Spironolactone Is More Effective Than Renal Denervation In Lowering Blood Pressure In Resistant Hypertension: A Systematic Review

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Abstract

Background: Spironolactone is the main addition for triple therapy for resistant hypertension, which has been proven by previous studies about how effective the drug is on reducing blood pressure. Renal denervation (RDN) is a catheter-based ablation procedure designed to treat resistant hypertension (RH). Both of these interventions are considered the main choices on treating resistant hypertension, however the use of spironolactone and renal denervation to decrease blood pressure in individuals with resistant hypertension has not before been compared in a systematic study.
Methods: We performed the present systematic review according to preferred items in the 2020 PRISMA. A systematic search was conducted through Pubmed, Sciencedirect, Scopus, and Web of Science selecting randomized control study until July 2022
Results and Discussion: Our search yielded 987 studies of which we included 6 studies for the final analysis. A total of 224 patients were treated with spironolactone and 211 patients treated with RDN, however 1 study performed RDN combined with PVI. From the 6 studies included in this review, it has been found that spironolactone has a better lowering effect on both 24-hour and office blood pressure.
Conclusion: Spironolactone is more effective than renal denervation in reducing blood pressure in patients with resistant hypertension.

Keywords: spironolactone; renal denervation; blood pressure; resistant hypertension

1. Introduction

Patients with resistant hypertension (RH) have been given new hope with catheter-based renal denervation (RDN)[1,2]. Resistant hypertension (RH) and uncontrolled hypertension (UH) may be treated with renal denervation (RDN) . Early research on the effects of RDN on decreasing blood pressure (BP) such as the Symplicity HTN-1 single-arm experiment and the Symplicity HTN-2 randomized controlled trial (RCT) showed promising results; however, the Symplicity HTN-3 sham-controlled trial in 2014 revealed neutral results. Negative results can be attributed to patients' noncompliance with antihypertensive therapy as well as the inexperience of those doing the renal ablation[3,4]. Additionally, based on the data at hand, the Czech Society for Hypertension has not advocated the use of RDN in everyday clinical practice since 2015[5]. As a result, thorough new information is required about the use of renal denervation and other potential alternatives, including the use of spironolactone, in the treatment of individuals with resistant hypertension. When tolerated and maintained for at least a year, spironolactone addition alone appears to be more successful at lowering blood pressure than total RDN[6]. The use of spironolactone and renal denervation to decrease blood pressure in individuals with resistant hypertension has not before been compared in a systematic study. To find out how well RCTs of RDN and the use of spironolactone in reducing blood pressure in patients with RH, we undertook a systematic evaluation of these studies.

2. Methods

We performed the present systematic review according to the preferred items in the 2015 PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines.

2.1. Searching Strategy

The studies of the recent decade in the field of renal denervation and spironolactone in resistant hypertension patients were identified by two independent reviewers (CFA and NPM) through PubMed, Sciencedirect and Google Scholar databases using the search terms alone and combinations; renal denervation, RSNA (renal sympathetic nerve activity), spironolactone, resistant hypertension, ambulatory blood pressure or 24-h blood pressure, office blood pressure, SBP, DBP. Also, manual searches for additional articles were performed. The literature search was restricted to papers in the English language and published articles within 2012 – 2022. Abstract and full text was reviewed by four authors (CFA, NPM, RA, and BZT). The authors were contacted for supplementary information if there were incomplete data from the full texts. Disagreements were resolved through debate.

2.2. Selection Criteria

Inclusion criteria (the guidelines to select the eligible studies which could be included in the process of the analysis) and exclusion criteria were chosen as follows

2.2.1. Inclusion Criteria:

The inclusion criteria in this study were: (1) Randomized Control Trial study (2) Patients with resistant hypertension (3) Renal denervation (all methods) (4) Giving spironolactone (5) Human subject only (6) Age >18 years.

2.2.2. Exclusion Criteria:

The exclusion criteria in this study were: (1) non-English language published studies; (2) non related studies to renal denervation and using spironolactone in resistant hypertension patients; (3) review, editorial, case reports, conference abstracts, meta-analysis, and systematic articles; and (4) inadequate/unavailable data and repeated studies.

