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A history of chronic opioid usage prior to kidney transplantation may be associated with increased mortality risk

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Chronic opioid usage (COU) for analgesia is common among patients with end-stage renal disease. In order to test whether a prior history of COU negatively affects post-kidney transplant outcomes, we retrospectively examined clinical outcomes in adult kidney transplant patients. Among 1064 adult kidney transplant patients, 452 (42.5%) reported the presence of various body pains and 108 (10.2%) reported a prior history of COU. While the overall death or kidney graft loss was not statistically different between patients with and without a history of COU, the cumulative mortality rate at 1, 3, and 5 years after transplantation, and during the entire study period, appeared significantly higher for patients with than without a history of COU (6.5, 18.5, and 20.4 vs. 3.2, 7.5, and 12.7%, respectively). Multivariate Cox regression analysis adjusted for potential confounding factors in entire cohorts and Cox regression analysis in 1:3 propensity–score matched cohorts suggest that a positive history of COU was significantly associated with nearly a 1.6- to 2-fold increase in the risk of death (hazard ratio 1.65, 95% confidence interval 1.04–2.60, and hazard ratio 1.92, 95% confidence interval 1.08–3.42, respectively). Thus, a history of chronic opioid usage prior to transplantation appears to be associated with increased mortality risk. Additional studies are warranted to confirm the observed association and to understand the mechanisms.

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Chronic pain is a common symptom in patients with end-stage renal disease (ESRD) affecting ~50% of patients undergoing maintenance dialysis therapy.[1–3] The etiology of pain in this patient population is often multifactorial, resulting from their underlying kidney disease, prolonged kidney failure or the dialysis procedure itself, and other coexistent chronic medical conditions. Chronic pain has negative impact on the quality of life and can lead to potentially harmful consequences in this patient population.[4–6] The importance of appropriate management of chronic pain in ESRD patient population has been increasingly recognized.[3,7,8] Treatment options range from nonpharmacologic to pharmacologic interventions including the use of opioid and nonopioid analgesics. However, the choice of analgesics is limited because of the altered pharmacokinetics and pharmacodynamics of these agents in the setting of ESRD, which has contributed to often inadequate treatment of pain in this patient population.[8–10]

The reluctance to prescribe nonsteroidal anti-inflammatory drugs as analgesics in the presence of chronic kidney disease and/or ESRD deprives many patients with chronic pain of the use of nonopioid analgesia, and may lead to reliance on opioid therapy for pain management. However, the use of opioid analgesics, both short and long term, is associated with a variety of adverse effects.[11] Common adverse effects include central nervous system depression, respiratory depression, sleep disturbance, constipation, bladder dysfunction, tolerance, and physical dependence; some of these adverse effects may be more pronounced in patients with advanced kidney disease.[12–16] Less common adverse effects may include cardiac arrhythmia, immune dysregulation, and hepatic and renal toxicity.[17–20] In addition, the chronic use of opioid analgesics may result in opioid-induced hyperalgesia,[21] a condition of enhanced pain severity because of the action of opioid analgesics, or increase the likelihood of misuse and abuse,[22–24] with associated adverse clinical outcome.[25–28]

The extent of chronic usage of opioid analgesics among ESRD patients who subsequently undergo kidney transplan-

tation is currently unknown, and its relationship to post-transplant outcomes has not been explored. We performed a single-center retrospective study to test the hypothesis that a history of chronic opioid usage (COU) before kidney transplantation is common and can be associated with adverse clinical outcomes following transplantation.

RESULTS

Patient characteristics

During the study period, 1064 kidney transplant patients met the criteria to be included in the analyses. The mean length of follow-up was 48.4 ± 19.7 months and the median 47.8 (33.7–63.4) months. Among them, 452 patients (42.5%) reported the presence of various degrees of chronic pain before transplantation, with majority of them (52.9%) attributed to neuropathy. The most frequently reported was limb pain (38.1%), lower back pain (15.7%), headache (migraine; 13.3%), abdominal/pelvic pain (11.3%), and others (nonspecified and/or generalized body pain; 33.6%; Figure 1a). A total of 108 patients (10.2%) reported a positive history of COU. The most commonly used opioid analgesics were hydrocodone (43.1%), propoxyphene (18.1%), oxycodone (16.4%), tramadol (13.8%), and others (8.6%; Figure 1b).

