COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

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Case SIGNOUT:

39-year-old woman with history of well-controlled hypertension prior to pregnancy, preeclampsia during pregnancy, and refractory hypertension during the 7 months since giving birth despite compliance with 5-antihypertensive regimen (QD amlodipine 10, olmesartan 40, HCTZ 25, nifedipine 90, and BID nebivolol 10) who presents with chest pain, blurry vision, headache, lightheadedness, and dyspnea in setting of BP 181/101. This is the latest of a series of identical presentations since delivery. Records and collateral information obtained from cardiologist's office (incl. normal stress test, normal TTE, normal renal ultrasound, no urine metanephrines, normal aldosterone/renin ratio) have not provided a cause for secondary HTN. The patient's cardiologist has offered to enroll her in the Simplicity-3 trial, a study of the effectiveness of renal denervation in patients with uncontrolled hypertension. The patient anxiously seeks advice from the primary team.

Clinical Question: What is the effectiveness and safety profile of renal denervation in patients with refractory hypertension?

Background

Refractory Hypertension

Def. BP > 140/90, or 130/80 if DM or renal disease, despite adherence to regimen of 3 antihypertensives, including a diuretic[i].

Epi. Prevalence difficult to come by. May be as high as 40% HTN pts.[ii] More common in >60 YO.

Clinical significance. Risk of HF, CVA, MI, RF correlated to degree of BP elevation.

Mechanism. Refractory to pharmacological intervention? Limitations of present medications? Physician inertia? Pts reluctant to adhere to complex multimedication regimen for asymptomatic disease?

Renal Involvement in HTN

Essential HTN: efferent sympathetic outflow >> renin release >> increased tubular sodium reabsorption >> reduced renal blood flow >> afferent sympathetic outflow >> modulation of central sympathetic outflow >> neurogenic HTN.[iii]

1950s: surgical sympathectomy was effective treatment for HTN[iv], [v].

2009: radiofrequency ablation of renal nerves via endovascular catheter in renal artery lumen showed successful reduction of sympathetic activity and renin release, sustained decrease in BP.[vi]

Symplicity HTN-1: nonrandomized pilot studies (n=153) of renal denervation demonstrated sustained reduction in BP. Pts still being followed.

Search Strategy: Database Pubmed

"Symplicity HTN-2 Trial": 10 results

Esler et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomized controlled trial. Lancet 2010; 376, 9756: 1903-1909

Group	Criteria or definition	n
Population screened	Patients with treatment-resistant HTN in 24 centers in Europe, Australia, and New Zealand. Pts required to record BID automated BP measurements and document med compliance for 2 weeks prior to start of trial. Pts whose BP below enrollment criteria at clinic visit were excluded.	190
Inclusion criteria	Age 18-85, SBP > 160 mmHg (or >150 if DM2) despite compliance with 3 or more hypertensive agents	106
Exclusion criteria	eGFR < 45 mL.min per 1.73 m^2, DM1, contraindications to MRI, substantial stenotic valvular heart disease, pregnancy or planned pregnancy during the study; h/o of MI, unstable angina, or CVA during previous 6 months	84
Treatment group	Renal denervation + baseline HTN regimen	52
No treatment group	Baseline HTN regimen	54

Primary endpoints: between-group change in average office-based measurements of systolic blood pressure from baseline to 6 months after randomization.

Secondary endpoints: acute procedural safety, chronic procedural safety (reduction of >25% or new stenosis >60% confirmed by angiogram at 6 months), a composite cardiovascular endpoint (MI, sudden cardiac death, new-onset heart failure, death from progressive heart failure, stroke, aortic or lower limb revascularization procedure, lower limb amputation, death from aortic or peripheral arterial disease, dialysis, death because of renal failure, hospital admission for hypertensive emergency unrelated to non-adherence or non-persistence of drugs, and hospital admission for atrial fibrillation), and additional measurements of BP reduction at 6 months after randomization consisting of occurrence of 10 mm Hg or more systolic response, achievement of target SBP (<140), change in 24-h ambulatory BP, and change in home-based BP measurements.

- Are the Results of the Trial Valid?
  - Randomized? Yes, one-to-one randomization done by sealed envelopes.
  - All patients accounted for at end? No. 3 pts in RD did not attend 6-month f/u (1 withdrew consent, 2 missed visit). 3 pts in control group did not attend 6-month f/u (2 withdrew consent, 1 missed visit).
  - Intention to treat? There was no crossover reported. Only patients present at 6-month visit analyzed.
  - Blinding? No, data analyzers were not masked to treatment assignment.
  - Groups similar at start of trial? Yes. Same mean baseline SBP (178), similar DBP (97 RD vs, 98 control), age (58), race (98% vs. 96%), BMI (31), HLD (52%), **Cystatin C (superior to Cr for estimating GFR 0.9 vs. 0.8)**, HR (75 vs. 71), number of HTN meds (5.2 vs 5.3), pts on HTN meds >5 yrs (71% vs 78%), pts >5 meds (67% vs 57%), medication drug classes including aldosterone antagonists.

