eISSN (Online): 2598-0580

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Effectiveness of Renal Denervation Therapy in Persistent Hypertension: A Meta-Analysis

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ARTICLE INFO

Keywords:
Meta-analysis
Persistent hypertension
Renal denervation therapy

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i8.1049

A B S T R A C T

Background: Persistent hypertension is a global health problem that requires effective therapy. Renal denervation (RDN) therapy is emerging as a promising new option. This meta-analysis aims to evaluate the effectiveness of RDN in patients with persistent hypertension. **Methods:** We performed a systematic search in PubMed, Scopus, and the Cochrane Library for studies evaluating the effectiveness of RDN in patients with persistent hypertension. Data were extracted and analyzed using a random effects model. **Results:** A total of 12 studies with a total of 1,024 patients were included in this meta-analysis. RDN demonstrated significant reductions in systolic and diastolic blood pressure compared with controls (MD -12.3 mmHg [95% CI -15.8 to -8.8] for systolic blood pressure and MD -6.1 mmHg [95% CI -8.2 to -4.0] for blood pressure diastolic). The effectiveness of RDN is higher in patients with more severe hypertension and in patients who are unresponsive to antihypertensive drugs. **Conclusion:** RDN is an effective therapy for persistent hypertension, especially in patients with more severe hypertension and in patients who are unresponsive to antihypertensive drugs.

1. Introduction

Hypertension, or high blood pressure, is one of the main cardiovascular diseases that stalks human health throughout the world. Behind blood pressure numbers that look simple, hypertension hides hidden dangers that can be fatal. This disease is analogous to a "silent killer" because it often does not show obvious symptoms, but can silently damage vital organs such as the heart, kidneys, and brain. Hypertension is defined as a consistent increase in blood pressure above normal values. Normal blood pressure in adults ranges from 120/80 mmHg to 130/85 mmHg. The World Health Organization (WHO) estimates that by 2025, 1.28 billion adults will suffer from hypertension, with 725 million of them living in low- and middle-income countries. This makes hypertension one of the main risk factors for cardiovascular disease, responsible for 8.5 million deaths in 2020. The impact of hypertension is not only limited to individual health but also results in a significant economic burden for countries. The costs of treating and treating cardiovascular disease associated with hypertension are very high and are estimated at trillions of dollars per year. Persistent hypertension, or resistant hypertension, is a more complex and difficult-to-treat subcategory of hypertension. Persistent hypertension is defined as blood pressure that remains high above 160/100 mmHg despite being given a maximum dose of antihypertensive drug therapy with a combination of three or more drugs. Patients with persistent hypertension often have additional risk factors such as diabetes, obesity, and kidney disease, further complicating blood pressure management. Failure to control persistent hypertension can increase the risk of serious complications such as coronary heart disease, stroke, kidney failure, and diabetic retinopathy.[1-3]

Renal denervation (RDN) therapy has emerged as an innovative solution to treat persistent hypertension. RDN is a minimally invasive catheter procedure that aims to disrupt the kidney nerves that contribute to blood pressure regulation. This kidney nerve, known as the renal sympathetic nerve, sends signals to the brain that can increase blood pressure. RDN is performed by inserting a catheter into the renal artery and using radiofrequency energy to modulate or destroy the renal sympathetic nerves. This procedure is usually performed under local anesthesia and takes approximately 30-60 minutes. Several clinical studies have demonstrated the effectiveness of RDN in lowering blood pressure in patients with persistent hypertension. In a randomized, controlled study involving 461 patients, RDN demonstrated a reduction in systolic blood pressure by 15 mmHg and diastolic blood pressure by 10 mmHg compared with the control group. However, the effectiveness of RDN is still a matter of debate. Several other studies have shown less consistent results, and further research is needed to determine the long-term effectiveness of RDN and its long-term safety.[4-6]

2. Methods

The first step in this research was to determine clear inclusion criteria to select relevant and high-quality studies. These criteria aim to ensure that only studies that meet high methodological standards are included in the meta-analysis. In this study, the inclusion criteria set were as follows: 1. Type of study: Randomized controlled trial (RCT) comparing the effectiveness of RDN with control (antihypertensive drugs alone or placebo) in patients with persistent hypertension. 2. Study population: Adult patients with a diagnosis of persistent hypertension defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg despite using maximum doses of antihypertensive medication. 3. Intervention: The RDN procedure is carried out using a catheter and radiofrequency energy to disrupt the kidney nerves. 4. Main outcome: Reduction of systolic and diastolic blood pressure.

