Pill burden does not influence compliance with oral medication in recipients of renal transplant

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Introduction

Chronic kidney disease is a major public health issue worldwide and an important contributor to the overall noncommunicable disease burden. The prevalence of end-stage renal disease (ESRD) in India is not known but is estimated to be approximately 55,000, and growing by approximately 10% every year.¹⁰ Transplant Procurement Management 2011 reported that kidney transplant is the most widely performed transplantation procedure worldwide.¹⁰ However, only about 10–15% of all ESRD patients receive renal replacement therapy in China and India.¹¹

A recent review¹² revealed that the magnitude of nonadherence to immunosuppressive medication in kidney transplant recipients is as high as 36 cases per 100 patients per year.

ABSTRACT

Objectives: Insights about the predictors of noncompliance are key to develop compliance enhancing strategy in a given therapeutic situation. Renal transplantation is a critical surgical procedure that imposes a large medication burden on patients. There is a suspicion that the large pill burden may lead to noncompliance. Our objective was to ascertain the influence of pill burden on medication compliance in renal transplant patients in the Indian sociocultural context.

Methods: A longitudinal observational study was conducted in two Tertiary Care Hospitals in Kolkata running renal transplant program – one each from the government and private sectors. Totally 120 literate adult transplant recipients were recruited through purposive sampling and followed up at 3 months intervals for 1 year. Data were collected through interview and review of prescriptions and medical records.

Results: Data of 110 subjects were analyzed. The pill burden was high – ranging from 10-21 (median 14) at first visit shortly after discharge to 7–22 (median 11) at last visit at 12 months in the government sector; corresponding figures in the private sector were 14–32 (median 21) and 10–28 (median 17). Pill burden increased with age. Only 60.91% of the patients were fully compliant until 1 year after transplantation. The rate of immunosuppressant noncompliance was 27.78% in government sector and 25.00% in private sector. There was no significant association between median pill burden and medication compliance. Satisfaction with caregiver support was associated with better immunosuppressant compliance.

Conclusions: Noncompliance in renal transplant recipients is likely to be multifactorial. Contrary to popular belief, pill burden was not a major determinant of noncompliant behavior.

KEY WORDS: Compliance, India, pill burden, renal transplant
while nonadherence to immunosuppressants in the overall population of solid organ transplant recipients is 22.6 cases per 100 patients per year. This suggests that nonadherence rate may be higher in renal transplantation. The consequences of nonadherence can be serious. Another systematic review suggests that median 36% (interquartile range 14–63%) of graft losses may be associated with nonadherence in renal transplant patients.\[^{11}\]

Securing the patient’s compliance remains a significant, multidimensional challenge towards achieving the best long-term treatment outcomes in transplant patients. Previous research suggests that renal transplant recipients may be especially prone to nonadherence because of complexity and lifelong character of their immunosuppressive therapeutic regimens.\[^{7}\] Medication for co-morbidities adds to the pill burden. The high pill burden decreases compliance with drug therapy since the need to take a large quantity of pills on time on a daily basis negatively impacts the quality of life.\[^{5,6}\] However, the relationship between pill burden and compliance in renal transplant recipients has not been explored adequately in the Indian sociocultural context. We aimed to evaluate the influence of pill burden on compliance status for 1 year following renal transplantation in Indian patients.

**Methods**

A longitudinal observational study was conducted with adult subjects attending the nephrology posttransplant clinic of a Tertiary Care Government and a Private Hospital in Kolkata, following Institutional Ethics Committee approval. A total of 120 kidney transplant recipients were recruited between July 2011 and December 2012 and followed up at 3-month intervals for 12 months. Written informed consent was obtained from all subjects. Purposive sampling technique was used to select the subjects for the study.

To screen for noncompliance status, the 4-item Morisky Medication Adherence scale,\[^{7}\] with dichotomous response options was used. This scale is a standard tool for assessing medication adherence. It’s internal consistency coefficient (Cronbach’s α) value is 0.61 and its reliability has been studied across a variety of disease groups including with dialysis and transplant populations.\[^{7}\] Patients responding “yes” to one or more items of the scale were probed further.

Pill burden was defined as the number of tablets, capsules or other unit doses taken by a patient daily and was ascertained by reviewing prescriptions and medication records. Total pill burden was distributed into two components – immunosuppressants and others. Taking compliance to denote the extent to which medication taking behavior conforms to that which is advised, noncompliance was taken to be failure to take doses on time or missing doses. Overall, a patient was deemed to be noncompliant if he or she failed to take medicines on appointed time (doses missed or delayed by more than 2 h) more than 3 times in any month during the observation period. Satisfaction was ascertained on the basis of a dichotomous question regarding satisfaction with the caregiver support since the last visit.

