Lowering the Dose of Corticosteroid Regimen in Kidney Transplantation: Is It Effective in Decreasing Post-operative Surgical Complications?

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Purpose: To investigate the impact of reducing post-operative oral corticosteroid regimen on associated postoperative surgical complication rate, patient and graft survival in kidney transplant patients.

Materials and Methods: In this retrospective cohort study, we enrolled patients who received a kidney transplant during two periods of distinct corticosteroid protocols. 592 patients in group 1 received prednisone 2 mg/kg (maximum dose 120 mg) on post-operative days (POD) 1, 2 and 3, 1mg/kg for a week, and tapered it to 10 mg by 3 months post-transplant and sustained the daily 10mg from 3 months post-transplant as maintenance therapy. 639 patients in group 2 received prednisone 50 mg on POD 1, 40mg on POD 2, 30mg on POD 3, 20mg on POD 4, 15mg on POD 5 and continued with 10mg daily from POD 6, as maintenance therapy. The two groups were similar in terms of other immunosuppression drug regimens.

Results: 75 (12.7%) patients in group 1 and 24 (3.4%) patients in group 2 developed corticosteroid-related postoperative surgical complications ($P < .001$). Wound infection ($P = .035$), incisional hernia ($P = .003$), infectious collection ($P = .004$), post-op hemorrhage ($P = .005$) and ureteral fistula ($P = .076$) occurred with lower frequency in group 2. Patient survival (1-year: 97.3% vs 97.1%, respectively; $P = .85$, 5-year: 89.9% vs 94.9%, respectively; $P = .06$) and graft survival (1-year: 94.6% vs 93.3%, respectively; $P = .29$, 5-year: 81.2% vs 85.1%, respectively; $P = .39$) were similar in both groups.

Conclusion: Post-operative corticosteroid dosage decrement through our protocol would lessen the serious associated postoperative surgical complications, without negative impacts on overall patient and graft survival.

Keywords: kidney transplantation; corticosteroid; administration and dosage; postoperative complications; survival analysis

INTRODUCTION

Corticosteroids are an important part of the immunosuppression regimen following kidney transplantation. Corticosteroids are used to prevent graft rejection through the capability of immunosuppression and anti-inflammatory effects. Since its introduction in the 1960s, it has been accepted that corticosteroid has been playing a significant role in increasing graft survival[1, 2]. However, taking corticosteroids may be associated with various post-operative surgical complications including wound infection, incisional hernia, lymphocele, wound or anastomosis healing impairment and bleeding, probably due to interference with the tissue healing process [3-7]. The occurrence of these steroid-related side effects is accompanied by additional costs, post-transplant noncompliance and decreased graft survival[8]. It is interesting to know that prednisone is the immunosuppressive drug that the kidney transplant recipients who survived, would most like not to take[9].

Monitoring the side effects of oral corticosteroids alongside with the disease process seems necessary to decide how to reduce the dose of corticosteroids, post-operatively[10]. Nowadays, to minimize steroid-related complications, steroid minimization protocols are taken into consideration.[8]. Many efforts have been made either to avoid taking steroids or decrease the dosage through other immunosuppressive drugs replacement[11,12]. However, the main concern in this respect is how corticosteroid minimization would affect the graft and the patient's survival.

In this study, we aimed to investigate if decreasing post-operative oral corticosteroid regimen following kidney transplantation would reduce the postoperative surgical complication rate, with no change in patient and graft survival.

MATERIALS AND METHODS

Study Population

In this retrospective cohort study, we enrolled patients who received kidney transplants during two periods of distinct corticosteroid protocols in our center between 2013 and 2019.