After determining the inclusion criteria, the next step is to conduct a systematic and comprehensive literature search. In this study, three main scientific databases were used: PubMed, Scopus, and the Cochrane Library. Keywords used in the search included: Renal denervation; Hypertension; blood pressure; Randomized controlled trial; Meta-analysis. Reference lists obtained from each database are then exported to reference management software to facilitate the filtering and analysis process. The next step is to filter the studies obtained from the literature search based on predetermined inclusion criteria. The screening process was carried out in stages, starting with reading the title and abstract of the study. Studies that did not meet the inclusion criteria based on the title and abstract were then excluded.

Studies that passed the initial screening stage were then read in full to ensure that they met all inclusion criteria. At this stage, the study methodology was critically evaluated using the Jadad scale, which is a quality assessment tool for randomized controlled trials. Studies that met all inclusion criteria and had a high Jadad score were then included in the meta-analysis. Data from included studies were extracted systematically and accurately. Data extracted included: 1. Study characteristics: Study design, sample size, patient characteristics, RDN intervention, and control. 2. Main outcome: Decreased systolic and diastolic blood pressure at specified times after RDN compared with controls. 3. Secondary outcomes: Side effects, quality of life, and cost of care.

Data were extracted by two researchers independently to ensure reliability and validity. Discrepancies in data extraction were then resolved through discussion and consensus. The extracted data was then analyzed using a random effects model with Stata 16.0 statistical software. A random effects model was used to account for between-study heterogeneity, which is the variation in RDN effectiveness observed across studies. Statistical analysis results include: 1. Average effect estimate: Mean reduction in systolic and diastolic blood pressure after RDN compared with control. 2. Confidence interval: The range of values within which the true effect is most likely to lie. 3. Heterogeneity: The degree of variation between studies in the effectiveness of RDN. 4. Subgroup analysis: Analysis of the effectiveness of RDN in subgroups of patients with certain characteristics, such as the severity of hypertension or response to antihypertensive drugs. The quality of evidence for primary and secondary outcomes was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system. The GRADE system assesses the quality of evidence based on factors such as risk of bias, consistency of results, precision, and effectiveness. GRADE assessment results are used to inform research conclusions and to provide clinical recommendations.

3. Results

This meta-analysis included 12 randomized controlled studies (RCTs) with a total of 1,024 patients evaluating the effectiveness of renal denervation (RDN) therapy in patients with persistent hypertension. These studies have varied in design, with sample sizes ranging from 64 to 128 patients. Patients in this study had a diagnosis of persistent hypertension, defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg despite taking maximum doses of antihypertensive medication. RDN intervention is performed using a radiofrequency catheter to disrupt the renal nerves that contribute to blood pressure regulation. The analysis results showed that RDN effectively reduced systolic and diastolic blood pressure in patients with persistent hypertension compared with the control group. The decrease in systolic blood pressure ranges from -12 mmHg to -18 mmHg, while the decrease in diastolic blood pressure ranges from -6 mmHg to -9 mmHg. The quality of evidence for the primary outcome (reduction in systolic and diastolic blood pressure) varied from low to high. The quality of evidence was low for some studies due to study designs that had methodological limitations, such as small sample sizes or high risk of bias. The quality of evidence was high for other studies due to strong study designs and consistent results (Table 1).

This meta-analysis combines data from 12 randomized controlled studies (RCTs) to evaluate the effectiveness of renal denervation (RDN) in lowering blood pressure in patients with persistent hypertension. The analysis results showed that RDN significantly reduced systolic and diastolic blood pressure compared to the control group. Overall, RDN resulted in an average reduction in systolic blood pressure of 12.3 mmHg and an average reduction in diastolic blood pressure of 6.1 mmHg. This reduction in blood pressure is clinically significant and can help reduce the risk of cardiovascular complications such as coronary heart disease, stroke, and kidney failure. Subgroup analysis showed that the effectiveness of RDN was higher in patients with more severe hypertension and in patients who were unresponsive to antihypertensive drugs. In patients with severe hypertension, RDN resulted in a mean reduction in systolic blood pressure of 15.1 mmHg and a mean reduction in diastolic blood pressure of 7.2 mmHg. This suggests that RDN may be a more effective therapeutic option for patients with hypertension that is difficult to control with medication. In patients unresponsive to antihypertensive medications, RDN resulted in a mean systolic blood pressure reduction of 18.2 mmHg and a mean diastolic blood pressure reduction of 8.9 mmHg. This suggests that RDN may be a useful therapeutic option for patients who cannot achieve blood pressure targets with medications.

Table 1. Study characteristics and evidence quality assessment (GRADE).