2.3. Data extraction and quality assessment

After a careful review of the included studies, details were obtained from the articles which qualified for final inclusion. The following important headings were extracted from these studies: author, years, duration of intervention, number of samples and average ages, hypertension criteria, RDN method, 24h-systole (daytime and nighttime), 24h-dyastole (daytime and nighttime), office systole (daytime and nighttime), office dyastole (daytime and nighttime), and heart rate (daytime and nighttime).

3. Results

3.1. Overview of Literature Searching

There were 2426 studies identified through database searching from Pubmed, Sciencedirect, Scopus, and Web of Science. We screened 987 titles and abstract after removing duplicates, leaving the 6 studies to be selected and then analyzed for qualitative synthesis.

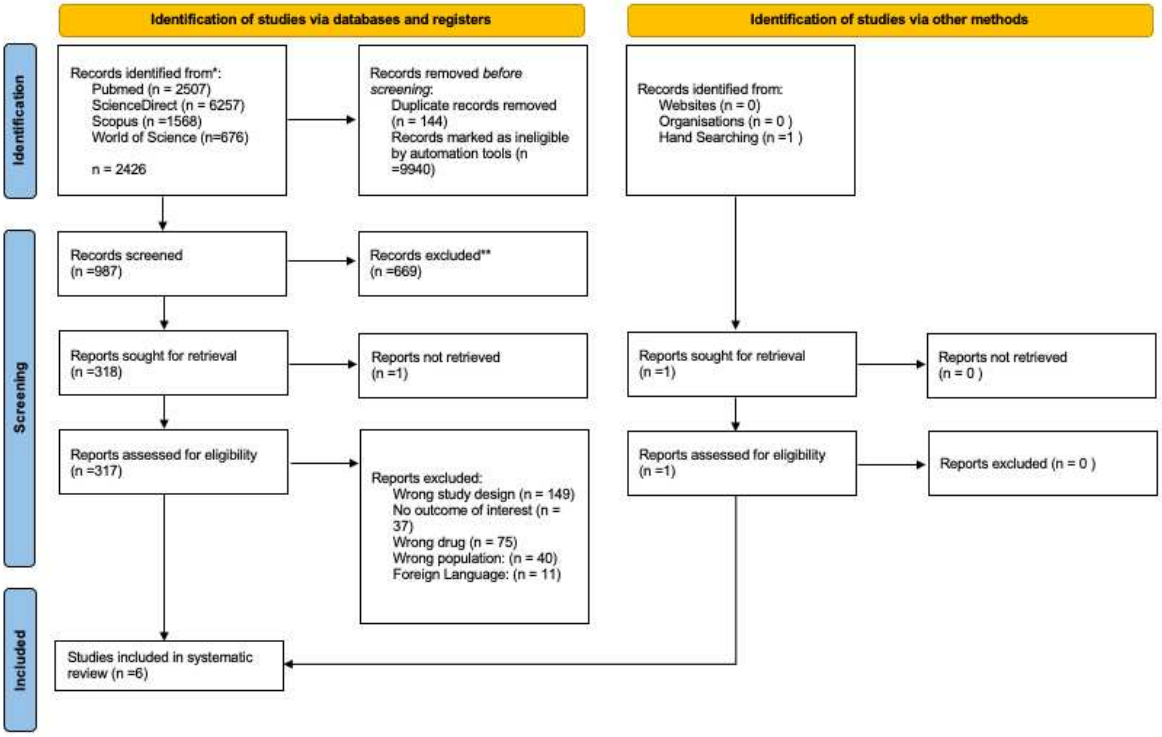

Figure 1. PRISMA 2020 Flow Diagram

3.2. Study Characteristics

In this review, 6 studies were included. A total of 24, 69, 24, 106, 106, 106 participants were enrolled in the study of renal denervation and spironolactone in resistant hypertension patients.