A total number of 592 patients who received their first kidney transplantation between Jan 2013 and Jan 2016 (group 1) were compared to 639 patients receiving kidney alone transplant between Jan 2016 and Jan 2019

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Received November 2022 & Accepted April 2023

Table 1. Patients' characteristics of group 1 and 2

	Group 1	Group 2	*p*-value
Number (n)	592	639	
Age (±SD)	40 (±15)	41 (±17)	0.148
Sex (F/M)	206/386	213/426	0.588
BMI (±SD)	24.30 (±4.89)	24.54 (±5.11)	0.386
Pre-op DM (%)	112 (19%)	129 (20.2%)	0.585
Pre-op HTN	412 (69.7%)	450 (70.4%)	0.786
Donour type (living/cadaver)	309/283	320/319	0.458

(group 2). The follow-up of all patients in both groups started at the time of surgery and continued until the end of 2022.

Exclusion criteria

Exclusion criteria were patients with multi-organ transplantation, repeated kidney transplantation in the same recipients, history of corticosteroid usage for whatever reason like autoimmune disease and loss to follow up.

Immunosuppression protocols

In group 1, patients received prednisone 2 mg/kg (maximum dose 120 mg) on post-operative days (POD) 1,2 and 3, 1 mg/kg for a week, and tapered to 10 mg by 3 months post-transplant and continued with 10mg daily from 3 months post-transplant as maintenance therapy. In group 2, patients received prednisone 50 mg on POD 1, 40mg on POD 2, 30mg on POD 3, 20mg on POD 4, 15mg on POD 5 and continued with 10mg daily from POD 6, as maintenance therapy. All patients in both groups were similar in chronic immunosuppression maintenance including Mycophenolate Mofetil and Tacrolimus.

Evaluations

We used electronic medical records and organ transplant tracking record database to extract the variables. All the kidney transplantation survival data in our center are registered in Collaborative Transplant Study (CTS) of Heidelberg, prospectively. The primary goal of this study is to evaluate and compare the associated post-operative surgical complications including incisional hernia, lymphocele information requiring percutaneous drainage or exploration, hemorrhage which lead to exploration; nephrectomy or anastomosis repair, infectious collection formation, wound infection, ureteral stenosis and ureteral fistula leading to exploration between the two groups. The secondary goal is to compare the patient and graft survival between these two groups. The study protocol was approved by the institutional board of research and committee of medical ethics (code: IR.SBMU.MSP.REC.1398.690). This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

All the statistical analyses were performed using SPSS software version 25.0 (IBM, Chicago, Illinois, USA). Data are shown as mean ± standard deviation (SD) and frequency (percentage) for quantitative and qualitative variables, respectively. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. The independent sample T test or Mann-Whitney test was also used to compare the mean outcome quantities between the two groups studied. Chi Square test or Fisher exact test (where the 20% of expected cell counts were less than 5) was also used to compare qualitative factors between the two groups. Kaplan-Meier survival analysis along with log rank test was performed by CTS of Heidelberg to compare patient and graft survival between the study groups. Univariable and multivariable Logistic regression analysis was used to assess the effect of variables on binary outcomes. The normality of data distribution was assessed using the Kolmogorov-Smirnov test and also graphically through Q-Q plot. In this study, *P*-value of less than 0.05 was considered as statistically significant.

RESULTS

In this study, we evaluated the data of 1231 patients who underwent kidney transplantation. Table 1 shows the patients characteristics of group 1 and 2, separately. A total number of 99 (8.04%) patients including 75 (12.7%) in group 1 and 24 (3.8%) in group 2 developed corticosteroid-associated postoperative surgical complications ($P < .001$). Wound infection ($P = .035$), incisional hernia ($P = .003$), infectious collection formation ($P = .004$) and post-op hemorrhage ($P = .005$) occurred with significantly lower frequency in group 2. Ureteral fistula was also decreased in group 2 but not significant (9 in group 1 versus 3 in group 2, $P = .076$). **Table 2** shows the types of postoperative complications among group 1 and 2, separately.

