

Treatment of Refractory Hypertension Due to Tertiary Hyperaldosteronism with Spironolactone Following Percutaneous Renal Artery Intervention (PTRI): A Prospective Randomized Control Trial

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A. Study Purpose and Rationale

Renal artery stenosis (RAS) is a well-established cause of secondary hypertension with renovascular disease being recognized as the underlying cause in 1-5% of patients with hypertension and 5-15% of those with dialysis dependent end-stage renal disease [1]. Furthermore, several studies demonstrate that the prevalence of renovascular disease in high-risk categories exceeds 15–20% [2].

Currently Percutaneous Renal Artery Intervention (PTRI, includes angioplasty with or without stenting) is the most common procedure utilized in the treatment of hypertension thought to be caused by renal artery stenosis. The current data that exists is conflicting and controversial however. Although several controlled clinical trials have shown that PTRI can indeed lower blood pressure, prospective randomized control trials do not clearly corroborate those findings [6]. In fact, the two largest randomized control trials evaluating the efficacy of PTRI completed to date, although arguably flawed in their methodology, have both been negative studies [3-4]. Beyond the inherent flaws of the studies, the most predominate theory to explain why patients who undergo PTRI for hypertension secondary to atherosclerotic renal artery stenosis (ARAS) do not improve is thought to be due to the diffuse involvement of atherosclerotic disease distal the lesions intervened upon. This theory is further supported by the data indicating an 89-97% technical success rate for patient who undergo PTRI for RAS caused by fibromuscular dysplasia [5].

We however, propose tertiary hyperaldosteronism as a second and under recognized mechanism by which individuals continue to have elevated BP following PTRI. The Goldblatt phenomena attributes the driving force of elevated blood pressure in RAS is due to the pathophysiologic mechanism of a revved up renin-angiotensin-aldosterone (RAA) system [1]. Experimental animal models of renal artery occlusion have shown that there is an increased release of renin from the juxtaglomerular cells of the kidney. The elevated renin then leads to activation of RAA system that culminates in the release of aldosterone from the zona glomerulosa of the adrenal gland. In this cascade the cause of hyperaldosteronism is thought to be secondary to the elevation in renin. Given this well-known and studied mechanism of secondary hypertension, we propose the controversial concept of tertiary hyperaldosteronism which is analogous to the process of tertiary hyperparathyroidism in which there is constitutive activation of the parathyroid gland.

The entity of tertiary hyperaldosteronism is presumed to result from chronic elevations in plasma renin levels and secondary hyperaldosteronism, which eventually establishes a state of autonomous unregulated hyperaldosteronism [7]. Only a few well-described cases exist, but nonetheless it has been observed, and is apparently underappreciated as pathophysiologic process [9-15]. This hypothesis was in fact postulated as far back as 1958. Ironically, Jerome Conn himself disputed its existence in analyzing a case study of a patient with persistent hyperaldosteronism, suppressed renin and renal artery stenosis [16]. We however propose that over a long period of time the effects angiotensin II stimulation leads to a yet to be defined constitutive activation of the adrenal gland leading to true tertiary hyperaldosteronism.

In this randomized double-blind clinical control trial we assume the mechanism of tertiary hyperaldosteronism is at play when individuals who have PTRI continue to have elevated BP with low renin and elevated aldosterone. We actually go one step further by treating the hyperaldosterone-induced hypertension with the aldosterone antagonist spironolactone, which will not only further substantiate the theory of tertiary hyperaldosteronism, but most importantly provides a clinically relevant solution to the problem of persistent hypertension following PTRI.

B. Study Design and Statistical Analysis

Study Design

Patients with previously identified renovascular hypertension who are referred for PTRI will be recruited into the study. Of these patients, only those found to have both elevated renin and aldosterone prior to PTRI will be included. Following PTRI, individuals who continue to have both an elevated BP, decreased renin, but an elevated aldosterone level will be included in this study. This subgroup will then be randomized to placebo versus spironolactone one week after PTRI. BP will be checked prior to treatment and rechecked at two and four weeks by both manual and automatic BP devices three times at each visit, with the average of these three BP readings being recorded.

Statistical Analysis

A BP change of 5mmHg or greater will be considered significant. The difference between the blood pressures of the spironolactone group versus placebo will be calculated utilizing an unpaired t-test.

It is expected that the variability of blood pressure change will be about 10mmHg in the entire group. The standard deviation is therefore calculated at 5mmHg. Using a beta error of 80% and an alpha error of 5%, a total of 17 patients will be needed in each group.

$$n \text{ (in each group)} = 1 + 16 (\text{std-devn/effect})^2$$

$$n = 1 + 16 (5/5)^2 = 17$$

C. Study Procedures

Procedures for standard PTRI will be followed. Once patients are randomized to placebo versus treatment, they will be given unlabeled pills with either spironolactone or placebo on a daily basis. Both the investigators and the subjects will be blinded to the nature of the treatment that the subjects are receiving. Venous renin and aldosterone levels will be measured prior to and following PTRI. Serum basic metabolic profiles will also be checked prior to the treatment period and will be rechecked at two and four weeks during the treatment period.

D. Study Drugs

Spironolactone

Class: Potassium-sparing diuretic

MOA: Competitive antagonist of aldosterone

Indications:

- Hyperaldosteronism
- Edematous conditions (CHF & Cirrhosis)
- Essential hypertension
- Hypokalemia

Pregnancy: Category C

Side-Effects (By system in order of decreasing frequency):

- **Digestive:** Gastric bleeding, ulceration, gastritis, diarrhea and cramping, nausea, vomiting.
- **Endocrine:** Gynecomastia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding. Carcinoma of the breast has been reported in patients taking spironolactone but a cause and effect relationship has not been established.
- **Hematologic:** Agranulocytosis.
- **Hypersensitivity:** Fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis.
- **Nervous system /psychiatric:** Mental confusion, ataxia, headache, drowsiness, lethargy.

E. Medical Devices

Only those related to PTRI. Patients will not be further exposed to medical devices as a result of this study.

F. Study Questionnaires

None

G. Study Subjects

Inclusion Criteria

- 1) All patients undergoing PTRI for renovascular hypertension
- 2) Documented elevated renin and aldosterone levels prior to PTRI

Exclusion Criteria

- 1) Those with any contraindication to spironolactone
- 2) Those who require the use of spironolactone for another indication other than HTN
- 3) Those with continued elevation in renin or decrease in both renin and aldosterone following PTRI
- 4) Those who develop complications as a result of PTRI

H. Recruitment of Subjects

We will be recruiting patients who are referred for to cardiology, interventional radiology, and vascular surgery for PTRI. Please refer to parts B, C, and G for further information regarding inclusion and exclusion criteria and recruitment methods.

I. Confidentiality of Study Data

Every effort will be made to maintain the confidentiality of patient data. All patient information will be coded and will remain in the possession of the investigator. Additionally, all investigators have completed HIPPA training and will be expected to adhere to HIPPA guidelines throughout the course of the study.

J. Potential Risks

Please refer to section D for potential side-effects of spironolactone. Also there is the theoretical risk of adverse effects for continued elevation of BP following the PTRI.

K. Potential Benefits

Spironolactone is also indicated in the treatment of hypokalemia and edematous conditions and would therefore be beneficial to patients who incidentally suffer from these conditions.

L. Alternatives

Currently no other alternatives exist for the treatment of elevated BP due to tertiary hyperaldosteronism following PTRI.

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