Surgery ■■ (2017) ■■–■■

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/ymsy

Society of University Surgeons

Incidence and impact of adverse drug events contributing to hospital readmissions in kidney transplant recipients

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ARTICLE INFO

Article history:
Accepted 26 September 2017

ABSTRACT

Background. The incidence and impact of adverse drug events (ADEs) leading to hospitalization and as a predominant risk factor for late graft loss has not been studied in transplantation.

Methods. This was a longitudinal cohort study of adult kidney recipients transplanted between 2005 and 2010 and followed through 2013. There were 3 cohorts: no readmissions, readmissions not due to an adverse drug event, and adverse drug events contributing to readmissions. The rationale of the adverse drug events contribution to the readmission was categorized in terms of probability, preventability, and severity.

Results. A total of 837 patients with 963 hospital readmissions were included; 47.9% had at least one hospital readmission and 65.0% of readmissions were deemed as having an ADE contribute. The predominant causes of readmissions related to ADEs included non-opportunistic infections (39.6%), opportunistic infections (10.5%), rejection (18.1%), and acute kidney injury (11.8%). Over time, readmissions due to under-immunosuppression (rejection) significantly decreased (−1.6% per year), while those due to over-immunosuppression (infection, cancer, or cytopenias) significantly increased (2.1% increase per year [difference 3.7%, $P = .026$]). Delayed graft function, rejection, creatinine, graft loss, and death were all significantly greater in those with an ADE that contributed to a readmission compared the other two cohorts ($P < .05$).

Conclusion. These results demonstrate that ADEs may be associated with a significant increase in the risk of hospital readmission after kidney transplant and subsequent graft loss.

Due to major surgical and medical advancements during the past 40 years, kidney transplantation has become the gold standard treatment for end-stage renal disease, as it has demonstrated improved quantity and quality of life compared with remaining on dialysis. Currently, ≈400,000 Americans have end-stage renal disease and ≈93,000 await transplant.[1] Improving long-term graft survival will facilitate the reduction of the organ shortage disparity and it is likely that immunosuppression side effects, or adverse drug effects (ADEs), are a significant contributor to late graft loss, although this is not well-studied.[2]

In the general population, medication side effects and ADEs are common and preventable, particularly those that lead to hospitalization.[3] However, there is limited data available to assess this within kidney transplantation.[1] In nontransplant patients, the overall rate of ADEs is 50.1 per 1,000 person-years, 13.8 being preventable and 38% categorized as serious or fatal.[4] More research on the true incidence rates of ADEs in kidney transplant recipients is needed, particularly those that are severe enough to lead to hospitalization. This may help facilitate a better understanding of mechanisms to optimize posttransplant immunosuppression monitoring and medication therapy management. This is particularly an issue as ADEs are associated with medication nonadherence, which is a major contributor to late acute rejection leading to graft loss.[5]

There are high rates of hospital readmissions in kidney transplant recipients. Rehospitalization after kidney transplant is a strong

Supported through grants from the National Institute of Diabetes and Digestive under Award numbers K23DK099440 and T35DK007431 and from the Agency for Healthcare Research and Quality under award number R18HS023754.

Presented at the 12th Annual Academic Surgical Congress in Las Vegas, NV, February 7–9, 2017.

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https://doi.org/10.1016/j.surg.2017.09.027
0039-6060/

predictor of future adverse events, including graft loss and death.[6] Readmissions also are very costly to the health care system; 28% of Medicare payments for kidney transplants recipients were due to 30-day readmission payments.[7] It is likely that a substantial proportion of hospital readmissions after kidney transplantation are related to immunosuppression side effects and ADEs, although etiologic studies in transplantation are limited. Thus, the aim of this study was to establish foundational information regarding the rate of ADEs contributing to hospitalization, the proportion of these that may be preventable, and the impact of ADE hospitalizations on posttransplant outcomes, including graft loss and death.

Materials and Methods

Study design and patients

This was a retrospective longitudinal cohort study. Institutional review board approval was obtained to conduct a detailed evaluation of medical records for all kidney recipients who received a transplant between July 2005 and December 2010 at our institution. We analyzed any hospital readmission to our hospital system from 2005 to 2013. We chose 2005 as a starting date because this is when contemporary immunosuppression started being used at our center (tacrolimus, mycophenolate, and antibody induction). We utilized the most contemporary cohort possible while allowing for long-term follow-up, which provides adequate power to assess impact on graft outcomes. All hospitalization records were reviewed in detail to determine the specific causes of the admission. All solitary kidney transplants occurring at our institution in the specified period were assessed for inclusion. Pediatrics, multiorgan transplants, those with a history of a nonrenal transplant and those lost to follow-up were excluded from this study.