After adjusting the covariates, in a multivariable logistic regression, the corticosteroid dosage group was an independent predictor for infectious collection formation (OR[CI]: 0.05[0.007-0.37]; $p = .004$), wound infection (OR[CI]: 0.45[0.21-0.94]; $P = .035$) and postoperative bleeding (OR[CI]: 0.12[0.028-0.530]; $P = .005$). We did not perform multivariate analysis for incisional hernia because it did not occur to any patient in the low-dose group at all (**Table 3**).

Figure 1a shows the Kaplan-Meier overall patient survival, comparing group 1 with group 2. Patient survival was similar between two groups, 1-year survival: 97.3% vs 97.1%, respectively; ($P = .85$), 3-year survival: 94.3% vs 95.5%, respectively; ($P = .38$), 5-year survival: 89.9% vs 94.9%, respectively; ($P = .06$). **Figure 1b** shows the Kaplan-Meier graft survival comparing the

Table 2. Types of postoperative complications among group 1 and 2.

	Group 1	Group 2	*p*-value	Odds ratio (95%CI)
Lymphocele	5 (0.8%)	4 (0.6%)	0.654	0.740 (0.198-2.767)
Incisional hernia	8 (1.4%)	0 (0%)	0.003	-
Infectious collection	17 (2.9%)	1 (0.2%)	0.004	0.053 (0.007-0.400)
Ureteral fistula	9 (1.5%)	3 (0.5%)	0.076	0.306 (0.082-1.134)
Ureteral stenosis	6 (1%)	3 (0.5%)	0.275	0.461 (0.115-1.850)
Wound infection	22 (3.7%)	11 (1.7%)	0.035	0.454 (0.218-0.944)
Hemorrhage (anastomosis leakage)	15 (2.5%)	2 (0.3%)	0.005	0.121 (0.028-0.530)
any kind of side effects	75 (12.7%)	24 (3.8%)	< 0.001	0.269 (0.167-0.432)

Table 3. Multivariable logistic regression of the postoperative complications after adjusting the covariates.

	p-value	Odds ratio (95%CI)
Lymphocele	.557	.67(.17, 2.55)
Infectious collection	.004	.05(.007, .37)
Ureteral fistula	.084	.31(.08, 1.16)
Ureteral stenosis	.241	.43(.10, 1.75)
Wound infection	.035	.45(.21, .94)
Hemorrhage (anastomosis leakage)	.005	.12(.02, .53)
overall complications	< .001	.27(.68, 1.67)

two groups. Graft survival was also similar between the two groups. 1-year survival: 94.6% vs 93.3%, respectively; (P = .29), 3-year survival: 88.2% vs 89.1%, respectively; (P = .81), 5-year survival: 81.2% vs 85.1%, respectively; (P = .39).

DISCUSSION

Steroids are used against inflammation, edema and autoimmunity and have a role in the treatment of a wide range of diseases. Considering its benefits, in this study we intended to address its disadvantages including post-surgical complications following kidney transplantation. Tissue-healing process following vascular anastomosis, ureterovesical reimplantation and abdominal wall repairment begins immediately in kidney transplant patients. It is proven that corticosteroids would affect all major steps of healing process including inflammatory, proliferative and remodeling phases. By inhibiting vascular permeability and leukocyte adhesion, steroids impair the initiation of tissue matrix layout and healing process[13,14]. Conventionally, high-dose corticosteroids are used immediately following kidney transplantation, just when the tissue-healing process has begun. This effect led us to the hypothesis that using high dose steroids post-operatively might increase surgical complications. Many studies have evaluated the role of corticosteroids in postoperative complications in different types of surgeries. Hasselgren et al.[6] found out in a prospective study of 1243 different surgeries that treatment with high-dose steroids is associated with high wound infection rate. Golub et al.[15] in a retrospective study of 764 patients who underwent intestinal anastomoses found out that the use of corticosteroids could predict anastomotic leakage. In a retrospective cohort study of post-operative complications after esophagectomy, Jeong et al.[16] realized that using corticosteroids may be related to graft dehiscence and fistula. Weisberger et al.[5] analyzed the impact of corticosteroid use on free flap reconstruction and concluded that chronic corticosteroid usage conferred increased major bleeding complications requiring blood transfusion by a factor of four. In a multivariate analysis, Togo et al.[4] discovered that steroid use is a risk factor for incisional hernia following partial hepatectomy. Fink et al.[7] showed that patients with a history of using corticosteroids are at a higher risk of vascular complications and post-surgical bleeding following transfemoral aortic valve implantation. Based on the findings of these studies and other similar studies, and in agreement with the association of corticosteroids usage and post-operative healing process, we hypothesized that we could reduce the post-surgical complications by corticosteroid dosage decrement following kidney transplantation. In this study, we experienced 8 incisional hernias in group 1 (high-dose steroid), some of whom were inoperable (**Figure 1**), while no patients in group 2 (low-dose steroid) suffered an incisional hernia post-operatively (P < .05). Some studies address the issue of association between steroid usage and incisional hernia following liver transplantation[17-20] but to our best knowledge, there is no study in the literature having specifically evaluated this relationship in kidney transplant recipients. In addition, we observed a considera-

