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The Experience and Outcome of Renal Transplantation in Yemen

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Abstract: Access to renal transplantation in the developing world remains limited It remains the treatment of choice for end-stage kidney disease. This procedure not only improves quality of life, but also markedly increases patients' survival rates. Therefore, this study aimed to evaluate clinical outcomes of renal transplants in our center and to compare the outcomes between the patients who received induction therapy and those patients without such induction. It was a retrospective study conducted at Al Thawra General Hospital, Sana'a on 154 patients. Data were collected on all patients who underwent a renal transplant from 2004 to t 2015. Analyses were performed to assess baseline characteristics, graft and patient survival, as well as the outcomes of patients who given induction therapy. A total of 154 renal transplants were carried out at Al Thawra center. The mean age of patients was 32.42 ± 10.4 years (rang 14 – 66) and the male sex was predominant accounting for 72.7%. There were 93.5% of patients on dialysis and the dialysis time was ≥ 3 years in 72%. The major causes of end-stage kidney disease (ESKD) were chronic pyelonephritis (77.9%), hypertension (13%), glomerulonephritis (3.9%) and diabetes mellitus (2.4%). During the first year following renal transplants, 6 patients (3.9%) complicated by acute rejection episodes that did not reach statistical significance (P > 0.05). It is found that the mortality rate during the 1st, 5th, and 10th years was 1.9%, 9% and 14.9%respectively and the infectious conditions were the most frequent cause of death (13%) followed by cardiovascular events (3.9%) and others (2.5%). Although, the process of renal transplants in Yemen started slowly with the initial support and cooperation of the Egyptians' transplant surgeons, the overall outcomes are satisfactory and comparable to the universal reports.

Keywords: Renal Transplantation, Graft Survival Rate, Yemen, Immunosuppressive

1. Introduction

Organ transplantation has become one of the most effective ways to save lives and improve the quality of life for patients with end-stage organ failure in developing and developed countries [1]. Renal transplantation, one of the most common transplant procedures in the world, has, besides the medical or pharmaceutical aspects, cultural, educational, ethical and psychological elements. It is the treatment of choice for end-stage kidney disease (ESKD). Renal transplantation profoundly improves quality of life and longevity of end-stage renal disease patients and remains the only curative option for patients with end-stage renal disease [2]. The first kidney transplantation in the Arab world was performed in Jordan in 1972 at King Hussein Medical Center [3].

The process of renal transplantation (RT) practice in Yemen has met a lot of challenges because of influencing a combination of factors including poor infrastructure, insufficient trained transplant surgeons, and restricted genetically related living donors, thereby it is started slowly and went through many phases. Initially, it was performed in cooperation with the Al Mansura University, urology and nephrology center, Egypt. During this phase both the donors and recipients were sent to Egypt where all investigations including tissue matching were performed, then returned to Yemen with the transplant surgeons team as well as the nephrologists. The first case of RT was performed at 1998 in Al Thawra hospital, Sana`a. Since then, the visiting renal transplants team had come every 6 months and this situation continued until 2003.

The second phase witnessed the establishment of the

nephrology and urology center in Al Thawra hospital with the increasing number of Yemenis transplant surgeon and physicians who being trained abroad and began to work independently without participation of the Egyptian team.

It is interesting that the initial 13 patients of recipient RT received only two drugs namely mycophenolate mofetil and prednisolone without further immunosuppressive drugs which seems unusual. Thereafter, for the new cases cyclosporine- A and tacrolimus were added. However, upon the availability of tissue matching test, those patients with poorly identical tissue matching received induction therapy in the form of basiliximab (simulect) which was administered for 39 patients. The objective of this study was to evaluate the renal transplant outcome in our center and to compare the outcomes between the patients who received induction therapy and those patients without such induction.