Data have been summarized by routine descriptive statistics. Median and interquartile ranges have been reported for skewed data. Numerical variables were compared for changes over time by Friedman’s test and between subgroups by Mann–Whitney U-test. Fisher’s exact test was employed for intergroup comparison of categorical variables and McNemar’s Chi-square test for comparing paired proportions. All tests of significance were two-tailed and \( P < 0.05 \) was considered statistically significant. Spearman’s rank correlation coefficient (\( r_{pb} \)) was calculated to correlate age with median pill burden. Point biserial correlation coefficient (\( r_{pb} \)) was calculated to quantify association between median pill burden and dichotomized compliance status in individual subjects. The association between caregiver satisfaction status and the compliance status was explored by calculating odds ratios with their 95% confidence intervals (CI). Statistica version 6 (StatSoft Inc., Tulsa, Oklahoma, USA, 2001) and GraphPad Prism version 5 (GraphPad Software Inc., San Diego, California, 2005) software were used for statistical analysis.

**Results**

Out of 120 patients, 5 were lost to follow-up within first 3 months and another 5 died before completing 1 year. The analysis was restricted to the remaining 110 patients. The basic demography of the sample is depicted in Table 1. Evidently, although the gender distribution was comparable between the two sectors there was greater representation of younger patients in the government sector.

Table 2 and Figure 1 depict the total (immunosuppressant and others) oral pill burden in the government and private sector patients at successive study visits. In both sectors, the pill burden was high but showed a statistically significant decline over the 12-month observation period (\( P < 0.001 \) by Friedman’s ANOVA in both groups). At each visit, the pill burden was significantly higher (\( P < 0.001 \) by Mann–Whitney U-test) in the private sector than in the government sector. The scatter plot in Figure 2 indicates that there was approximately a direct linear relationship between age of the study subjects and median total pill burden. Spearman’s rho for this relationship was calculated to be 0.584 (\( P < 0.001 \); 95% CI: 0.445–0.695).

The compliance status in the two sectors is depicted in Table 3. The overall noncompliance rate was high – only 60.91% of the renal transplant recipients were fully compliant at the end of 1 year of observation. The extent of noncompliance was comparable between government and private sector patients, both with respect to immunosuppressants as well

| Demographic profile of the study subjects |
|-------------------------------------------|
| **Parameter** | **Overall** | **Government** | **Private** | **P** |
| Age (years) | 38.1±12.82 | 33.7±11.39 | 42.3±12.81 | <0.001 |
| Gender (%) | | | | |
| Male | 72 (65.45) | 37 (68.52) | 35 (62.50) | 0.552 |
| Female | 38 (34.55) | 17 (31.48) | 21 (37.50) | |

\(^{11}\)The P-value (two-tailed) in the last column is from comparison between the two sectors by Mann–Whitney U-test for age and Fisher’s exact test for gender. SD=Standard deviation, IQR=Interquartile range
The overall medication noncompliance rate was also high at 39%; that for immunosuppressants was over 26%. Interestingly, no association was observed between median pill burden across the 12-month observation period in individual patients and their compliance status. Application of Mann–Whitney U-test also indicated that there was no statistically significant difference in median pill burden between compliant and noncompliant subgroups.

Table 5 summarizes the proportion of subjects at individual follow-up visits satisfied with the caregiving they have been receiving. The level of satisfaction declined significantly between the first and final visits for the whole cohort (P<0.001, McNemar’s Chi-square test) as well as for transplant recipients in the government sector (P<0.005) and the private sector (P<0.01) separately.

A positive association was noted between caregiving satisfaction and compliance with immunosuppressant medication in the whole cohort (odds ratio: 2.667; 95% CI: 1.104–6.441). A similar pattern was observed in the government sector and private sector separately although the association was weaker as indicated by 95% CI.

Discussion

This study highlights points that are important in the management of renal transplant patients. The oral pill burden in these patients was very high ranging from 10 to 32 initially (after discharge following transplant) to 7–28 at the end of the 12-month observation period. In addition, there may have been parenteral and topical medicaments in some patients. However, this kind of pill burden has also been reported in the previous study of renal transplant recipients. A positive association was noted between age and pill burden. The number of co-morbidities increase with age. Therefore, the pill burden usually increases with age, even though there may be no increase in the number of transplant-related medication being received.

