Original Research Article

A prospective randomized study comparing the impact of twice divided versus once daily prednisolone dosing on hyperglycemia and glycemic variability among renal transplant patients

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Abstract

Aim: Prednisolone exerts high glycemic variability leading to endothelial dysfunction and coronary events. This study compares glycemic excursions, hypothalamic–pituitary–adrenal axis suppression, sleep disturbance, lipid profile between divided twice daily (BD) and once daily (OD) prednisolone groups. **Materials and Methods:** Thirty-two renal transplant recipients without diabetes were randomized to BD or OD prednisolone. Two hepatitis C positive patients under BD group and three serology negative patients from OD group developed NODAT and hence excluded. One BD group patient suffered graft nephrectomy and was excluded. After three weeks post-transplant, 4th hourly venous glucose monitoring was performed for 3 days. Mean glucose, highest glucose and lowest glucose, exposure to hyperglycaemia, glycemic variability and HbA1C levels were assessed. 8AM serum cortisol, lipid profile, Athens Insomnia score, creatinine, sodium, potassium, urine culture and sensitivity were also assessed. **Results:** Median age was 32yrs, 88.43% were males. Mean tacrolimus level [between 8-12 ng/ml (P< 0.512)] and mean glucose(P<0.68) among both groups were similar. BD group has less higher glucose value [206 versus 216 (P<0.007)] and exposure to hyperglycaemia ≥180mg/dl [4(30.8%) versus 11(84.6%) patients(P=0.034)]. Glycemic variability scores MAGE (P=0.0007), CONGA (P=0.0009), J-index (P=0.007) and Mean absolute glucose (P=0.0001), mean HbA1C (P=0.026), creatinine (P=0.016), cholesterol (P=0.665), triglycerides (P=0.112), LDL (P=0.243), VLDL (P=0.398), cholesterol/HDL ratio (P=0.717), urinary tract infections were less with BD group. HDL (P=0.605) was more with BD group. Fasting cortisol was suppressed in both groups (P=0.285). No difference noted in hemoglobin (P=0.379), sodium (P=0.942), potassium (P=0.166), Athens Insomnia score (P=0.19). **Conclusions:** Divided prednisolone dosing reduces glycemic variability and hyperglycemia early post-transplant period. HbA1C was lower in the divided dose group. BD group patients have not developed NODAT except those with Hepatitis C infection. Fasting serum cortisol level appears suppressed in OD group also. Athens insomnia score showed no sleep disturbance among both groups

Key Word: hyperglycemia.

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Glucocorticoids have become the prime immunosuppressant drug with the increasing number of organ transplantation surgeries. Steroids block APC and T-cell derived expression of cytokines, inhibit cytokine gene transcription and also decrease levels of interleukins, TNF-α and IFN-γ. As a result, cytokine production and lymphocyte proliferation are inhibited. Since prednisolone has got a half life of 200min only, once daily dosing cannot maintain a steady state plasma level in the latter half of the day. Few studies state divided dose appears more

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efficacious than once daily dosing with less diabetogenic effect. Steroids cause adverse side effects involving gastrointestinal system, abnormal lipid metabolism, weight gain, cushingoid habitus, stunting particularly in children, abnormal bone metabolism, abnormal glucose metabolism impairing the graft function and hence patient survival. Patients with same mean serum glucose or glycosylated hemoglobin (HbA1c) can have different glucose profiles due to differences in the frequency and duration of glycemic excursions. Glycaemic variability and hyperglycemia are associated with induction of oxidative stress, pancreatic beta cell dysfunction and interference with normal endothelial function by generation of reactive oxygen species that results in micro and macro vascular diabetic complications by many molecular mechanisms. Such endothelial dysfunction is associated with a 1.8 times increase in cardiovascular mortality, which is the leading cause of post transplant deaths. Divided dose steroids reduce such variability of glucose compared to once daily dosing. The main intension to use once daily morning dosing of steroid is not to suppress the integrity of hypothalamo-pituitary adrenal axis. But long-term low dose steroids of 5-10 mg once a day itself causes suppressed cortisol levels and abnormal ACTH stimulation test suggesting that hypothalamo-pituitary adrenal axis appears suppressed even with maintenance doses of ≥5 mg. This prospective study uses 4th hourly venous glucose levels of post renal transplant recipients taking twice daily (BD) and once daily (OD) prednisolone, to determine differences in glycaemic variability among both groups. Also this study has been extended to compare HbA1C, lipid profile and also the fasting serum cortisol level to assess the suppression of hypothalamo pituitary adrenal axis.

AIM

1. To compare highest glucose, mean glucose and glycemic variability among subjects grouped into once a day and twice divided dose prednisolone.
2. To compare early morning serum cortisol level between the two groups to assess the suppression of hypothalamic–pituitary–adrenal axis.
3. To compare the degree of sleep disturbance between the two groups by means of Athens sleep score.
4. To compare HbA1C, serum fasting lipid profile between the two groups.