Table 1. Characteristic of included studies

No.	Author, year	Number of Sampels		Average age		Hypertension Criteria
		Spironolactone	Renal Denervation	Spironolactone	Renal Denervation	
1	Delasierra, 2016[7]	13	11	(64.9±8.2)	(61.9±6.6)	RH: office systolic blood pressure (SB mm Hg and 24-hour SBP ≥140 mm H treatment with 3 or more full-dose antihypertensive medications, one of diuretic, but without minreral corticoic antagonist
2	Kiuchi, 2017[8]	36	33	(58.4 ± 5.1)	(56.8 ± 6.5)	Uncontrolled hypertension: mean 24- ambulatory blood pressure measurer (ABPMs) of ≥ 130 mmHg for systolic ≥ 80 mmHg for diastolic BP values
3	Oliveras, 2016[9]	13	11	(64.9 ± 8.2)	(61.9 ± 6.6)	RH: with an office SBP at least 150 m a 24-h SBP at least 140 mmHg despi prescribed therapeutic schedule with appropriate combination of three or m dose antihypertensive drugs, includin diuretic, and maintained for the last 3
4	Rosa, 2015[10]	54	52	(59±9)	(56±12)	RH: with an office systolic BP >140 m treatment with ≥3 antihypertensive dr optimal doses, including a diuretic
5	Rosa, 2016[8]	54	52	(59±9)	(56±12)	RH: with an office systolic BP >140 m treatment with ≥3 antihypertensive dr optimal doses, including a diuretic

6	Rosa, 2017[11]	54	52	(59±9)	(56±12)	RH: with an office systolic BP >140 m treatment with ≥3 antihypertensive dr optimal doses, including a diuretic

Table 2. Summary result of pooled studies

No.	First Author (year)	Duration	RDN										SPN					
			Systole (24h)		Diastole (24h)		Systole (office)		Diastole (office)		HR		Systole (24h)		Diastole (24h)		Systole (o	
			Day time	Night time	Daytime	Night time	Day time	Night time	Day time	Night time	Day time	Night time	Day time	Night time	Day time	Night time	Day time	
1	Delasiera (2016)	6 months	Baseline: 153.0±8.3 change: −3.4±12.8	Baseline: 75.4±8.6 change: −3.9±9.6	Baseline: 84.2±10.3 change: −1.8±8.3	Baseline: 141.2±11.4 change 141.2±11.4	-	-	-	-	Baseline: 66.4±7.7 change: 2.4±7.6	Baseline: 56.5±6.9 change: 2.5±6.8	Baseline: 158.1±9.9 change: −25.6±17	Baseline: 146.5±15.6 change: −23.4±15.6	Baseline: 83±10 change: −10.3±8.4	Baseline: 75.1±12.4 change: −11.1±9.7	-	
2	Kiuchi, 2017	12 months	Baseline: 142 ± 6, 6 months: 132 ± 5,12 months: 123 ± 4	-	Baseline: 103 ± 8, 6 months: 95 ± 8, 12 months: 82 ± 4	-	-	-	-	-	-	-	Baseline: 140 ± 6, 6 months: 135 ± 6, 12 months: 130 ± 6	-	Baseline: 103 ± 7, 6 months: 99 ± 8, 12 months: 89 ± 5	-	-	
3	Oliveras, 2016	6 months	Baseline: 152.6 7.9, change: -5.7 (-14.8 to 3.4)	Baseline: 141.9 11.4, change: -7.7 (-18.8 to 3.4)	Baseline: 83.8 10.5, change: -3.0 (-7.4 to 1.5)	Baseline: 141.9 11.4, change: -5.5 (-11.2 to 0.3)	Baseline: 168.0 13.8, change: -17.5 (-29.7 to 5.1)	-	Baseline: 89.6 12.8, change: -7.5 (-15.5 to 0.5)	-	Baseline: 66.5 7.8, change: 0.4 (-3.4 to 4.1)	Baseline: 141.9 11.4, change: 0.6 (-3.0 to 4.3)	Baseline: 158.9 9.4, change: -23.6 (-31.9 to -15.3)	Baseline: 147.7 15.5, change: -22.3 (-32.4 to -12.2)	Baseline: 158.9 9.4, change: -9.8 (-13.9 to -5.8)	Baseline: 75.9 11.7, change: -10.9 (-16.1 to -5.9)	Baseline: 67.1 10.6, change -29.4 (-40.7 to -18.1)	
4	Rosa, 2015	6 months	Baseline: 152±12, 6 months: 143±13	Baseline: 141±16, 6 months: 133±14	Baseline: 88±10, 6 months: 83±10	Baseline: 80±11, 6 months: 74±10	Baseline: 159±19, 6 months: 147±20	-	Baseline: 92±14, 6 months: 85±12	-	Baseline: 72±12, 6 months: 70±10	Baseline: 63±9, 6 months: 62±9	Baseline: 150±13, 6 months: 141±16	Baseline: 141±17, 6 months: 141±17	Baseline: 84±10, 6 months: 79±11	Baseline: 75.9 11.7, change: -10.9 (-16.1 to -5.9)	Baseline: 155±17, 6 months: 141±18	