Baseline and demographic characteristics between patients with and without a history of COU for whole and propensity score–matched cohorts are displayed in Table 1. As a whole, patients in the COU cohort were more likely to be African American (25.0% vs. 17.5%, $P = 0.055$), to have a higher Charlson comorbidity score (4.3 ± 1.8 vs. 4.0 ± 1.7, $P < 0.001$), and a higher prevalence for a positive history of alcohol (18.5% vs. 9.9%, $P = 0.006$) and illicit drug abuse (20.4% vs. 11.1%, $P = 0.005$). They reported more often chronic bodily pain (81.5% vs. 38.1%, $P < 0.001$), more frequent use of nonopioid analgesics (26.9% vs. 8.2%, $P < 0.001$), had a higher prevalence of a positive psychiatric history (51.9% vs. 27.8%, $P < 0.001$), less use of private health insurance (30.6% vs. 43.8%, $P = 0.008$), and lower employment rate at the time of initial transplant evaluation (18.5% vs. 44.1%, $P < 0.001$). At the time of transplantation, patients in the COU cohort received more often kidneys from younger (37.3 ± 13.9 vs. 40.3 ± 13.3 years, $P = 0.033$) and male donors (61.1% vs. 51.5%, $P = 0.057$), and experienced more frequently delayed graft function (16.7% vs. 7.6%, $P = 0.001$).

Because of such striking differences in baseline patient characteristics between the two cohorts in the whole population, we created matched strata at a 1:3 ratio by applying propensity score approach: 96 patients from COU cohort and 288 patients from non-COU cohort. The matched data demonstrated overall balanced baseline characteristics.[29]

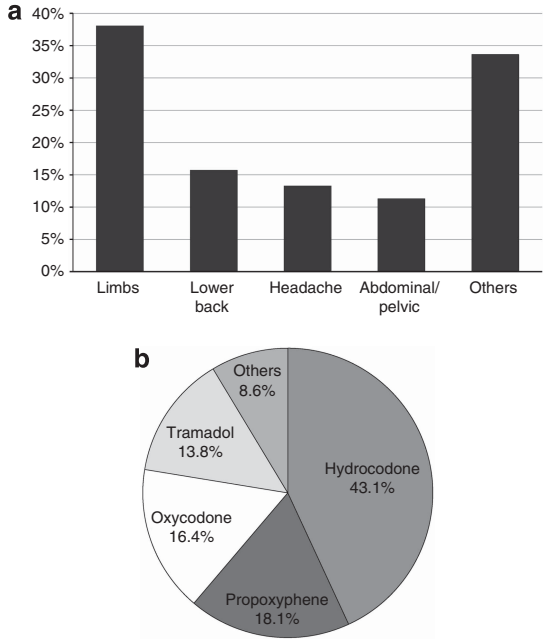

Figure 1 | Self-reported chronic pain and chronic opioid usage prior to transplantation. (**a**) Distribution of chronic pain and (**b**) type of opioid analgesics used by patients.

COU and death/kidney graft loss

During the study period, 202 patients had either died or lost kidney graft. The cumulative incidence of death or kidney graft loss was higher for patients with than without a history of COU, as evidenced by Kaplan–Meier survival analysis (Figure 2, log-rank, $P = 0.038$). However, Cox regression analysis failed to confirm the increased risk for composite end point of death or kidney graft loss associated with the history of COU (hazard ratio (HR) 1.39, 95% confidence interval (CI) 0.85–2.25, $P = 0.194$ for whole cohorts, and HR 1.64, 95% CI 0.97–2.77, $P = 0.065$ for 1:3 matched cohorts, respectively).

COU and mortality

We further investigated the association between a positive history of COU and risk of death. A total of 147 deaths were documented. The cumulative incidence of death appeared higher for patients with than without a history of COU within 1 year (6.5% vs. 3.2% $P = 0.086$), 3 years (18.5% vs. 7.5%, $P < 0.001$), and 5 years (20.4% vs. 12.7%, $P = 0.026$) after transplantation, and over the entire duration of the study (log-rank, $P = 0.003$; Figure 3a and b). Applying Cox regression model, a history of COU was independently associated with nearly a 1.5- to 2-fold increase in the risk for death (HR 1.65, 95% CI 1.04–2.60, $P = 0033$ for entire cohorts and HR 1.92, 95% CI 1.08–3.42, $P = 0.027$ for 1:3 matched cohorts, respectively). Other variables associated with increased mortality risk included old recipient age (HR 1.05, 95% CI 1.03–1.06, $P < 0.001$) and higher Charlson comorbidity score (HR 1.25, 95% CI 1.12–1.39, $P < 0.001$). On the other hand, the use of living donor kidney was associated with reduced mortality risk (HR 0.50, 95% CI 0.33–0.74, $P = 0.001$; Table 2). It is important to point out that although patients with a history of COU had higher