

Review Article

Renal denervation- its current status & future prospects for management of Hypertension

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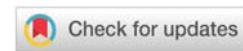
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Introduction

Hypertension is one of the major contributing factor for global burden of cardiovascular morbidity and mortality. It was estimated that 1.13 billion people were affected worldwide and most of them are residing in low and middle income countries [1]. Hypertension was strongly associated with coronary artery disease, cerebrovascular events and peripheral artery disease. The pathogenesis of hypertension is multifactorial and sympathetic nervous system hyperactivity is one of the contributing factor for development and poor control of blood pressure [2]. Oral medications are the mainstay of therapy for hypertension but however around 50% of patients were non adherent to prescribed medication at 1 year follow up [3]. Despite the availability of multiple classes of effective drugs for treatment of Hypertension a large number of patients were not attaining the recommended blood pressure goals. There were multiple reasons for the poor control of Blood pressure like drug non adherence, drug resistance and improper treatment protocols. We need more complementary alternative treatment modalities for effective treatment of Hypertension [4]. The Renal denervation was one such therapy which was done with various energy sources like Radiofrequency energy, ultrasound energy ablation or chemical ablation with Alcohol [4]. Activation of renal efferent nerves leads to renal artery vasoconstriction, reduced renal blood flow there by leading to activation of renin angiotensin system with increased renin secretion and salt and water retention [4,5]. The stimulation of renal afferent nerves leads to activation of central sympathetic activity there by leading to adverse cardio metabolic systemic effects. The renal denervation allows ablation of both efferent and afferent sympathetic nerves there by leading to reduced

sympathetic drive to and from the renal arteries [6]. Such procedures if done effectively and with long term good follow up results are likely to prevent the target organ damage and the possible cardiovascular events secondary to uncontrolled hypertension. The outcomes would also not be dependant on individual patient drug compliance and would also avoid side effects of the medication.

Evolution of renal denervation

The Renal denervation therapy has provided much hope with initial SYMPLICITY HTN1 AND 2 trials [7,8] with double digit blood pressure reduction in office BP, but the sham controlled SYMPLICITY HTN 3 [9], trial did not provide any added advantage with RDN when compared with medical therapy alone [10]. Post hoc analysis of the SYMPLICITY HTN 3 trial found that several limitations like inadequate ablation technique, frequent uncontrolled changes in prescribed medication and heterogeneity of operator experience in ablation techniques had hampered the benefits of the RDN [10,11].

The resurgence of RDN – the new technical principles of ablation

Since then learnings from shortcomings of SYMPLICITY HTN 3 trial, with improved study designs, redesigned ablation catheters and more homogenous population newer trials were initiated to re-evaluate RDN for Hypertension. With careful analysis of the nerve innervation patterns in animal models we now know that we need to target distal renal artery branches rather than proximal bigger vessels and also need to ablate at multiple sites within arteries in a helical manner rather than

circumferentially at a single level. This has become possible now as the newer ablation catheters because of their modified designs can be deployed over a thin a guide wire and will become helical once the guide wire is withdrawn before delivering radio frequency energy for ablation.

RDN – Newer clinical trials

Spiral HTN on med study: The results of the recently published studies were encouraging as they showed a realistic consistent reduction of blood pressure. The SPIRAL HTN ON MED study randomised patients who were already on antihypertensive drugs to either RDN or sham procedure .At the end of 6 months the RDN arm group showed a 7.4 mmHg BP reduction in ambulatory BP and 6.8 mmHg reduction in Office Blood pressure [12].

The spiral HTN Off med study: This study included patients who were drug naive to either RDN or sham procedure. At 3 months follow up there was a 7.7 mmHg reduction in office systolic Blood pressure and 5 mm Hg reduction in 24 hr Ambulatory BP [13].

The radiance - HTN solo study: This study randomised hypertensive patients to either RDN with Ultrasound energy or Sham procedure . At 2 months follow up ambulatory BP was reduced by 6.3 mmHg and 6.5 mmHg reduction in office Blood pressure. At 6 moths follow up also RDN group had a sustained reduction in blood pressure and RDN group patients were on fewer number of anti hypertensive drugs when compared to sham procedure [14]. These newer studies established the efficacy and safety of RDN in low risk uncomplicated patients with very low incidence of procedure related complications like new renal artery stenosis which was seen only in 0.3% of patients after RDN.

Global simplicity registry: This registry observed that there was consistent reduction in blood pressure in the range of 8.6 to 10.4 mm Hg seen across all high-risk subgroups, including those with resistant hypertension ,older patients , type 2 diabetes, isolated systolic hypertension, chronic kidney disease, and Atrial-fibrillation ($P < 0.0001$ for all). The sustained reductions were seen in patients at all baseline levels of atherosclerotic cardiovascular disease (ASCVD) risk scores. The investigators divided patients according to baseline ASCVD risk ($< 10\%$, 10% to $< 20\%$, and 20% or more) and found that BP declined after denervation in all of the groups. At 3 years, the drops in 24-hour systolic BP were 8.6, 6.0, and 7.6 mm Hg across the three risk groups, respectively.This registry data also proved that renal denervation had achieved a sustained,modest systolic BP reduction among real world populatio [15]. A decrease of 10 mmHg in office BP is related to a relative risk reduction for total mortality of 13%,cardiovascular diseases of -17%, heart failure of -28%, and cardio vascular event rate of -20% [16].

Radiance-HTN trio and require trials: These two randomised studies are underway to assess the safety and efficacy of ultrasound based RDN in patients with uncontrolled HTN [17].

Future prospects

Methods to assess effective ablation post procedure: We need to have reliable methods to test the adequacy of RDN procedure on table, so that results will be uniform and reproducible across spectrum of all patients. This is an active area for further research .Various methods had been proposed like direct neural stimulation with selective ablation of pressor sites, reflex elicitation before and after RDN during the index procedure ,and passive monitoring like renal Norepinephrine spillover [18]. Animal studies had shown that regrowth of both afferent and efferent renal sympathetic nerves after RDN there by evading the benefits of RDN [19]. The long term sustainability of benefits of RDN needs to be studied further in human trials .The device based therapies like RDN with Radio-frequency or Ultrasound based ablation therapies will soon be incorporated in to wide spread clinical practice. But the number of issues remain to be determined, like optimal location of ablation sites , energy dosage, penetration depth as well as long-term outcome and efficacy.

Methods to assess hypertensive patient responders immediately and on long term follow up: We should try & identify newer parameters to determine as to which patient will respond to RDN therapy immediately and why some patients have a delayed response to RDN. It is not clear if functional re-innervation occurs after RDN and how this might affect the BP response. Furthermore research is needed to provide evidence of the effectiveness of RDN treatment for heart failure, insulin resistance, obstructive sleep apnea, atrial fibrillation, end-stage renal disease and mild-resistant hypertension. Finally, further research is warranted to provide data on the effect of RDN on morbidity and mortality in patients with resistant hypertension or other diseases [6]. However the optimum patient selection, renewed devices ,adequate renal nerve ablation techniques, adequate training of operators, cost effectiveness and long term durability of the results are the key to success of resurgence of RDN.

Summary

The results of recent sham controlled trials were promising in reducing the blood pressure in Hypertensive patients. The Device based therapies for Hypertension needs further validation in a large group of selected patients to unfold the true future potential of these therapies.RDN therapy is currently to be done only in select group of patients with compassionate grounds and is not recommended temporarily for routine clinical use.

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