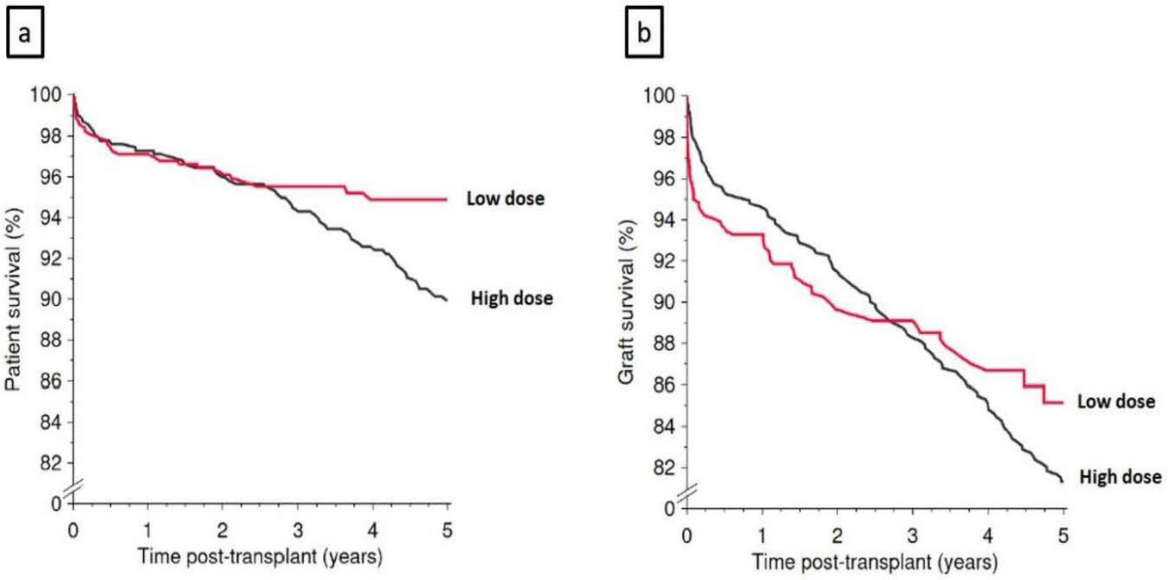

Figure 1. a. The Kaplan-Meier overall patient survival, comparing group 1 with group 2.
Note: Patient survival was similar between two groups. **b.** The Kaplan-Meier graft survival comparing the two groups.
Note: Graft survival was also similar between the two groups.

