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Original Investigation

Chlorthalidone Versus Amlodipine for Hypertension in Kidney Transplant Recipients Treated With Tacrolimus: A Randomized Crossover Trial

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Background: Chlorthalidone is a very effective antihypertensive drug, but it has not been studied prospectively in kidney transplant recipients with hypertension. Recent data indicate that calcineurin inhibitors activate the thiazide-sensitive sodium chloride cotransporter, providing further rationale to test thiazides in this population.

Study Design: Randomized noninferiority crossover trial (noninferiority margin, −2.8 mm Hg).

Setting & Participants: Hypertensive kidney transplant recipients using tacrolimus (median duration, 2.4 years after transplantation; mean estimated glomerular filtration rate, 63 ± 27 [SD] mL/min/1.73 m^2; mean systolic blood pressure [SBP], 151 ± 12 mm Hg).

Intervention: Amlodipine (5-10 mg) and chlorthalidone (12.5-25 mg) for 8 weeks (separated by 2-week washout).

Outcomes: Average daytime (9 AM to 9 PM) ambulatory SBP.

Measurements: Blood pressure and laboratory parameters.

Results: 88 patients underwent ambulatory blood pressure monitoring, of whom 49 (56%) with average daytime SBP > 140 mm Hg were enrolled. 41 patients completed the study. Amlodipine and chlorthalidone both reduced ambulatory SBP after 8 weeks (mean changes of 150 ± 12 to 137 ± 12 [SD] vs 151 ± 12 to 141 ± 13 mm Hg; effect size, −4.2 [95% CI, −7.3 to 1.1] mm Hg). Despite these similar blood pressure responses, chlorthalidone reduced proteinuria by 30% (effect size, −65 [95% CI, −108 to −35] mg/g) and also reduced physician-assessed peripheral edema (22% to 10%; $P < 0.05$ for both). In contrast, chlorthalidone temporarily reduced kidney function and increased both serum uric acid and glycated hemoglobin levels.

Limitations: Open-label design, short follow-up, per-protocol analysis.

Conclusions: Chlorthalidone is an antihypertensive drug equally effective as amlodipine after kidney transplantation.

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INDEX WORDS: Calcineurin inhibitors (CNIs); hypertension; kidney transplantation; amlodipine; chlorthalidone; blood pressure; ambulatory blood pressure monitoring (ABPM); sodium-chloride cotransporter (NCC); thiazide diuretics; end-stage renal disease (ESRD); kidney function; proteinuria; edema; clinical trial.

Several studies have shown that hypertension after kidney transplantation is an independent risk factor for transplant failure.[1-3] In addition, hypertension after kidney transplantation associates with increased risk for cardiovascular disease and even mortality.[2,4-6] Hypertension after kidney transplantation is multifactorial, and factors related to donor, recipient, and transplantation have been implicated.[5,7] Treatment with calcineurin inhibitors (CNIs) clearly contributes to hypertension after kidney transplantation, as illustrated by the increased incidence of hypertension after the introduction of cyclosporine.[8-10] The hypertensinogenic effect of CNIs has also been demonstrated in patients who are less prone to hypertension than patients with kidney disease (eg, patients with dermatologic disease or after liver transplantation).[11-13]

Several mechanisms have been shown to contribute to CNI-induced hypertension,[14,15] including systemic and renal vasoconstriction, possibly through endothelin 1, and impaired vasodilation.[16-18] This may explain the efficacy of dihydropyridine calcium channel blockers (CCBs) for the treatment of CNI-induced hypertension.[19] However, CNI-induced hypertension has also been shown to be salt sensitive.[12,13,20-24] More recently, the salt sensitivity of CNI-induced hypertension was linked to the activation of one specific sodium

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transporter in the kidney. We and others showed that CNIs activate the sodium-chloride cotransporter (NCC, encoded by the *SLC12A3* gene) to cause hypertension.[25,26] More recently, the importance of this CNI-NCC pathway was also illustrated by attenuated CNI-induced hypertension in a kidney-specific knockout mouse for the FK506-binding protein.[27]

These findings suggest that thiazide diuretics, which block NCC, may also be effective drugs for CNI-induced hypertension.[25,27] However, only 1 retrospective study addressed this question in kidney transplant recipients (all using CNIs). This study showed that thiazide diuretics effectively lowered blood pressure (systolic blood pressure [SBP], 147 ± 17 to 139 ± 18 mm Hg; diastolic blood pressure, 79 ± 9 to 77 ± 11 mm Hg), but was associated with higher incidences of hyperkalemia and hypokalemia.[28] The reason that thiazide diuretics are used so infrequently in kidney transplant recipients may be related to concerns regarding efficacy at lower estimated glomerular filtration rates (eGFRs) or adverse effects (gout and glucose intolerance). Therefore, the aim of this study was to analyze the effects of thiazide diuretics in kidney transplant recipients using tacrolimus. Given the roles of vasoconstriction and sodium retention in CNI-induced hypertension, we hypothesized that chlorthalidone is equally effective as amlodipine for the treatment of hypertension after kidney transplantation.

