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Case Report

Renal Sympathetic Denervation: is it Effective in the Management of Resistant Hypertension?

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Abstract

Prevalence of Resistant Hypertension (RHTN) is increasing. Uncontrolled Hypertension (HTN) increases risk for stroke, and ischemic heart disease. Renal Denervation (RDN) was developed as a treatment procedure for RHTN. Currently there are no markers to determine the technical success of the procedure. There is evidence both in favor and against the procedure and it is based on performing the procedure with a catheter from a single manufacture.

Keywords: Percutaneous renal denervation; Renal denervation; Resistant hypertension

Introduction

Hypertension (HTN) has significant impact both at the patient level and also on health care. Nearly 25% of the world population suffers from HTN accounting for nearly 13% of the deaths worldwide [1]. Maintaining Blood Pressure (BP) levels at recommended targets is crucial. Between the ages 40-69 a sustained decrease in the Systolic Blood Pressure (SBP) by 20 mmHg or the Diastolic Blood Pressure (DBP) by 10 mmHg, reduces the incidence of stroke, ischemic heart disease, and other vascular diseases by approximately half [2]. Above the age of 69, the average annual absolute risk reduction in the incidence of complications is much higher. Lowering the BP target ranges to a SBP <115 mmHg and/or DBP to < 75 mmHg has also demonstrated increasing benefits [2].

RHTN is defined as a SBP > 140 or DBP > 90 mmHg despite optimal dosing of at least three different classes of antihypertensive agents or the near maximal dosing of four or more agents including one diuretic [3,4]. The prevalence of RHTN has gradually increased to its current level of almost 21% of all HTN patients [3,4]. This high prevalence is partially explained by an increase in risk factors for RHTN which include old age, obesity, DM, CKD, high salt consumption and female gender [1,3]. It is crucial to differentiate between resistant HTN, secondary HTN and pseudo-resistant HTN. The latter involves improper technique, inappropriate cuff size and timing of BP check during the office visit, patient non-adherence to medications and inadequate treatment by the provider [3]. Patients with RHTN are at higher risk for cardiovascular events than patient with non-resistant HTN [5].

The sympathetic nervous system has a significant role in both initiating and sustaining HTN [1,6,7]. Historically, surgical sympathectomy was used as a treatment for HTN but fell out of favor due to its significant morbidity and mortality as well as the development of multiple safe and effective pharmacological agents. However, sympathectomy helped establish the role of the sympathetic nervous system in the pathophysiology of HTN as well as generated a large volume of literature demonstrating its effects on Blood Pressure (BP), cardiac chamber size, cerebrovascular events and renal function [1,7]. The kidneys play a critical role in overall sympathetic nervous system activity with the presence of both afferent and efferent nerve endings. Changes in the renal pelvis hydrostatic pressure and renal interstitial chemical milieu transmit impulses through the afferent nerve endings via the sympathetic dorsal root neurons to the central sympathetic nervous system. Sympathetic nervous system activation increases sodium and water retention (alpha 1B Receptor), reduces renal blood flow by vasoconstriction (alpha 1A receptors), and increases renin release from juxtaglomerular apparatus (B1 receptors) thus activating the renin angiotensin system. These responses are driven by the amount of sympathetic tone and not by an all or none phenomenon. Moreover, sympathetic nervous system activation can be organ specific with local regulation at specific organ sites [1,7].

Percutaneous Renal Sympathetic Denervation (PRDN)

Multiple companies have developed percutaneous radiofrequency catheters for performing PRDN. However, the Medtronic SYMPLICITY catheter is used most frequently. Prior to the procedure, patients will be heparinized and a renal angiogram is usually done to identify anatomical details about renal artery size, and the presence or absence of accessory renal arteries. PRDN is performed percutaneously, accessing the renal vasculature via the femoral artery. The SN neurons in the tunica adventitia are then ablated from distal to proximal segments. Currently, there are no reliable markers for establishing success of the procedure. Some studies have used norepinephrine spill over as a marker of the success [8,9], while others have measured sympathetic nervous system activity in skeletal muscles as a surrogate success marker [6]. Currently, there are no reliable markers for technical success of the procedure.

The overall complication rate is very low with femoral artery pseudo aneurysm and renal artery stenosis occurring occasionally [9,10].

The Hawthorne effect is a common bias seen in many clinical trials that test a procedure. It occurs when some or all of the outcome effects of a study occur secondary to changes in the behavior of the patients or researches and not because of the intervention being studied.