ble decrease of ureteral fistula in the low-dose group (9 versus 3, $P = .076$). Given that ureteral fistula is a rare complication following transplantation, we believe that with a larger sample size, a significant p-value may be achievable. Collins et al.[21] showed that the use of corticosteroid may interfere with the healing of vesicovaginal and urethrovaginal fistula when an early repair is attempted but to our best knowledge, no study has been designed to evaluate the association of corticosteroid dosage and ureteral fistula following kidney transplantation yet. We observed a significant decrease of wound infection and infectious collection formation during corticosteroid dosage decrement (22 versus 11 $P = .035$, 17 versus 1 $P = .04$, respectively). Ahern et al. [22] in a study about general infectious complications associated with renal transplant, concluded that the incidence of serious infections was higher in recipients receiving high-dose steroid versus recipients receiving lower doses of steroids. Wound infections were easily managed in low-dose steroid groups patients, while we faced a few refractory wound infections among high-dose steroid group, which needed to be left open and required regular washing for a long time period. We did not observe changes in lymphocele formation incidence in different corticosteroid dosage recipients. In a univariate analysis, Khauli et al.[23] detected high-dose corticosteroid as a risk factor for lymphocele development beside acute tubular necrosis and rejection in kidney recipients. However, in the multivariate analysis only rejection rather than corticosteroid dosage was a predictor for lymphocele formation in their study.

Our results showed that our corticosteroid minimization protocol would reduce the serious postoperative surgical complication rate, without negative impacts on patient and graft survival. There are some studies in the literature, which are comparable to our results regarding corticosteroid dosage decrement and survival. In a comparative study about patient and graft survival among 1689 patients with a historical approach and 2097 patients in the early steroid withdrawal group following kidney transplantation, Adebiyi et al.[24] showed no difference in patient survival but better death-censored graft survival in the second group. In a large study, Luan et al.[25] evaluated the data of 95,755 kidney transplant recipients, 16,491 (17.2%) of whom were steroid-free at discharge. It was interesting to notice that steroid-free regimen was associated with a reduced risk of graft failure and death.

In a study about corticosteroid minimization protocol, Jaber et al.[26] found out that early steroid withdrawal (day 6, postoperatively) would not affect the graft survival. In a 15-year period kidney transplantation study, Serrano et al.[27] evaluated 1553 patients and concluded that rapid discontinuation of prednisone does not lead to a decrease in patient or graft survival. These two recent studies evaluated the association of corticosteroid dosage decrement and medical steroids side effects, the patient and graft survival. Along with reducing medical steroid-associated side effects, similar to us, they found out that reducing steroid dosage would not adversely impact on patient and graft survival. They, however, did not investigate the relationship between corticosteroid dosage decrement and post-operative surgical complications.

Our patient survival Kaplan-Meier curves (**Figure 1a**) show that as the follow-up time increases, patient survival decreases further in high-dose corticosteroid group than low-dose corticosteroid group. In other words, high-dose post-operative corticosteroid is associated with lower patient survival in the long term, probably through increasing the risk of medical comorbidities including diabetes mellitus, osteoporosis, ischemic heart disease.

Based on our results, early steroid decrement has promising outcomes and deserves more attention in renal transplant patients to prevent serious post-transplant surgical complications, a goal that has been underappreciated in the literature. Nevertheless, it is evident that careful monitoring of the patient and graft function seems to be necessary. We perform kidney transplantation from living or deceased donor in our center[28, 29] and including a high proportion of living donors in this study is different in comparison to many other studies. Retrospective nature is the main limitation of this study and prospective studies through randomized clinical trial settings seem to be mandatory to confirm our findings. Large OR estimates and CI due to low rate of some surgical complications were another limitation of this study.

CONCLUSIONS

Reducing the dose of corticosteroid through our protocol seems to be beneficial following kidney transplantation. Our study indicates that post-operative corticosteroid dosage decrement would lessen the post-operative surgical complications including incisional hernia, wound infection, infectious collection formation, post-operative hemorrhage and ureteral fistula without negative impacts on overall patient and graft survival.

ACKNOWLEDGEMENT

We would like to thank Collaborative Transplant Study (CTS) team, Heidelberg University Hospital, for their assistance with Kaplan-Meier survival analysis.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interests.

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