2. Materials and Methods

2.1. Study Design

This is a retrospective, descriptive cohort study included all recipients of living-donor transplants carried out at Al Thawra General Hospital (TGH), Sana`a, Yemen from 2004 to 2015. Combined organ transplants were excluded from this study. During this period, 154 renal transplant procedures were recorded in TGH. Ethical clearance was obtained from the hospital ethics committee.

2.2. Data Source

Data were obtained from the hospital records and also the patients files were retrieved from the TGH statistics department which contains all patients files and database.

2.3. Study Variables

Data sheet was prepared and included demographic and clinical information such as age, sex, BMI, underlying disease, comorbidity, history of prior transplant, blood transfusion, history of previous operation in the urinary tract, dialysis before renal transplant (RT), use of induction therapy, immunosuppressive agents, timing of RT procedures, post-operative complications, creatinine levels at two weeks, six months, after a year and after 3 years thereafter.

Comparing between induced and non-induced groups was analyzed using the induced (n = 39) as a study group and the non-induced (n=115) as control group.

The standard pre RT operation investigations included blood grouping, complete blood count (CBC), white blood cells with differential, platelet count, blood sugar, liver function test, urea, creatinine, urine analysis, and virology screening. Imaging study such as ultrasonography in addition to the intravenous pyelography (IVP) and renal angiography for the donors were recorded. All patients received antibiotic prophylaxis before and during surgery.

Induction therapy administered was basiliximab as 20 mg IV intraoperatively and postoperative day-4 (POD-4). Immunosuppressive therapy consisted of combination of two of either: cyclosporine-A, prednisolone, and mycophenolate mofetil, or tacrolimus, prednisolone, and mycophenolate mofetil. The combination of these drugs was based on the transplantsurgical team preference as well as the availability of the drug on time.

Acute rejection episode was confirmed by biopsy and treated per visiting team protocol. The follow-up period was one year after discharge. Graft dysfunction was defined based on the serum creatinine level > 2.5 mg /dl. The outcome measures were acute rejection, graft loss and death.

2.4. Statistical Analysis

Data were analyzed using SPSS (IBM, 21). Categorical variables are presented as frequencies and percentages and continuous variables as mean ± standard deviation. Chi – square test (X^2) was used for categorical variables comparisons and t – test for continuous variables. Difference between groups that used induction therapy and the other group without induction therapy was assessed with odds ratio (OR) and 95%confidential interval (95% CI) for odds. A *P* value of < 0.05 was considered statistically significant.

3. Results

A total of 154 renal transplants were carried out at Al Thawra center. The mean age was 32.42 ± 10.4 years (rang 14 – 66). The male sex was predominant accounting for 72.7%. There were 93.5% of patients on dialysis and the dialysis time was ≥ 3 years in 72%. The major causes of end-stage kidney disease (ESKD) were chronic pyelonephritis (77.9%), hypertension (13%), glomerulonephritis (3.9%) and diabetes mellitus (2.4%). Table 1 summarizes the population characteristics.

Table 1. *Characteristics of renal transplant patients at Al Thawra General Hospital.*

Variable	N (%)
Age (year)	
> 40	119 (77.2)
< 40	35 (22.7)
Mean ± SD	32.42 ± 10.4
Rang	(14 – 66)
Sex	
Male	112 (72.7)
Female	42 (27.3)
Blood group	
O^+	114 (74)
Others	40 (25.9)
On dialysis	144 (93.5)
Duration of dialysis	
< 3 years	33 (21.4)
≥ 3 years	111 (72)
Causes of ESKD	
Chronic pyelonephritis	120 (77.9)
Hypertension	20 (13)
Glomerulonephritis	6 (3.9)
Diabetes mellitus	4 (2.6)
Cardiac ± liver disease	2 (1.3)
Unknown	2 (1.3)

Number (%). ESKD:End stage kidney disease.