Differences:	RD	Control
Female	35%	50%
DM2	40%	28%
CAD	19%	7%
eGFR	**77**	**86**
eGFR 45-60	21%	11%
sCr	91 mmol/L	78 mmol/L
	1.02 mg/dL	0.88 mg/dL
uAlb/uCr	128 mg/g	109 mg/g

  - Equal treatment of groups? Patients in the control group did not receive sham procedure. Changes in baseline anti-HTN meds not allowed unless medical necessary due to changes in BP in association with signs and symptoms. Specific changes at discretion of individual providers.
  - Did randomization work? Yes.
  - **Funding provided by Ardian of Mountain View, CA, makers of the Symplicity Catheter System.**
- Are the results of the trial important?
  - Size of treatment effect? Yes, mean BP decreased, see below.

- Precision of the estimate of the effect? Error bars do not overlap. Therefore, measured effect is large compared to the confidence interval. Therefore, measurement of effect is relatively precise.

Endpoint	Result	Significance	ARR	NNT
Difference, office-based BP	**33/11 mm Hg**	**p<0.0001**	n/a	n/a
Difference, home-based BP, 2 wks, 6x/day, (n=32 RD, n=40 control)	22/12 mmHg	p<0.0001	n/a	n/a
Avg 24 hr ambulatory BP reduction, Q15 daytime, Q30 night time (n=20 RD, n=25 control)	11/7 mmHg RD 3/1 mmHg control	p=0.006 SBP p=0.014 DBP p=0.51 SBP p=0.75 DBP	n/a	n/a
Achievement of defined threshold SBP reduction at 6 months (>10 mmHg)	**84% RD** **35% control**	**p<0.0001**	**n/a**	**n/a**
Pts with drug reductions	20% RD 6% control	p=0.04	n/a	n/a
Pts requiring drug increases	8% RD 12% control	p=0.74	n/a	n/a
Subanalysis, censored data after drug increases, difference in BP at 6 months	31/11	p<0.0001	n/a	n/a
Morbidity	**Result**	**Significance**	**ARI**	**NNH**
Serious complications related to device or procedure	**None**	n/a	n/a	n/a
Minor periprocedural events	1 femoral artery pseudoaneureysm, 1 post-procedural drop in BP, 1 UTI, 1 extended hospital admissions for paresthesias, 1 back pain, 7 intraprocedural bradycardia	n/a	n/a	n/a
Renal function	0 decreases in eGFR >50%, 2 RD and 3 control decrease eGFR >25%	n/a	n/a	n/a
U Albumin/Cr ratio (n=38 RD, n=37 control)	**-3 mg/g RD** **+1 mg/g control**	**p=0.26**	n/a	n/a
Renal Imaging in RD (37 renal duplex, 5 MRI, 5 CTA)	1 progression of atherosclerotic lesion not at location of radiofrequency energy	n/a	n/a	n/a
Hospital Admissions for Hypertensive Urgency	3 RD 2 control	n/a	n/a	n/a
Additional Events, RD	1 nausea w/edema, 1 HTN crisis after stopping clonidine, 1 TIA, 1 hypotension, 1 stent for angina	n/a	n/a	n/a
Additional Events, Control	2 TIA, 1 stent for angina	n/a	n/a	n/a

Can I apply these results to my patient? My patient was similar to study patients in terms of age, BMI, presenting BP, lack of exclusion criteria. However, once hospitalized, patient's BP decreased from 181/101 to 120s/70s on inpatient regimen that was very similar to stated outpatient regimen. Given this in-hospital response to antihypertensives, patient was advised to adhere to medications and obtain renal artery catheterization as outpatient to rule out renal artery stenosis. Furthermore, given reduction in BP with verified adherence to HTN regimen, patient would likely not meet inclusion criteria for Symplicity-3 trial. Lastly, given that patient's hypertension was seemingly controlled with well-studied pharmacological therapy, it seems unwise to expose her to risks described above when not medically necessary.

Symplicity HTN-2: newer study 2012, published by AHA, 1 year f/u of all analyzed pts. Crossover allowed at 6 months. Comparable reduction in BP in crossover group.
Symplicity HTN-3: currently recruiting pts in USA, including Columbia. Greater emphasis on aldosterone antagonists; more ambulatory BP monitoring to prove: 1. presence of HTN, 2. around-the-clock effectiveness of renal denervation.

[i] Moser M, Setaro J. Resistant or Difficult-to-Control Hypertension. N Engl J Med 2006; 355:4

[ii] Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med 2002;346:544.
[iii] Kopp UC, Cicha MZ, Smith LA, Mulder J, Hokfelt T. Renal sympathetic nerve activity modulates afferent renal nerve activity by PGE2-dependent activation of alpha1- and alpha2-adrenoceptors on renal sensory nerve fibers. Am J Physiol Regul Integr Comp Physiol 2007; 293: R1561–72.
[iv] Hoobler SW, Manning JT, Paine WG, et al. The effects of splanchnicectomy on the blood pressure in hypertension; a controlled study. Circulation 1951; 4: 173–83.
[v] Smithwick RH, Thompson JE. Splanchnicectomy for essential hypertension; results in 1,266 cases. J Am Med Assoc 1953; 152: 1501–04
[vi] Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. N Engl J Med 2009; 361: 932–34