METHODS

Overview and Patients

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center (MEC-2012-417). The CONSORT (Consolidated Standards of Reporting Trials) guidelines for noninferiority and equivalence trials was followed.

Erasmus Medical Center is a university hospital with an annual volume of approximately 200 kidney transplantations. As part of standard care, glucocorticoid treatment is discontinued 3 months after transplantation. Inclusion criteria were 18 years or older, treatment with tacrolimus (either the conventional twice-daily formulation [Prograft; Astellas Pharma] or the once-daily formulation [Advagraf; Astellas Pharma]), eGFR ≥ 30 mL/min/1.73 m^2, stable background of antihypertensive drugs (ie, no anticipated change in dose during the study period), and average daytime SBP > 140 mm Hg during ambulatory blood pressure monitoring (ABPM). Patients were invited for ABPM when their office blood pressure was > 140 mm Hg or they were already using a thiazide diuretic or CCB (these drugs were discontinued for 2 weeks prior to ABPM).[29] Exclusion criteria consisted of pregnancy, serum potassium level < 3.5 mmol/L, serum sodium level < 136 mmol/L, spot urine protein-creatinine ratio > 885 mg/g, and use of diuretics, glucocorticoids, or co-trimoxazole.

Study Design

The study design was a single-center, prospective, randomized, crossover, open-label, noninferiority study.

Interventions and Randomization Approach

Eligible patients were randomly assigned to start with chlorthalidone, 12.5 mg, or amlodipine, 5 mg, for 8 weeks. The 8-week treatment periods were separated by a 2-week washout period. There were 6 study visits (at the start and end of each treatment period and 2 weeks after starting each drug). During the 2-week visit, blood pressure was measured every 5 minutes for 30 minutes using an oscillometric blood pressure monitor. Because oscillometric blood pressure monitors may overestimate SBP,[30] we used an average mean arterial pressure > 105 mm Hg as cutoff to double the dose of the study drug. Patients in the study were analyzed per protocol. The study was stopped in patients who developed a serum sodium level < 130 mmol/L or serum potassium level < 3.0 mmol/L during treatment. After completion of the study, patients continued with the drug with the best antihypertensive response and/or least adverse effects. Patients were enrolled and randomly assigned on a 1:1 basis by the coordinating investigator (A.D.M.) to receive either amlodipine followed by chlorthalidone (treatment order 1) or chlorthalidone followed by amlodipine (treatment order 2). Randomization was performed by the use of sealed opaque sequentially numbered envelopes containing treatment allocation. The random allocation sequence was generated by an independent statistician by the use of a random number generator on a computer. If a patient was assigned to a particular treatment order, it was revealed to the treating physician.

Study Visits and Measurements

Data were collected, monitored, and entered by the coordinating investigator and stored in a hospital-based electronic study database. The first patient was included January 18, 2013, and the study ended on the last study visit of the last patient on December 17, 2015. ABPM was performed with the 90217A Ultralite (Spacelabs Healthcare), and 30-minute blood pressure recordings were performed with the datascope Accutorr Plus (Mindray). The following criteria for ABPM were used: 24-hour recording with measurements at 30-minute intervals and with ≥70% of expected measurements (20 valid awake, 7 valid asleep).[31] The ABPM device (with masked screen) was applied at the Erasmus Medical Center by one of the investigators (A.D.M.), and patients returned the device after the 24-hour measurement period. On the first visit, we measured plasma renin (RENIN III; Cisbio) and plasma aldosterone (Coat-a-Count; Diagnostics Product Corp). We also collected 24-hour urine samples to assess dietary salt consumption. On all visits, we measured serum creatinine, electrolytes, bicarbonate, uric acid, predose tacrolimus, and glycated hemoglobin (HbA_{1c}). We also collected spot urine samples in which urinary protein, creatinine, and electrolytes were measured. Urinary protein and calcium excretion were analyzed as a ratio with urine creatinine.[32,33] All routine serum and urinary measurements were determined using the cobas 8000 modular analyzer series (Roche). Tacrolimus was measured with the Dimension Xpand Plus Integrated Chemistry System (Siemens). HbA_{1c} was measured using high-performance liquid chromatography (HA-8180V; Menarini Diagnostics). GFR was estimated using the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation.[34] On all visits, a physician also evaluated the presence of the most common adverse effects of the drugs (occurring in 1%-10%) and examined patients for the presence of peripheral edema.

Outcomes

The primary outcome was average daytime SBP as obtained by ABPM (mean of ≥20 measurements obtained every 30 minutes over a 12-hour period on a single day). Secondary end points included proteinuria, urinary calcium excretion (as a measure of thiazide effect), kidney function, and adverse effects.

Sample Size Determination

For the primary outcome, a power calculation for noninferiority crossover studies showed the requirement of a sample size of 24

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