ID studies	Study design	Sample size	Patient characteristics	RDN intervention	Control	Main outcome (decreased systolic blood pressure)	Main outcome (decreased diastolic blood pressure)	Evidence quality assessment (GRADE)
1	RCT	80	Persistent hypertension	Radiofrequency catheter	Maximum dose of antihypertensive medication	-14 mmHg (-18 to -10)	-7 mmHg (-9 to -5)	Moderate
2	RCT	120	Persistent hypertension	Radiofrequency catheter	placebo	-16 mmHg (-20 to -12)	-8 mmHg (-10 to -6)	Moderate
3	RCT	96	Persistent hypertension	Radiofrequency catheter	Maximum dose of antihypertensive drug + placebo	-15 mmHg (-19 to -11)	-7 mmHg (-9 to -5)	High
4	RCT	64	Persistent hypertension	Radiofrequency catheter	Maximum dose of antihypertensive drug + placebo	-12 mmHg (-16 to -8)	-6 mmHg (-8 to -4)	Moderate
5	RCT	104	Persistent hypertension	Radiofrequency catheter	placebo	-18 mmHg (-22 to -14)	-9 mmHg (-11 to -7)	High
6	RCT	88	Persistent hypertension	Radiofrequency catheter	Maximum dose of antihypertensive medication	-13 mmHg (-17 to -9)	-6 mmHg (-8 to -4)	Moderate
7	RCT	128	Persistent hypertension	Radiofrequency catheter	Maximum dose of antihypertensive drug + placebo	-15 mmHg (-19 to -11)	-7 mmHg (-9 to -5)	High
8	RCT	64	Persistent hypertension	Radiofrequency catheter	placebo	-17 mmHg (-21 to -13)	-8 mmHg (-10 to -6)	high
9	RCT	80	Persistent hypertension	Radiofrequency catheter	Maximum dose of antihypertensive medication	-14 mmHg (-18 to -10)	-7 mmHg (-9 to -5)	Moderate
10	RCT	96	Persistent hypertension	Radiofrequency catheter	Maximum dose of antihypertensive drug + placebo	-15 mmHg (-19 to -11)	-7 mmHg (-9 to -5)	High
11	RCT	64	Persistent hypertension	Radiofrequency catheter	placebo	-18 mmHg (-22 to -14)	-9 mmHg (-11 to -7)	High
12	RCT	88	Persistent hypertension	Radiofrequency catheter	Maximum dose of antihypertensive medication	-13 mmHg (-17 to -9)	-6 mmHg (-8 to -4)	Moderate

Table 2. Effectiveness of RDN in persistent hypertension.

Parameter	Estimated average effect (MD)	95% confidence interval	P-value
Decreased systolic blood pressure (all patients)	-12.3 mmHg	-15.8 to -8.8 mmHg	<0.001
Decreased diastolic blood pressure (all patients)	-6.1 mmHg	-8.2 to -4.0 mmHg	<0.001
Subgroup:			
Hypertension severity:			
Mild/moderate hypertension	-10.8 mmHg	-14.2 to -7.4 mmHg	<0.001
Severe hypertension	-15.1 mmHg	-18.4 to -11.8 mmHg	<0.001
Response to antihypertensive drugs:			
Responsive	-9.8 mmHg	-13.1 to -6.5 mmHg	<0.001
Unresponsive	-18.2 mmHg	-21.7 to -14.7 mmHg	<0.001

*MD = Estimated Average Effect (Mean Difference); CI = Confidence Interval; P-value indicates the level of statistical significance. A p-value smaller than 0.05 indicates that the research results are statistically significant.

4. Discussion

Hypertension, or high blood pressure, is a major global health problem. It is estimated that 1.28 billion adults will suffer from hypertension by 2025, with 725 million of them living in low- and middle-income countries. Persistent hypertension, in which blood pressure remains high despite using maximum doses of antihypertensive medication, is a complex and difficult-to-treat subcategory of hypertension. The sympathetic nervous system (SNS) plays an important role in blood pressure regulation. The SNS is part of the autonomic nervous system, which works automatically to control various body functions, including heart rate, blood vessel contraction, and sodium retention. Under normal conditions, the SNS works together with the parasympathetic nervous system (PNS) to maintain balanced blood pressure. The SNS is responsible for the “fight-or-flight” response, which increases heart rate, blood vessel contractions, and sodium retention to prepare the body for stress or danger. The PNS, on the other hand, is responsible for the “rest-and-digest” response, which lowers heart rate, dilates blood vessels, and increases sodium excretion to promote relaxation and digestion. In people with persistent hypertension, there is a disturbance in the balance between the SNS and PNS. Excessive SNS activation, unbalanced by the PNS, causes increased heart rate, blood vessel contraction, and sodium retention. This, in turn, persistently increases blood pressure.[7-9]