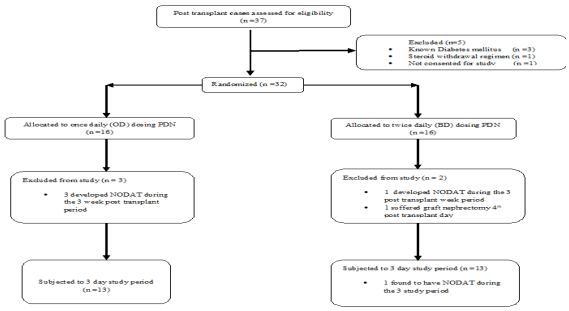
MATERIALS AND METHODS

A Prospective Randomized study done on renal transplant recipients who are not on a steroid free regimen, admitted at Nephrology ward, Govt Kilpauk Medical College Hospital (KMC) and Govt Royapettah Hospital, Chennai on the day of completion of 3rd post transplant week. Patients with known diabetes mellitus, active infection, those developing any complication within 3 week post transplant period needing withdrawal of steroid, and post transplant diabetes mellitus in the 3 week period got excluded.

METHODOLOGY

Thirty two renal transplant patients were included for the study at the end of their three weeks post transplant period. Of them 28 were live related transplants and 4 were deceased donor transplants. All live related transplant recipients received basiliximab induction 20 mg two doses (0 and 4th days) and deceased donors received rabbit anti thymocyte globulin 1.5mg/kg single dose induction. Renal transplant patients uniformly received an initial dose of 1g methyl prednisolone prior to kidney transplantation and 125mg methyl prednisolone 6th hourly on the first postoperative day. Maintenance immunosuppression comprised of tacrolimus, mycophenolate sodium and prednisolone, commencing 2–3 days prior to surgery. Tablet Prednisolone was started at 0.5 mg/kg/day with a minimum of 30 mg daily after the pulse steroids from post transplant day 2 onwards and slowly tapered after 2 weeks to reach 20mg a day in 4 weeks. Majority of the patients were taking 25 mg prednisolone during the study period. Target tacrolimus trough levels were adjusted for 8–12 ng/mL for the first and third weeks post transplantation. Patients were divided under stratified randomization into OD (8:00 am) or BD (50% of total daily dose at 8:00 am and 50% at 8:00 pm) prednisolone dosing regimens. At the end of three weeks with routine post transplant follow-up, they were subjected to a 3 day study period. After the study period patients continued their respective dosing regimen up to the period when BD group dose falls below 10mg, during which they will be converted back to OD group. We have not checked the efficiency of twice divided low dose steroid maintenance in post transplant setting lower than 10 mg as long term careful monitoring is needed to prevent rejection and also to define an endpoint for this study. Calorie intake was advised not to exceed 2500cal/day. Diet was split into breakfast, lunch and dinner with early morning beverage and evening snack. No added extra meals entertained. Protein intake was aimed to be around 0.5mg/kg/day. Fourth hourly venous blood glucose and blood pressure monitoring starting from 8AM on 1st day to 4AM on the 4th day, early morning cortisol level, fasting lipid profile, HbA1C, renal function tests, sodium, potassium, urine analysis, urine culture and sensitivity, haemoglobin, Athens sleep assessment score, bodyweight were recorded during the 3day study period. Screening to rule out active infections with clinical examination and relevant investigations was carried out.

RESULTS



24 had chronic glomerulonephritis with remaining 2 with chronic interstitial nephritis. 23 (88.46%) were males, the remaining 3 (11.59%) were females. The median age for the study group was 32. The median prednisolone dosage for both the groups at the end of 3 weeks was 25mg/day. The median tacrolimus levels were 9 ng/ml for BD and 9.6 ng/ml for OD group (P value=0.79) which fell within the range of 8-12 ng/ml, since Tacrolimus can cause NODAT.

4th Hourly Glycemic Measurements: Though the average mean glucose among the groups, (mean 129.2 versus 131 mg/dL (P <0.68)) were comparable, with regard to 4th hourly sugar levels, the below table clearly indicates lower levels with BD group than the OD group that were statistically significant.

Table 1:

timing	mean sugars od (mg/dl)	mean sugars bd (mg/dl)	p value
8AM	105.5	106.4	0.08
12	168.2	139.2	**0.0001**
4PM	186.8	159.3	**0.0002**
8PM	104.6	122.8	**0.0022**
12	125.5	138.6	**0.04**
4AM	96.3	109.4	**0.018**
24 hours	131	129.2	0.68

The highest glucose was lower with BD than OD group, median 206 versus 216 mg/dL (P < 0.007).