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Evidence in favor of the PRDN

Catheter-based renal sympathetic denervation for resistant hypertension: A multicenter safety and proof-of-principle cohort study: It was a sponsored study with the sponsor actively involved in the study design, data analysis and manuscript preparation. It was designed for evaluating the safety and efficacy of the procedure. It was conducted at five Australian and European centers. Only 4% of patients who underwent the procedure were non-white and 44% of patients were female. Baseline office BP was 177/101 mm of hg. Fifty (50) patients were enrolled in the study and five patients were excluded because of a dual renal arterial system. The remaining 45 patients had the procedure. The first 10 patients had bilateral PRDN done in two stages with a follow-up angiogram one month after second PRDN. The next eight patients had simultaneous bilateral RDN with a one month follow up angiogram. The remaining 38 patients had simultaneous RDN without angiographic follow up. Some patients had a renal MRI six months post-procedure. Investigators showed a drop of office systolic blood pressures by –14/–10, –21/–10, –22/–11, –24/–11, and –27/–17 mm Hg at 1, 3, 6, 9, and 12 months. One patient developed a femoral artery pseudoaneurysm, and other had a renal artery dissection requiring stent placement. Limitations of the study included active sponsor involvement, white coat HTN, placebo effect, and a relatively short duration of follow-up (12 months). Most of the patients who had the procedure were male [8].

Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension Durability of Blood Pressure Reduction Out to 24 Months: A multicenter, open label proof of principal study that was designed to evaluate the safety of PRND with a longer period of follow up of 24 months. Patients were excluded if they had renal vascular abnormalities, CKD, type 1diabetes, or secondary HTN. The study was done at 19 centers in Australia, Europe and US and was also a proof of concept study with a drop in office SBP as the primary end point. One hundred and fifty three (153) patients underwent the procedure with follow-up BP measurements at 1,3,6,12,18, and 24 months and corresponding SBP/DBP drops of 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg respectively. Mean baseline office BP was 176/98 mmHg ± 17/14. At the end of 24 months, 27 patients had a drop in the number of anti-hypertensive agents while 18 patients had an increase in the number of anti HTN agents (10 of who had increases in antihypertensive despite adequate drops in BP). Limitations of the study included the lack of a control arm, potential placebo and Hawthorne effects and failure to exclude white coat HTN. Another limitation of the study is only 5% of patients who underwent the procedure were non-white, while 39% of patients were female. As far as complications, one patient had renal artery dissection and three patients had pseudo aneurysm or hematoma but none had worsening renal function or symptomatic orthostatic hypotension [10].

The investigators found that two pre-procedural predictors of PRND success were the use of central sympatholytics and elevated BP [10].

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): A prospective, randomized sponsored study. Primary effectiveness end point of the study was change in the office BP measurement at the end of six months. Patients were excluded if they had renal vascular abnormalities, CKD, type 1diabetes, or secondary HTN. Investigators randomly assigned 106 patients from 26 centers in Australia and Europe into two groups, either PRDN or control with the control group not receiving any intervention. Nearly 98% of patients who underwent the procedure were white and only 35% of patients were female. In the control group, whites accounted for 96% and females accounted for 50%. Changes in antihypertensive agents were not performed unless patients had symptoms. Follow-up was for six months with office BP measurement. Renal function was assessed at 1, 3 and 6 months and renal imaging performed at 6 months. At the end of six months, both groups showed a drop in BP with the SBP/DBP difference between the two groups being 33/11 mmHg. Eighty-four (84) percent of the treatment group had a drop in BP by at least 10 mmHg, while 35% of the control group showed a similar BP drop. Study limitations included industry sponsorship, potential

Table 1:

Studies In favor of RDN	Study population	Results	Limitation
Catheter-based renal sympathetic denervation for resistant hypertension: A multicenter safety and proof-of-principle cohort study	Five Australian and European centers.	A drop of office systolic blood pressures by –14/–10, –21/–10, –22/–11, –24/–11, and –27/–17 mm Hg at 1, 3, 6, 9, and 12 months	Most of the patients are white. Short term follow-up
Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension Durability of Blood Pressure Reduction Out to 24 Months	Nineteen centers in Australia, Europe and US	Follow-up BP measurements at 1,3,6,12,18, and 24 months showed a corresponding SBP/DBP drops of 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg respectively	Most of the patients are white. Hawthorne effect
Symplicity HTN-2 Trial	Twenty six centers in Australia and Europe 98% who had the	Eighty-four percent of the treatment group had a drop in BP by at least 10 mmHg	Most of the patients are white. Hawthorne effect
Global SYMPLICITY registry	World wide	A drop in ambulatory systolic BP of 7.9 mm hg in patients with SBP greater than 140 and 9.2 mm hg is SBP greater than 160.	Real time data
Studies Against RDN			
SYMPLICITY HTN-3	Australia, Europe and US	RDN failed to show superiority to sham procedure	Hawthorne effect
Renal Sympathetic denervation in patients with treatment resistant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure	Oslo University Hospital Norway	Out of six patients only two patients had drop in BP.	Very small sample size
Adjusted Drug Treatment Is Superior to Renal Sympathetic Denervation in Patients with True Treatment-Resistant Hypertension	Oslo University Hospital Norway	Drug adjustment is superior to RDN	Single center study Small sample size

placebo & Hawthorne effects (35% control arm had BP decrease), failure to exclude white coat, secondary HTN and failure to obtain ambulatory BP measurements on all patients prior to randomization. The complications rate was minimal [9].