The overall medication noncompliance rate was also high at 39%; that for immunosuppressants was over 26%. Interestingly, no difference was observed between the government and private sector transplant recipients in this regard. Since patients receiving a transplant in government hospitals are generally

Table 2:

| Visit        | Overall (n=110) | Government (n=54) | Private (n=56) | P     |
|--------------|----------------|------------------|----------------|-------|
| Baseline     |                |                  |                |       |
| Range        | 10-32          | 10-21            | 14-32          | <0.001|
| Mean±SD      | 18.3±5.38      | 14.5±2.75        | 21.9±4.79      |       |
| Median (IQR) | 17 (14-21)     | 14 (12-16)       | 21 (18-24)     |       |
| 3 months     |                |                  |                |       |
| Range        | 10-31          | 10-20            | 12-31          | <0.001|
| Mean±SD      | 17.3±5.05      | 14.0±2.62        | 20.5±4.76      |       |
| Median (IQR) | 16 (13-20)     | 13.5 (12-15)     | 20 (17-24)     |       |
| 6 months     |                |                  |                |       |
| Range        | 9-29           | 9-20             | 11-29          | <0.001|
| Mean±SD      | 16.3±4.98      | 13.0±2.61        | 19.4±4.72      |       |
| Median (IQR) | 15.5 (12-19)   | 12 (11-15)       | 18 (16-22.5)   |       |
| 9 months     |                |                  |                |       |
| Range        | 8-28           | 8-20             | 11-28          | <0.001|
| Mean±SD      | 15.1±4.94      | 11.7±2.58        | 18.4±4.43      |       |
| Median (IQR) | 14 (11-18)     | 11 (10-13)       | 18 (15-21)     |       |
| 12 months    |                |                  |                |       |
| Range        | 7-28           | 7-22             | 10-28          | <0.001|
| Mean±SD      | 14.4±4.67      | 11.5±3.07        | 17.2±4.21      |       |
| Median (IQR) | 14 (10-17)     | 11 (9-13)        | 17 (14-20)     |       |
| Median pill burden over 12 months |                |                  |                |       |
| Range        | 9-29           | 9-20             | 11-29          | <0.001|
| Mean±SD      | 16.2±4.93      | 13.1±2.60        | 19.3±4.69      |       |
| Median (IQR) | 16 (12-19)     | 12.5 (11-15)     | 18 (16-22.5)   |       |

The P value (two-tailed) in the last column is from comparison between the two sectors by Mann–Whitney U-test. SD=Standard deviation, IQR=Interquartile range

Table 3:

| Compliance status | Overall (n=110) (%) | Government (n=54) (%) | Private (n=56) (%) | P     |
|-------------------|---------------------|-----------------------|-------------------|-------|
| Overall medication compliance |                     |                       |                   |       |
| Compliant         | 67 (60.91)          | 35 (64.81)            | 32 (57.14)        | 0.440 |
| Noncompliant      | 43 (39.09)          | 19 (35.19)            | 24 (42.86)        |       |
| Compliance with immunosuppressants |                |                       |                   |       |
| Compliant         | 81 (73.64)          | 39 (72.22)            | 42 (75.00)        | 0.830 |
| Noncompliant      | 29 (26.36)          | 15 (27.78)            | 14 (25.00)        |       |
| Compliance with other medication |              |                       |                   |       |
| Compliant         | 87 (79.09)          | 45 (83.33)            | 42 (75.00)        | 0.351 |
| Noncompliant      | 23 (30.91)          | 9 (16.67)             | 14 (25.00)        |       |

The P value (two-tailed) in the last column is from comparison between the two sectors by Fisher’s exact test

as other medication. The extent of noncompliance with immunosuppressants was 26.36% overall – 27.78% in the government sector and 25.00% in the private sector.

The association between compliance as a dichotomous variable and median pill burden as a numerical variable was quantified by calculating $r_a$. The values are depicted in Table 4. Evidently all $r_a$ values were way below the minimum cut-off (0.3) required to infer some association. Thus, no association was observed between median pill burden across the 12-month observation period in individual patients and their compliance status. Application of Mann–Whitney U-test also indicated that there was no statistically significant difference in median pill burden between compliant and noncompliant subgroups.

Table 5 summarizes the proportion of subjects at individual follow-up visits satisfied with the caregiving they have been receiving. The level of satisfaction declined significantly between the first and final visits for the whole cohort (P<0.001, McNemar’s Chi-square test) as well as for transplant recipients in the government sector (P<0.005) and the private sector (P<0.01) separately.

A positive association was noted between caregiving satisfaction and compliance with immunosuppressant medication in the whole cohort (odds ratio: 2.667; 95% CI: 1.104–6.441). A similar pattern was observed in the government sector and private sector separately although the association was weaker as indicated by 95% CI.