ADE assessment

Definition of an ADE

The World Health Organization definition of an ADE is "an injury resulting from medical intervention related to a drug," which includes both preventable and unpreventable events. For this study, we utilized this definition to determine the incidence of ADEs contributing to hospitalization.[8]

Determination if an ADE contributed to the hospital readmission

Three individuals, a medical student, a PharmD, and a transplant surgeon all independently reviewed the readmission to determine the likelihood that an ADE contributed to the event. Discrepancies between reviewers were adjudicated, using similar methodology to Bates criteria.[9,10] ADEs were categorized using the Naranjo criteria, thus assessing the relationship between each readmission event and the medications as "definite," "probable," "possible," and "doubtful."[9] In an attempt to dichotomize the results, the events categorized as "possible," "definite," or "probable" were counted as ADEs that caused or contributed to hospitalization.

ADE preventability

Using similar methodology to Bates et al, reviewers considered the timing of the symptoms and whether the symptoms could be contributed to the drug based on the strength of published data in order to assess for preventability.[9,10] Each ADE was classified as "nonpreventable," "preventable," and "ameliorable." Preventable events where those due to errors that could have been entirely avoided and were very rare. Ameliorable events were those whose severity or duration could have been substantially reduced had different actions been taken. Ameliorable events also were those in which medication doses or regimens were adjusted in the hospital which led to improved outcomes. Nonpreventable were idiosyncratic reactions and other events not fitting into the 2 aforementioned categories.

ADE severity

The severity of each ADE was assessed using the US Department of Health and Human Services Common Terminology Criteria for Adverse Events version 4.0. The severity of each ADE was categorized by assessing the symptoms with which the patient presented as well as various laboratory findings during the hospitalization and linking them with the criteria set in the Common Terminology Criteria for Adverse Events version 4.0.[11]

Outcome measures

The primary outcome of interest was to determine the proportion of posttransplant hospitalizations that were partially or fully attributable to ADEs in adult kidney transplant recipients. The secondary outcome of interest was to assess for risk factors associated with hospitalizations for posttransplant ADEs. Additional outcomes captured for this study were to determine if hospitalization for an ADE increases the risk of acute rejection, graft loss, or death compared with those hospitalized for other issues or those without hospitalization. We also assessed the impact of time on the incidence of hospitalizations due to ADEs in terms of under and overimmunosuppression.

Statistical analysis

First, we utilized standard descriptive statistics to categorize the incidence and primary etiologies of readmissions, with percentages for categorical data and rates, medians and means for continuous data. To conduct the baseline comparisons between the 3 groups and discern risk factors, we utilized the χ^2 test for categorical data and the Kruskal-Wallis test for ordinal and continuous variables. The etiologies of readmissions over time were assessed by categorizing these into 3 groups: overimmunosuppression (infection, cancer, cytopenias), underimmunosuppression (rejection), and other. Rates over time were compared using linear regression to estimate the slopes of each etiology and comparing the slope difference for statistical significance through interaction terms. To assess for patient and graft survival, multivariable modeling using Cox regression was utilized. Prior to multivariable modeling, proportional hazards assumptions were assessed and determined to be valid using a time by ADE interaction term. Covariates of theoretical and clinical importance were included in the models to adjust for potential confounding. Adjusted estimated graft and patient survival rates were output and plotted in survival curves, stratified by hospitalization and etiology. Statistical analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC) with adjusted survival curve plots created in SPSS version 23.0 (IBM Corp, Armonk, NY).

Results

Between 2005 and 2010, 837 adult patients receiving solitary kidney transplants and meeting inclusion criteria were analyzed for this study. During the 10-year follow-up period, the study cohort had 963 hospital readmissions, with 401 (47.9%) patients having at least one readmission to our institution and 626 (65.0%) of the hospital readmissions deemed to have an ADE causing or contributing to the event. Prevailing etiologies for hospital readmission were separated into 11 categories and compared across the readmission being due to an ADE (Table 1). The predominant etiologies for ADE readmissions included infections, rejections, and acute kidney injuries not due to rejection or infection (calcineurin inhibitors toxicity, dehydration, and other nephrotoxins). Common causes of non-ADE

Please cite this article in press as: Michelle A. Arms, James Fleming, Deep B. Sangani, Satish N. Nadig, John W. McGillicuddy, and David J. Taber, Incidence and impact of adverse drug events contributing to hospital readmissions in kidney transplant recipients, Surgery (2017), doi: 10.1016/j.surg.2017.09.027