The graft source was living-donor for all renal transplant recipients. The first – degree relative donors accounted for 96.1%. Induction therapy was used for 39 patients (25.3%) as a basiliximab drug. Immunosuppressive agents including combination of more than two of cyclosporine A, mycofenolate mofetil, tacrolimus and prednisolone. Cyclosporine A was given for (90.9%), mycofenolate (99.4%), tacrolimus (9.7%) and prednisolone (97.4%). The mean creatinine level preoperatively was 854.05 ± 429 mmol/L. (Table 2).

Table 2. *Parameters of renal transplant recipient patients preoperation.*

Variable	
Graft source	
Living-donor	154 (100)
Related donors	
1st degree relative	148 (96.1)
2nd degree relative	6 (3.9)
Induction therapy	
Yes	39 (25.3)
No	115 (74.7)
Immunosuppressive agent	
Cyclosporine	140 (90.9)
Mycofenolate	153 (99.4)
Tacrolimus	15 (9.7)
Predenisolone	150 (97.4)
Laboratory	
Hb (g/dl)	10.4 ± 2.4
WBC(mm^3)	15931 ± 2022.7
Albumin(g/dl)	38.93 + 25
Creatinine µmol/L	854. 05 ± 429
K mEq /L	5 ± 1.5

Data presented as n (%) or mean ± SD; K: Potasium

Three cases (1.9%) had developed surgical complications in terms of leakage, vascular and hematoma formation. During the first year following RT, 6 patients (3.9%) complicated by acute rejection episodes that did not reach statistical significance (P > 0.05).

There was one case had a positive HBV markers, another case HCV positive and the third case had positive CMV markers. Death following RT occurred in 30 cases (19.4%). The mortality rate during the 1st, 5th, and 10th years was 1.9%, 9% and 14.9%respectively. Infectious conditions were the most frequent causes of death (13%) followed by cardiovascular events (3.9%) and others (2.5%). (Table 3).

Table 3. *Outcomes of patients who had renal transplant.*

Variable	
Surgical complication	33 (1.9)
Leakage	1 (0.6)
Vascular	1 (0.6)
Hematoma	1 (0.6)
Emergency readmission	40 (2.5)
Acute rejection	6 (3.9)
Infection	
HBV	1 (0.6)
HCV	1 (0.6)
CMV	1 (0.6)
Early post RT dialysis	2 (1.3)
Death	30 (19.4)
Causes of death	
Sepsis	20 (13)
Cardiovascular	6 (3.9)
Others	4 (2.5)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; CMV: Cytomegalovirus

The patients who exposed to induction therapy using basiliximab showed an increase risk of having acute rejection episodes compared to the patients who did not have induction therapy (OR 1.5, 95% CI 0.263 – 8.52) but the difference between the two groups was not statistically significant (P = 0.46). Table 4 shows the comparison between the two groups.

Table 4. *Comparison between induced and non-induced groups*.

Variable	Induced group (n = 39)	Non induced (n = 115)	P value
Acute rejection episodes			
N (%)	2 (5.1)	4 (3.4)	
Odds ratio	(1.5)		
95% CI	0.263 – 8.52		0.46
Serum creatinine (mmol/l)			
2 weeks	106.42 ± 59	92.11 ± 58.0	?
6 months	74.27 ± 35.7	83.13 ± 61	0.39
1 year	75.02 ± 67.5	84.32 ± 62.3	0.43
3 years	71.6 ± 12.6	72.4 ± 16.4	0.78
Death			
N (%)	6 (15.3)	24 (20.9)	
Odds ratio	0.6		
95% CI	0.258 – 1.82		0.45