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The overall medication noncompliance rate was also high at 39%; that for immunosuppressants was over 26%. Interestingly, no difference was observed between the government and private sector transplant recipients in this regard. Since patients receiving a transplant in government hospitals are generally
from economically weaker sections of the society and have less avenues for getting reimbursed for medication costs, this suggests that economic factors may not directly influence noncompliance, in this case, at least for the initial 12 months following transplantation. Evidence from both controlled trials and observational studies indicate that such high rates of treatment noncompliance are by no means unusual – rates reported for immunosuppressive agents in renal transplant recipients have ranged from 18% to 68%.\textsuperscript{6-13}

Over the last few decades, pill burden has been recognized as an independent risk factor for compliance in patients suffering from various chronic diseases.\textsuperscript{15,16} In a large Spanish questionnaire based study analyzing the responses of 1983 renal and 1479 liver transplant recipients, the authors concluded that adjustment of daily treatment intensity by less frequent dosing may be a strategy to minimize barriers to adherence and improve the quality of life.\textsuperscript{14} There is, however, realization that although reducing pill burden can improve adherence to essential medication in renal transplant recipients, nonadherent patients are significantly less satisfied with their medical care and their relationships with the medical staff.\textsuperscript{66} Therefore, major effort is needed, going beyond simple reduction of pill burden, if that is possible, toward better patient satisfaction. Although not obvious, being able to assess and improve transplant recipients' experience of the common adverse effects of long-term postoperative drug therapy is one-way of positively influencing treatment compliance, and, therefore, their quality of life.\textsuperscript{13}

A supportive environment and knowledge of medication have been significant in increasing self-responsibility and adherence to treatment in heart transplant recipients.\textsuperscript{106}

Our study was unable to demonstrate any relationship between noncompliance and pill burden in the early postrenal transplantation period. Other factors obviously must be contributing to the development of noncompliance. Lack of adequate caregiving support could be a predictor as was noted with immunosuppressant noncompliance in this study. Gianotti et al.\textsuperscript{17} have reported that in HIV/AIDS patients, there is a complex relationship between dosing schedule, self-reported adherence, and health status and that the number of daily pills is related to self-reported health status but not to self-reported adherence. Thus, further studies are needed to identify the various contributors toward noncompliance in our setting and their relative contribution to this status. Appropriate remedial measures can then be undertaken, including a better patient appreciation of the purpose of the various medicines and their adverse event profile and a more supportive caregiver environment. The use of technological aids to improve adherence has been explored, such as mobile phone-based short messaging service reminders\textsuperscript{108} electronic medication monitoring systems,\textsuperscript{109} but they have their own cost and limitations as has been reported in a study of pediatric renal transplant recipients.\textsuperscript{166}

The strength of this study is the 12-month longitudinal follow-up. Furthermore, patients were recruited from government as well as private hospital thereby covering diverse socioeconomic background. There are limitations too. The sample size was limited, and the sampling was purposive rather than random. We looked at the oral pill burden but ignored topical and occasional parenteral medication.

**Figure 2:** Scatter plot showing association between age (in years) and median total (immunosuppressants and other drugs) oral pill burden (as simple count) in study subjects. Spearman’s rho 0.584 (P < 0.001; 95% confidence interval: 0.445–0.695)

**Table 4:**

| Type of medication | Overall (n=110) | Government (n=54) | Private (n=56) |
|--------------------|----------------|------------------|---------------|
| All medication     | +0.04          | +0.21            | +0.07         |
| P                  | 0.705          | 0.12            | 0.619         |
| Immunosuppressants | +0.02          | +0.21            | −0.11         |
| P                  | 0.826          | 0.135           | 0.416         |
| Other medication   | −0.04          | −0.03            | +0.06         |
| P                  | 0.661          | 0.834           | 0.676         |

The correlation coefficient values stated denote \( r_{pb} \), i.e., point biserial correlation coefficients. The \( P \) value indicates the result of the hypothesis test of correlation (\( P<0.05 \) would imply that the observed relationship in the sample is also likely to hold in the underlying population).

**Table 5:**

| Proportion of study subjects satisfied about their care status |
|---------------------------------------------------------------|
| Group | Baseline (%) | 3 months (%) | 6 months (%) | 9 months (%) | 12 months (%) |
|-------|--------------|--------------|--------------|--------------|---------------|
| Overall (n=110) | 98 (89.09) | 89 (80.91) | 82 (74.55) | 76 (69.09) | 74 (67.27) |
| Government (n=54) | 42 (77.78) | 37 (68.52) | 32 (60.38) | 30 (57.69) | 31 (58.49) |
| Private (n=56) | 56 (100.0) | 52 (92.86) | 50 (89.29) | 46 (82.14) | 43 (76.79) |
| \( P \)     | <0.001       | 0.001        | <0.001       | 0.006        | 0.064         |

The \( P \) value (two-tailed) in the last row pertains to between group comparison by Fisher’s exact test.
Notwithstanding these limitations, we can conclude that this longitudinal observational study suggests that high pill burdens and high rates of noncompliance are to be expected in renal transplant recipients in the Indian sociocultural milieu, both for immunosuppressants and other kinds of medication. However, it must not be assumed automatically that the high pill burden is responsible for the noncompliance and, therefore, nothing much can be done about it. Rather, a diligent search for other potential contributors toward noncompliance is warranted. Factors identified in individual patients must be addressed appropriately so as to achieve better long-term outcome.

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Conflicts of Interest

There are no conflicts of interest.

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