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PERIPHERAL

Externally Delivered Focused Ultrasound for Renal Denervation

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ABSTRACT

OBJECTIVES The aim of this study was to assess clinical safety and efficacy outcomes of renal denervation executed by an externally delivered, completely noninvasive focused therapeutic ultrasound device.

BACKGROUND Renal denervation has emerged as a potential treatment approach for resistant hypertension.

METHODS Sixty-nine subjects received renal denervation with externally delivered focused ultrasound via the Kona Medical Surround Sound System. This approach was investigated across 3 consecutive studies to optimize targeting, tracking, and dosing. In the third study, treatments were performed in a completely noninvasive way using duplex ultrasound image guidance to target the therapy. Short- and long-term safety and efficacy were evaluated through use of clinical assessments, magnetic resonance imaging scans prior to and 3 and 24 weeks after renal denervation, and, in cases in which a targeting catheter was used to facilitate targeting, fluoroscopic angiography with contrast.

RESULTS All patients tolerated renal denervation using externally delivered focused ultrasound. Office blood pressure (BP) decreased by 24.6 ± 27.6/9.0 ± 15.0 mm Hg (from baseline BP of 180.0 ± 18.5/97.7 ± 13.7 mm Hg) in 69 patients after 6 months and 23.8 ± 24.1/10.3 ± 13.1 mm Hg in 64 patients with complete 1-year follow-up. The response rate (BP decrease >10 mm Hg) was 75% after 6 months and 77% after 1 year. The most common adverse event was post-treatment back pain, which was reported in 32 of 69 patients and resolved within 72 h in most cases. No intervention-related adverse events involving motor or sensory deficits were reported. Renal function was not altered, and vascular safety was established by magnetic resonance imaging (all patients), fluoroscopic angiography (n = 48), and optical coherence tomography (n = 5).

CONCLUSIONS Using externally delivered focused ultrasound and noninvasive duplex ultrasound, image-guided targeting was associated with substantial BP reduction without any major safety signals. Further randomized, sham-controlled trials will be needed to validate this unique approach. (J Am Coll Cardiol Intv 2016;9:1292–9)

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Up to 65% of patients with hypertension have untreated and/or uncontrolled blood pressure (BP) and about 10% have treatment-resistant hypertension (TRH) (1). In an effort to address this clinical need, attention has been focused on addressing BP control by disrupting the nerves running along the renal arteries (2). Patients with primary hypertension generally have increased efferent sympathetic nerve drive to the kidneys as well as increased systemic drive resulting from afferent nerves, as evidenced by elevated rates of renal norepinephrine spillover (2) and globally increased sympathetic nerve activity (3).

Disruption of the renal nerves has been shown to diminish the development of hypertension and to reduce elevated BP in TRH (4-7).

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Several intravascular methods have been developed to denervate the renal artery, with intravascular radiofrequency ablation to safely and effectively attenuate renal sympathetic nerve activity, resulting in a significant reduction in renal norepinephrine spillover (2,4) and substantial and sustained decreases in BP in patients with TRH (4,5).

Despite the success of catheter-based renal denervation systems, a number of limitations exist. Perhaps the most important limitation is the inability of radiofrequency catheter systems to deposit energy uniformly in the nerves, which are located both circumferentially and at varying depths around the vessel wall (8,9). Furthermore, because the radiofrequency energy is highly concentrated at the tip of the catheter, more energy is deposited in the arterial wall adjacent to the catheter tip than in the outer adventitial layer, resulting in injury to the endothelium and surrounding tissue and reduced range of neurolysis. The catheter devices are also invasive and require the use of fluoroscopy and contrast agents, which pose increased risks to patients (10).

A new, noninvasive approach for renal denervation has been developed for the treatment of hypertension using externally delivered focused ultrasound. In this paper, we present the initial clinical experience with externally delivered focused ultrasound renal denervation using the Surround Sound System (Kona Medical, Bellevue, Washington).

METHODS

From June 2012 to July 2014, 3 consecutive multicenter, prospective, single-arm, nonrandomized studies (waves I, II, and III) (NCT01926951 and NCT01704170) were conducted. The Surround Sound System in the wave I and wave II studies used an intra-arterial targeting catheter with small ultrasound transducer (beacon) in its distal tip to facilitate targeting of the intended renal artery treatment sites. In the wave III study, the targeting catheter was substituted by a duplex ultrasound imaging technology to enable noninvasive treatment targeting.

A total of 69 eligible patients with uncontrolled TRH provided written consent and underwent treatment at 4 different centers (St. Vincent's Hospital, Melbourne, Australia; Homolka Hospital, Prague, Czech Republic; St. Anne Hospital, Brno, Czech Republic; and Mercy Angiographic Institute, Auckland, New Zealand). All 3 studies (waves I, II, and III) were approved by each institution's respective ethics committee. An independent data and safety monitoring board was engaged to monitor the safety and efficacy outcomes from the 3 studies. Patients were screened in 2 sets of baseline visits 2 weeks apart. At each visit, 3 office BP measurements were performed, and the average systolic BP was calculated. To be included in the study, systolic BP >160 mm Hg at each baseline visit was required. In addition, 24-h ambulatory BP monitoring was performed at baseline in all patients but was not pre-defined as an inclusion criterion in the protocols. All subjects underwent pre-treatment work-up to exclude secondary causes of hypertension that involved renal artery ultrasound and magnetic resonance imaging (MRI) to further confirm eligibility.

TREATMENT. All patients were treated using the Surround Sound System (**Figure 1**). The device is designed to generate and deliver an annular pattern of ellipsoid-shaped ultrasound foci to the renal nerves noninvasively while automatically tracking and correcting in real time for motions associated with breathing and other patient movements. In case of excessive motion beyond trackable boundaries, the treatment is paused automatically until accurate targeting and tracking functions have been reestablished. In all 3 studies, only a single artery was treated per side, regardless of whether multiple renal arteries

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

ECG = electrocardiogram

MRI = magnetic resonance imaging

TRH = treatment-resistant hypertension

conduct of the study. Dr. Schmieder received grants and personal fees from Kona Medical during the conduct of the study. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Neuzil and Ormiston contributed equally to this work.

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