4. Discussion

In Yemen, 1998 was a memorable year as the first case of renal transplantation (RT) was performed in AlThawra General Hospital (TGH), Sana`a. Since that time more than 240 RT have been carried out. Of these, 154 cases of RT were reviewed. This study aimed to analyze the outcome of RT in TGH. The majority of our patients are males (72.7%). A study carried out in Cairo university [4] found that the male recipients of renal transplants represented 68.1%. Kaballo MA et al [5] found that 64% of kidney transplants were performed for males. The predominance of male patients could in part be explained by the fact that male patients often seek health care early while female patients due to cultural barriers attend health care usually late with advanced disease. The mean age of patients who had RT in our series was 32.42 ± 10.4 years which is in agreement with the Davidson B et al [6] who reported the mean age as 38 ± 10.5 years. In contrast, recent report from the United States Renal Data System (USRDS) and organ procurement and transplantation Network (OPTN) [7, 8] showed the peak age bracket of RT was 45 – 64 and > 50 years respectively. Undoubtedly, the difference reflects the health situation in the developed and developing countries. There is evidence in the previous studies that the recipient age more than 40 years is considered a prognostic factor of higher risk of mortality in RT patients [9]. The causes of end-stage kidney disease (ESKD) observed in this study are chronic pyelonephritis

(77.9%), hypertension (13%), diabetes mellitus (2.9%) and chronic glomerulonephritis (2.6%). These results are comparable to another work [10]. Although, many investigators revealed similar etiologies of ESKD, their frequencies are different reflecting the impact of the community-related conditions. It is reported that glomerulonephritis is the most commonly recognized cause of ESKD [10, 11], another study found hypertension is the leading cause of ESKD (6). Only 1.3% of our population, the underlying causes are unknown, suggesting the importance of pre transplantation renal biopsy for identifying the actual etiology. In the current analysis, 72% of patients had prior dialysis time ≥ 3 years. Although some studies have linked pre renal transplant dialysis time to the adverse outcome [9], we could not observe a significant association between dialysis time an mortality following RT. Bsiliximab (simulect) is a chimeric monoclonal antibody directed against the α chain CD 25 subunit of the interleukin – 2 receptor (1L-2R) and competitively inhibits 1L -2 dependent T –cell activation in acute allograft reaction [12]. Basiliximab is one of the most commonly used induction agents due to it is short –term use, ease of administration, does not need blood level monitoring and lack of major toxicity [13]. It is reported that the 1L – 2 receptor antagonist (1L – 2RA). It has proven to be effective in reducing acute rejection episodes in large double-blind multicenter trials without significant side effects [12]. Early studies comparing basiliximab vs placebo [14], showed that at 6 months, the biopsy-proven rejection had been occurred in 15.3% of basiliximab group vs 26.6% of placebo group with no significant difference (P > 0.005). It is found that basiliximab significantly improved renal function in the first two weeks after transplant and concluded that basiliximab shows strong trend toward reduction in acute rejection in kidney transplant recipients on triple immunosuppressive therapy namely cyclosporine A, mycofenolate mofetil and prednisolone. Another study found similar results [15, 16]. Although basiliximab drug seems safe and effective, other investigators concluded that rabbit antithymocyte globulin (rATG) provides better allograft survival among patients with higher immunologic risk superior to basiliximab [17].

In the present study, 39 recipient patients (25.3%) received induction therapy as basiliximab and 115 patients (64.7%) did not have induction therapy. The overall rate of acute rejection episodes (ARE) was 3.9% during the first year of renal transplant. Bicalho PR et al [18] in a recent study from Brazil reported ARE in 18.3% out of 944 patients with RT. Davidson et al [6] found that 29.7% of renal transplant patients developed ARE during the first year. The low rate of ARE in our study could be related to the use of only living-donor as well as younger recipient patients. Among those received basiliximab, 2 patients (5.1%) developed ARE compared to 4 patients (3.4%) of non-induced group. Renal biopsy confirmed the diagnosis for 4 cases while the other 2 case, the diagnosis was suspected clinically. All patients with ARE were treated by intravenous methyl prednisolone administration, and the response rate was 66.6%, two patients did not respond to this modality and converted to dialysis.

