10.2016).

Informed Consent: Informed consent was obtained from patients who participated in this study.

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