Betel Nut Chewing Is Associated With Reduced Tacrolimus Concentration in Taiwanese Liver Transplant Recipients

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ABSTRACT

Purpose. Studies have shown that arecoline, the major alkaloid component of betel nuts, alters the activity of enzymes in the cytochrome P450 (CYP-450) family. Tacrolimus, an immunosuppressant that protects against organ rejection in transplant recipients, not only is mainly metabolized by CYP3A enzymes but also has a narrow therapeutic range. We aimed to investigate whether dose-adjusted blood trough levels of tacrolimus differed over time between betel nut-chewing and non–betel nut-chewing liver transplant recipients.

Methods. In this retrospective case-control study, 14 active betel nut-using liver recipients were matched at a 1:2 ratio to 28 non-betel nut-using liver recipients by sex, age, graft source, duration of follow-up after liver transplantation, and estimated glomerular filtration rate. Differences in liver function index, renal function index, and dose-adjusted blood trough levels of tacrolimus over an 18-month period were compared between the 2 groups by using the Generalized Estimating Equation approach.

Results. Dose-adjusted blood trough levels of tacrolimus tended to be significantly ($P = .04$) lower in betel nut chewers (mean = 0.81, medium = 0.7, 95% confidence interval [CI] = 0.73 to 0.90) than in nonchewers (mean = 1.12, medium = 0.88, 95% CI = 1.03 to 1.22) during the 18-month study period. However, there was no significant difference in renal and liver function index between the 2 groups.

Conclusion. Liver transplant recipients receiving tacrolimus tend to have lower blood trough levels of the drug over time if they chew betel nuts.

THE ARECA nut, also referred to as betel nut, is the fourth most commonly used psychoactive substance worldwide, after caffeine, nicotine, and alcohol [1]. Betel nut chewing is associated with various health problems including cancer, ulcers, and metabolic syndrome. Studies have shown that arecoline, the major alkaloid component in betel nut, significantly increases the activity of cytochrome P450 (CYP-450) [2–4], suggesting that metabolic interactions may exist when CYP-450 substrate drugs are combined with betel nut chewing.

Tacrolimus, a potent immunosuppressant agent commonly administered to patients after liver transplantation to protect against organ rejection, is mainly metabolized in liver by the CYP3A enzyme [5]. Thus, drugs or foods known to influence CYP3A activity are likely to alter tacrolimus concentrations. For example, CYP3A4 -inhibitors such as azole antifungal drugs and grapefruit juice have been shown to result in increased tacrolimus concentrations [6–8], and CYP3A4

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Table 1. Clinical Characteristics and Laboratory Values

Factors	Chewers (n = 14)	Nonchewers (n = 28)	*P* Value
Male, n (%)	13 (92.9)	26 (92.9)	>.99
Age (y), mean ± SD	50.3 ± 5.6	53.1 ± 8.4	.30
Cause of liver disease, n (%)			
Hepatitis B virus infection	2 (14.3)	12 (42.9)	
Hepatitis C virus infection	1 (7.1)	0	
Hepatitis B and C virus coinfection	1 (7.1)	3 (10.7)	
Alcoholism	10 (71.5)	13 (46.4)	.12
Graft source, n (%)			
Living donor	9 (64.3)	17 (60.7)	
Cadaver donor	5 (35.7)	11 (39.3)	.82
Duration of follow-up after liver transplantation (mo), mean ± SD	48.1 ± 30.4	52.8 ± 35.0	.82
Liver and renal function index, mean ± SD			
AST (U/L)	41.1 ± 15.6	37.1 ± 23.3	.30
ALT (U/L)	33.0 ± 16.4	37.4 ± 19.7	.58
SCr (mg/dL)	1.2 ± 0.3	1.1 ± 0.3	.88
eGFR (mL/min/1.73 m^2)	71.4 ± 21.9	72.2 ± 21.9	.79

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; SD, standard deviation.

inducers such as phenytoin and carbamazepine have been shown to result in decreased tacrolimus levels [9,10]. Tacrolimus has a narrow therapeutic range, and changes in tacrolimus level can result in clinically important effects such as nephrotoxicity resulting from overdosage of tacrolimus or organ/graft rejection resulting from underdosage of the drug. Therefore, knowledge of drug or food interactions with tacrolimus is essential. In this study, we examined the association between betel nut chewing and trough levels of tacrolimus over time in liver transplant recipients.