5	Rosa, 2016	12 months	Baseline: 149±12, change: −6.4 (−10.1, −2.7)	-	Baseline: 86±10, change: −5.6 (−7.8, −3.3)	-	Baseline: 159±19, change: −13.4 (−18.9, −7.9)	-	Baseline: 92±14, change: −8.4 (−11.9, −4.9)	-	Baseline: 71±14, change: −3 (−6.1, 0.1)	-	Baseline: 147±13, change: −8.2 (−13.2, −3.3)	-	Baseline: 84±10, change: −6.0 (−8.8, −3.2)	-	Baseline: 155±17, change: −11.3 (−17.1, −5.5)	-
6	Rosa, 2017	24 months	Baseline: 149 12, change: -9.1 (-13.3, -4.9)	-	Baseline: 86 10, change: -5.7 (-7.7, -3.6)	-	Baseline: 159 19, change: -17.7 (-24.7, -10.8)	-	Baseline 92 14, change: -12.6 (-16.6, -8.5)	-	Baseline: 69 10, change: -0.8 (-3.2, 1.6)	-	Baseline: 147 13, change: -10.9 (-16.4, -5.5)	-	Baseline: 84 10, baseline: -7.4 (-10.3, -4.5)	-	Baseline: 155 17, change: -14.1 (-20.1, -8.0)	-

4. Discussion

Previous studies had shown that both RDN and spironolactone have a blood pressure lowering effect on patients with resistant hypertension.

Spironolactone is a nonselective antagonist that can bind to both androgen and progesterone receptors. It is a member of the pharmacological class known as mineralocorticoid receptor antagonists. The renin-angiotensin-aldosterone system's hormone aldosterone binds to receptors in the distal tubules and collecting duct, increasing vascular remodeling and stiffness as well as cardiac remodeling, fibrosis, and remodeling, as well as sodium and potassium secretion. Spironolactone selectively affects aldosterone receptor-mediated function by competitively inhibiting it. The blockage has the effect of preventing sodium reabsorption with water retention and increasing potassium retention. Spironolactone may decrease sebum production in the treatment of acne vulgaris by preventing the binding of dihydrotestosterone to its androgen receptors and so preventing sebocyte growth[12]. Whereas the procedure of RDN consists of delivering radiofrequency energy into the lumen of renal arteries leading to thermal disruption of postganglionic sympathetic nerves directed to the kidney, which resulted in the reduction of blood pressure[13].

From the 6 studies included in this review, it has been found that spironolactone has a better lowering effect on both 24-hour and office blood pressure, which we use as the main parameter to compare the interventions mentioned above. A study needs to be highlighted, conducted by Rosa, et al. compared the two interventions since 2015 to 2017, the first 6 months on the 24-hour blood pressure shows that RDN almost has the same result on lowering blood pressure on resistant hypertension patients as spironolactone, however the next 6 months and 12 months show that spironolactone is more favorable than RDN. The office blood pressure result of this study on the first 6 months shows that both the interventions almost have the same blood lowering effect, however the next 6 months and 12 months show that RDN has a better blood lowering effect. However, the other studies, conducted by Delasierra, et al., Kiuchi, et al., and Oliveras, et al. show that spironolactone has a better blood lowering effect on the first 6 months and 12 months. Rosa, et al. administered 25 mg of spironolactone during their research, which is why there isn't a significant difference between the blood pressure-lowering effects of RDN and spironolactone in the first six months. In a different trial, spironolactone 50 mg was administered, which resulted in a more significant blood pressure lowering effect than RDN in the first 6 months. It should be noted that in a study by Kiuchi, et al., not only using spironolactone as a comparison intervention from RDN, but spironolactone in combination with Pulmonary Vein Isolation (PVI). Whereas the study by Olivieras, et al. used spironolactone at a dosage of 25 mg and subsequently the dosage was increased to 50 mg through titration. This finding shows that even with lower dose, the efficacy of spironolactone is almost equal to RDN. However, spironolactone has the better blood pressure lowering effect in the long run even with the same dose.

5. Conclusion

Spironolactone is more effective than renal denervation in reducing blood pressure in patients with resistant hypertension. The findings of present study may provide unequivocal support to the use of spironolactone. However, quantitative studies are still needed to provide an overview of the strength of the difference between spironolactone and renal denervation

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