Table 2:

Sugars	>180mg/dl	>200mg/dl
Number of BD patients	4	2
Number of OD patients	11	6

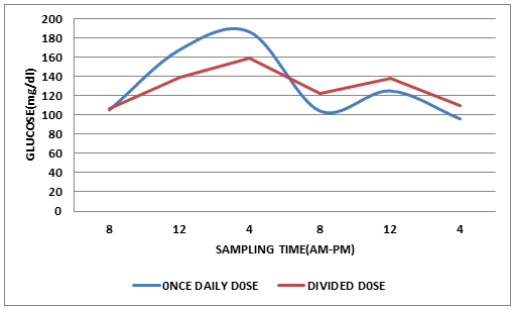


Figure 1: average sugars od and bd groups

In the above graph, mean venous glucose was highest at 4PM in both groups with OD group (186.8mg/dl) more higher than the BD group(159.3mg/dl). Also the lowest sugar levels were noted at 4AM with OD group sugar (96.3mg/dl) more lower than the BD group(109.4mg/dl). At 8PM also lower values were observed with OD (104.6 mg/dl) much lower than BD group(122.8mg/dl). Glycaemic variability indices namely MAGE, CONGA, J-index and MAG were low in BD group than in OD group as shown below.

Table 1: Mage

mage	mean	median	p value
OD	3.70	3.38	0.0007
BD	2.34	2.12	

Table 2: Conga`

Conga	Median	Mean	P Value
OD	7.00	6.70	0.0009
BD	5.47	5.36	

Table 3: J Index

J Index	Mean	Median	P Value
OD	29.6	31.3	0.007
BD	24.1	23.8	

Table 4: MAG

Mag	Mean	Median	P Value
OD	0.64	0.589	0.0001
BD	0.41	20.412	

DISCUSSION

Prednisolone with OD and BD doses are equally efficacious though some studies show higher efficacy with BD dose which can sustain steady state blood levels (t1/2 of prednisolone 3hrs). Glycemic variability imparts oxidative stress and endothelial dysfunction leading to coronary events and 'Post-transplant diabetes mellitus(PTDM)' or NODAT. Risk factors such as hypertension, calcineurin inhibitors, dyslipidemia and rapid erythropoiesis by the functioning kidney adds fuel to this. With cardiovascular mortality being the leading cause of post transplant deaths, this study was done between OD and BD prednisolone dosing with importance to dysregulated glucose metabolism. KDIGO transplantation guidelines 2012 suggest for those with low immunological risk and with induction therapy, corticosteroids could be discontinued during the first week after transplantation (Early steroid withdrawal) though the level of evidence is just 2B**.** But high-risk transplants and where steroid withdrawal protocols are not considered, the timing of administering steroids should be considered to minimize glycemic excursions and oxidative injury. Once daily dose is preferred, to minimize hypothalamic–pituitary–adrenal axis suppression. Also prednisolone clearance is lower in the morning increasing its efficacy and with less sleep disturbances and mood swings at night. Though patients from both groups developed NODAT, the two patients from BD group suffered from pre transplant Hepatitis C Genotype 1 infection after achieving sustained virological response (SVR). Two other hepatitis C patients from BD group were not complicated by NODAT. All the three NODAT patients from OD group had hepatitis negative serologies. The association of hepatitis C could have caused NODAT or else the BD group would have been NODAT-free. Hepatitis C causes fourfold increased risk for NODAT through blocking Insulin-stimulated IRS-1 tyrosine phosphorylation leading to insulin resistance. The fasting cortisol levels were 4.78 and 6.8 in BD and OD group (p value-0.28) both were adrenal suppressed states (<10µg/ml). There was no significant difference among serum sodium and potassium. Two from OD group (higher glucose exposure) had positive urine culture reports with E.coli and Klebsiella. The mean cholesterol, TGL, LDL, VLDL and cholesterol/HDL ratio were higher and HDL lower in OD group (not statistically significant). With Athens sleep score (AIS) regarded as an effective sleep analysis tool, the median values were 2 in BD and 3 in OD group (p 0.19). Less than the Insomnia cut-off score of ≥6, there is no sleep disturbance among groups.Though HbA1c estimation is not reliable before 3 months post transplantation, high normal value cohort when compared with low normal values has got significant increase in cardiovascular morbidity. Here a statistically significant decrease of nearly 0.4% (5.5 vs 5.1) HbA1C is observed among BD group patients.

CONCLUSIONS

1. The glycemic variability measures are significantly lower in divided dosing group than the single dosing group.
2. The highest and lowest sugar levels were noted in once daily regimen indicating wide glycemic variability.
3. HbA1C was significantly lower in the divided dose than the once daily dose group.
4. Patients from divided dose group has not developed NODAT except those with associated Hepatitis C infection.

5. Fasting serum cortisol level at 8 AM appears suppressed even with once daily regimen.
6. Athens insomnia score among both groups showed no sleep disturbance.
7. Culture positive urinary tract infections were observed in once daily regimen.

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