PATIENTS AND METHODS

This retrospective matched case-control study comprised 14 liver transplant recipients who were active betel nut chewers and being treated with prolonged-release tacrolimus (Advagraf, Astellas, Ireland) at the outpatient department of the Changhua Christian Hospital from January 2013 to June 2014. Individual matching of control group was used in this study. The control group comprised

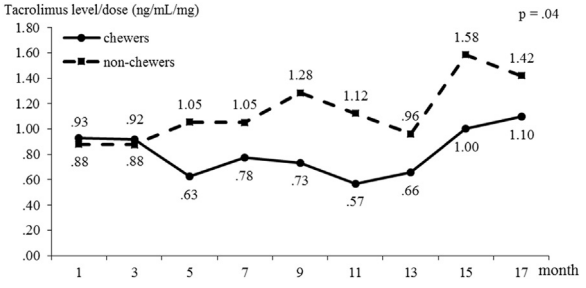

Fig 1. Comparison of the trend in blood tacrolimus trough level/dose between case and control groups.

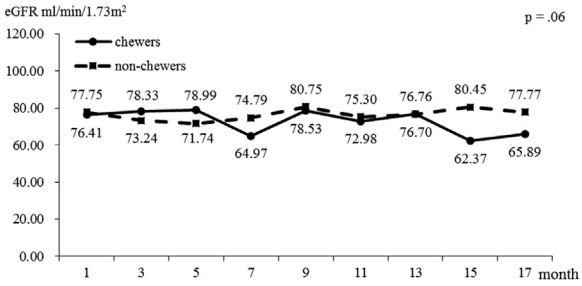

Fig 2. Comparison of the trend in blood estimated glomerular filtration (eGFR) rate level between the 2 groups.

28 recipients matched at a 1:2 ratio on gender, age, duration of follow-up after liver transplantation, graft source (living or cadaver donor), and estimated glomerular filtration rate (eGFR) at initial enrollment. All recipients in the control group were receiving Advagraf, and none of them were current betel nut users. The following data were retrospectively gathered from medical records including basic characteristics, tacrolimus information (daily dose and trough blood concentration), liver function index (aspartate transaminase [AST]; alanine aminotransferase [ALT]), and renal function index (serum creatinine and eGFR).

We used the Fisher exact test for categorical comparisons of data. Differences in means of continuous measurements were tested by the Mann-Whitney *U* test. A Generalized Estimating Equation (GEE) approach was used for comparison of panel data (dose-adjusted blood trough tacrolimus levels, AST, ALT, and eGFR). A *P* value of <.05 was considered to indicate statistical significance; all tests were 2-tailed. All statistical analyses were performed with the statistical package SPSS for Windows (Version 16.0, SPSS Inc, Chicago, Illinois, United States).

RESULTS

Most recipients in both groups were men and had received living donor transplantation. After matched, there were no significant differences in age, the duration of follow-up after liver transplantation, and causes of liver disease before transplantation (Table 1). During the study period, no graft rejection or death was observed. We adjusted for differences in daily doses among patients by dividing individual tacrolimus level by the recipient's daily dose to arrive at dose-adjusted blood trough levels of tacrolimus. The percent coefficient of variation of the tacrolimus levels in

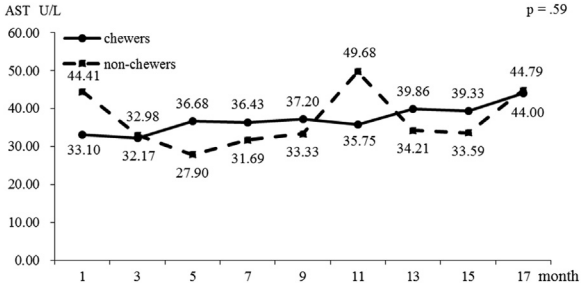

Fig 3. Comparison of the trend in blood aspartate transaminase (AST) level between the 2 groups.