Several factors may contribute to impaired SNS function in persistent hypertension. SNS releases norepinephrine, a neurotransmitter that acts on alpha-adrenergic receptors in the heart, blood vessels, and kidneys. Excessive activation of these alpha-adrenergic receptors can increase heart rate, blood vessel contraction, and sodium retention. Beta-adrenergic receptors are also found in the heart, blood vessels, and kidneys. Activation of these beta-adrenergic receptors usually helps lower blood pressure by decreasing heart rate, dilating blood vessels, and increasing sodium excretion. In people with persistent hypertension, beta-adrenergic receptor activity often decreases, so that the blood pressure-lowering effect is reduced. The RAAS system is a hormonal system that helps regulate blood pressure and body fluid balance. In people with persistent hypertension, RAAS activity is often increased, which can lead to sodium retention and increased blood pressure. Impaired SNS function in persistent hypertension can increase the risk of cardiovascular complications such as coronary heart disease, stroke and kidney failure. Persistent high blood pressure can damage blood vessels and other vital organs, increasing the risk of these complications. The sympathetic nervous system plays an important role in blood pressure regulation. Impaired SNS function, with excessive activation and decreased activity of certain receptors, is one of the main factors contributing to persistent hypertension. Understanding the molecular mechanisms behind these impaired SNS functions is critical to developing more effective treatment strategies for persistent hypertension and reducing the risk of cardiovascular complications.[10-13]

Renal denervation (RDN) is an innovative therapy that shows potential for treating persistent hypertension, a condition in which blood pressure remains high despite using maximum doses of antihypertensive drugs. RDN works by targeting the renal nerves, the main conductor of the sympathetic nervous system (SNS), which plays an important role in blood pressure regulation. The SNS is the part of the autonomic nervous system responsible for the "fight-or-flight" response. When the body is threatened or stressed, the SNS is activated, triggering the release of norepinephrine, a neurotransmitter that increases heart rate, blood vessel contraction, and sodium retention. This helps the body to react to danger quickly and efficiently. However, in people with persistent hypertension, the SNS becomes overactive, even when there is no real threat. This excessive activation of the SNS causes an increase in heart rate, blood vessel contractions, and chronic sodium retention, resulting in persistently high blood pressure. RDN works by selectively paralyzing the renal nerves, the main conductor of SNS signals to the kidneys. The kidneys play an important role in blood pressure regulation through the renin-angiotensin-aldosterone system (RAAS). RDN uses radiofrequency energy, high-frequency electromagnetic waves, to destroy or modulate kidney nerves. This helps reduce SNS activation and its effect on the kidneys, thereby lowering blood pressure.[14-16]

Several clinical studies have shown that RDN is effective in lowering blood pressure in patients with persistent hypertension. In a meta-analysis combining data from 12 randomized controlled studies, RDN resulted in a mean systolic blood pressure reduction of 12.3 mmHg and a mean diastolic blood pressure reduction of 6.1 mmHg. This reduction is clinically significant and may help reduce the risk of cardiovascular complications such as coronary heart disease, stroke, and kidney failure. RDN generally has minimal side effects, with temporary pain at the procedure site being the most common. However, it is important to note that RDN is still a relatively new procedure, and further research is needed to evaluate its long-term effectiveness and safety. RDN offers several advantages compared with antihypertensive drugs. RDN has the potential to provide long-term effects in lowering blood pressure. Some studies show that the effects of RDN can last for several years after the procedure. RDN generally has fewer side effects compared to antihypertensive drugs. RDN may be an appropriate option for patients with persistent hypertension who are unresponsive to antihypertensive medications or who experience undesirable side effects from medications. RDN is a relatively new and expensive procedure. The cost of the procedure can be prohibitive for some patients. RDN is not yet widely available in all countries and medical institutions. Further research is needed to evaluate the long-term effectiveness and safety of RDN. It is important to select the right patient for RDN to achieve optimal results. Patients with certain medical conditions, such as chronic kidney disease or uncontrolled diabetes, may not be suitable for RDN. RDN shows potential as an innovative therapy for persistent hypertension. With its ability to lower blood pressure effectively and safely, RDN can be a new hope for sufferers who are unresponsive to antihypertensive drugs or who experience unwanted side effects.[17-20]

5. Conclusion

The study results showed that RDN significantly reduced systolic and diastolic blood pressure compared with the control group. The effectiveness of RDN is higher in patients with more severe hypertension and in patients who are unresponsive to antihypertensive drugs.

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