Global SYMPLICITY registry: A real world observational data base of patients who had the procedure. It followed 1000 patients over the course of six months and showed that the procedure was safe with minimal complications. It showed a significant reduction in ambulatory BP (11.9 mmHg for all patients and 19.8 mmHg for patients with office SBP>160 mmHg). Study limitations include lack of generalizability and industry sponsorship. It has been proposed that some of the difference in the results between SYMPLICITY HTN-3 and the global SYMPLICITY registry could be due to the differences in the studied populations (rigorous screen in the study vs. database) [11].

Evidence against PRDN

A Controlled Trial of Renal Denervation for Resistant Hypertension: SYMPLICITY HTN-3: It is a major negative trial that has questioned the utility of the RDN. It is a randomized, prospective single blind study, sponsored by Medtronic, with the control group receiving a sham procedure. Primary efficacy end point was change in mean office SBP at the end of six months. Pre-procedure ambulatory BP was performed on all the patients who were on maximally tolerated doses of at least 3 antihypertensive agents including at least one diuretic. A 2:1 ratio (PRDN: control) was used to randomly assign 535 patients to the two groups. The control group had a sham procedure which consisted of a femoral puncture followed by a renal angiogram. The intervention group received PRDN. Both patients and primary physicians were blinded. Office BPs was measured at the end of 6 months. Nearly 25% of patients who received PRDN and nearly 29% of patients in sham group were African Americans. Nearly 41% of patients were female in the PRDN group while they accounted for 64% in sham group. Whites accounted only for 73% in the PRDN group and nearly 70% in sham group. PRDN failed to show superiority over the sham procedure. Office BP and ambulatory BP in the PRDN group was 2.4 mmHg and nearly 2 mmHg lower respectively than in the sham group. African Americans included in the sham group appeared to have an overall improvement in blood pressure when compared to those included in the procedure group suggesting a possible Hawthorne effect. The procedure was performed with a catheter from a single manufacture. There was no immediate biomarker to determine the technical success of the procedure [12].

Renal Sympathetic denervation in patients with treatment resistant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure: A prospective single center, non-blinded, nonrandomized study with true resistant HTN patients. In this study resistant HTN was confirmed by witnessed medication intake and both ambulatory BP monitoring and mean office BP measurement. Fadl Elmula et al enrolled a total of 18 patients who were specifically referred for PRDN procedure in Norway. After witnessed medication intake and ambulatory BP monitoring five patients were excluded because the BP did not meet the criteria for PRDN. Seven patients were excluded because of renal artery abnormalities, autoimmune disease, overt proteinuria, alcohol abuse or hyperaldosteronism. Six patients underwent the procedure. Out of six, only two patients had a decrease in the BP at 3 and 6 months (33% response rate) as confirmed by ambulatory BP monitoring. Stringent pre-procedural evaluation made lead to have a (33.3% of referred patients were candidates for the procedure) to have small sample size as well as the relatively low success rate of the procedure makes interpretation of this study difficult but does not lend support for PRDN [13].

Adjusted Drug Treatment Is Superior to Renal Sympathetic Denervation in Patients with True Treatment-Resistant Hypertension: A randomized study comparing the efficacy of PRDN with drug adjustments. Fadl Elmula et al randomized patients with true resistant HTN into PRDN and drug adjustment groups. In the drug adjustment group, authors adjusted the drug treatment at baseline, 1 month, and 3 months using noninvasive integrated hemodynamic measurements. In the PRDN group the Simplicity catheter was used to perform the procedure. None of the patients in the drug adjustment group were female while 22% of PRDN group were female. A significant BP drop in the drug adjusted group when compared to the PRDN group resulted in the study being terminated early. Office SBP and DBP in the drug-adjusted group changed from 160±14/88±13 mmHg (±SD) at baseline to 132±10/77±8 mmHg at 6 months while in the PRDN group the changes were from 156±13/91±15 to 148±7/89±8 mmHg. This study showed the superiority of antihypertensive agent adjustments compared to a PRDN procedure. In the drug adjustment group 50% of the patients needed to take at least one additional antihypertensive agent. Yet, in the PRDN group only one patient had a decrease in the number of antihypertensive agents. Forty-five (45) of 65 patients were excluded from the study due to secondary or white coat HTN reiterating the importance of careful evaluation of these conditions when managing HTN. There were several limitations to this study. The study was small (N=20) and non-blinded, using hemodynamic BP measurements to adjust the drug doses. This raises questions about the applicability of this cumbersome process in an actual office setting [14].

Conclusion

RDN is a physiological approach to address HTN. Unfortunately, at this time there is not enough evidence to either refute or support the procedure. Reliable, real-time end points, for the procedural success are not currently available. Most of the studies used a Medtronic catheter, making data extrapolation with the use of other ablation catheters difficult. It is unclear which patients, if any, benefit from the procedure. Further investigation is needed to determine patient selection criteria as well as reliable end points for the success of procedure.

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