The odds ratio of ARE of patients exposed to basiliximab is 1.5 (OR 1.5, 95% CI 0.263 – 8.52, P = 0.64), which appears insignificant. Our analysis shows that the absolute risk increase in ARE was 1.65% and the number needed to treat (risk) was 60.6%, meaning that for every 60.6 patients received induction therapy with basiliximab, one patient may develop ARE. There was no statistically significant increase in the absolute risk of harm (P > 0.05). Although not statistically significant, the increase in ARE among the group received basiliximab drug could be related to inadequate use of the standard triple immunosuppressive agents during RT rather than basiliximab per se. Notably, the prescription of immunosuppressive regimens was based on the limited availability of these drugs in our country particularly during the early time, and the preference of the transplant surgeons who managed the patients. Certainly, use of a particular immunosuppressive regimen in conjunction with basiliximab appears necessary to reveal a substantial advantages of the this drug.

Parrott et al [19] reported that in the setting of monotherapy or calcienuria inhibitor free regimens, basiliximab has not been shown to be useful. The overall mortality rate of patients after RT in this study was 19.4% over ten years of follow-up. The mortality rate after 1st, 5th and 10th years was 1.9%, 9% and 14.9% respectively. Based on these findings, 1-year graft survival rate was 98.06% that is satisfactory and comparable to another study [10]. The 5-years and 10-years graft survival rates were 96.8% and 85.07% respectively, which are comparable to other studies [19, 12]. Another study found the 1-year and 5-years survival rates for living-donors recipients as 97.8% and 92.9% respectively [9], similar to our results. There was no statistically significant difference regarding the rate of death between the group that received basiliximab and those without (OR 0.6, 95% CI 0.258 – 1.82, P =0.45).

Infectious disease was the commonest cause of death in our cohort (13%) followed by cardiovascular events (3.9%). These are in agreement with other studies (6, 9). There is evidence that the degree of preexisting cardiovascular in renal transplant recipients is a major determinant of post transplantation survival [5]. However, there are many factors affecting the graft survival rate including delayed graft function (DGF), acute rejection, immunosuppressive regimens and panel reactive antibodies [6]. We therefore, suggest that adherence to the standard immunosuppressive protocol, combined with the use of the appropriate induction therapy, correction of the existing cardiovascular risk factors pre transplantation, and long-term follow-up in the transplant center rather than in the non-specialized clinics could improve the survival rate post RT.

Living-donor renal transplants were performed for all patients in this study. Most patients (96.1%) had a first-degree relative donors. The deceased donor organs are not available and not permissible in our country due to religious, social and cultural barriers. It is documented that living-donor renal transplants are associated with superior outcome

following RT compared with deceased donor transplants [15]. The results of this series demonstrated that one case has infected with cytomegalovirus (CMV), one case with hepatitis B virus (HBV) and the third patient has hepatitis C virus (HCV). Ribeiro et al [20] in a study from Brazil found that the major infectious cause of the hospitalized renal transplant patients is CMV which accounted for 16.1%. There is evidence that over immunosuppression has been linked to both CMV infection and also malignancies [21]. Both HBV as well as HCV can be found among renal transplants and cause a higher frequency of complications including membranous nephropathy in renal transplant patients [22, 23]. It is therefore important to maintain patients with prophylaxis antiviral, antibacterial and antifungal drugs.

Some limitations of this study should be highlighted. Basiliximab drug was given with different combinations of immunosuppressive agents rather than to a particular regimen which might influence the true efficacy of basiliximab. Therefore, further studies to explore the true degree of basiliximab effectiveness using a particular immunosuppressive regimen are required.

4.1. Conclusion

This analysis showed that the causes of ESKD are not very different from the other study results. Although, the process of renal transplants in Yemen started slowly with the initial support and cooperation of the Egyptians team, the overall outcomes are satisfactory and comparable to the universal reports. Basiliximab was administered to a subgroup of RT patients combined with different and often inadequate immunosuppressive agents, thus this study could not derive a meaningful conclusion whether it has a substantial protective advantages.

4.2. Disclosure

The authors declare that they have no competing interests.

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