INFORMATION BRIEF (RAPID REVIEW)

Interventional Renal Denervation for Resistant Hypertension

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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TITLE: INTERVENTIONAL RENAL DENERVATION FOR RESISTANT HYPERTENSION

PURPOSE

To review the evidence on effectiveness, safety and cost-effectiveness of interventional renal denervation for resistant hypertension based on request from Director of Medical Practice Division, Ministry of Health Malaysia following a proposal from National Heart Association of Malaysia (NHAM) to include the procedure in *Jadual ke-13 Perintah Kemudahan dan Perkhidmatan Jagaan Kesihatan Swasta*.

BACKGROUND

Hypertension is defined in the Malaysian Clinical Practice Guidelines on Management of Hypertension (Fifth Edition) as persistent elevation of systolic blood pressure (BP) of 140 mmHg or greater and/or diastolic BP of 90 mmHg or greater, taken at least twice on two separate occasions.[1] Resistant hypertension (RH) refers to uncontrolled hypertension (>140/90 mmHg) in individuals with good medication adherence despite on three or four antihypertensive agents including a diuretic in adequate doses.[2] A recent meta-analysis found the prevalence of resistant hypertension among patients with arterial hypertension was between 10 – 15%.[3] Patients with hypertension in general are at increased risk for cardiovascular disease, stroke and chronic renal diseases.[4] Those with RH had approximately 47% higher risk of getting cardiovascular events compared with those with controlled hypertension.[5]. Based on a few large scale RCTs on pharmacologic reduction in BP for primary and secondary prevention of cardiovascular diseases, results showed that the risk of developing cardiovascular events decreased by 10% for each 5-mmHg reduction in systolic BP. Sympathetic nervous system plays a crucial role in the pathogenesis of RH as shown in several studies.[6; 7] Chronic activation of the sympathetic nervous system and renal sympathetic nerve activity leads to increased level of catecholamine spillover that has been linked to RH.[7]

Since the introduction of renal denervation, a decade ago, the intervention has been proposed as a treatment option for treating hypertension when hypertension remains uncontrolled despite antihypertensive therapy and lifestyle changes. Since then, there have been numerous studies that evaluate the efficacy and safety of interventional with variable results.

Renal denervation can be done through a few techniques; radiofrequency ablation of the main renal artery only; radiofrequency ablation of the main renal artery, branches, and accessories and ultrasound-based ablation of the main artery etc. Renal denervation procedure uses catheter-based radiofrequency of ultrasound energy to ablate the sympathetic nerves in the renal arteries that may contribute to RH. The rationale behind this procedure is a decrease in efferent and afferent renal signaling will reduce norepinephrine spillover, increase blood flow and lower plasma renin activity.[7]

A few guidelines have been recommending renal denervation as one of the treatment options for RH. The 2021 European Society of Hypertension position paper states that renal denervation is an evidence-based options to treat hypertension in addition to pharmacological therapy and lifestyle modification.[8] A consensus statement on renal denervation developed by the Malaysian Renal Nerve Denervation Working Group in 2022 recommends renal denervation as one of the treatment options for those with RH.[9]

EVIDENCE SUMMARY

A total of eighty-nine articles were retrieved from scientific databases of Medline and PubMed, general search engine (Google Scholar) and reference list on renal denervation using the following search terms "resistant hypertension, drug resistant, renal denervation, and interventional renal denervation". The last search was done on 20 October 2022. A total of seven studies were included in this review which consisted of one network meta-analysis, two systematic review and meta-analyses and four randomised controlled trials (RCTs). A total of six studies were on adults with resistant hypertension while one network meta-analysis was on mixed populations of uncontrolled and RH. There were no local evidence on cost-effectiveness of renal denervation, however two cost-effectiveness studies from other countries were included in this review.

EFFICACY/ EFFECTIVENESS

Silverwatch J et al. conducted a network meta-analysis on the efficacy and safety of renal denervation for adults >18 years old with uncontrolled and RH. Twenty randomised controlled trials (RCTs) with moderate quality were included, in which 75% of included studies (15/20) were on RH. The interventions included in this review were radiofrequency in main renal artery, radiofrequency in main renal artery and branches, radiofrequency in main renal artery plus antihypertensive therapy, ultrasound in main renal artery, sham and antihypertensive therapy alone. The results showed that radiofrequency in main renal artery and branches ranked as the best treatment to reduce 24-h ambulatory, daytime and nighttime systolic BP and diastolic BP and when compared with other interventions (p-scores: 0.83 to 0.97) in patients with uncontrolled and RH.[10]

A Cochrane systematic review of 15 RCTs published in 2021 evaluated the short- and long-term effects of renal denervation in adults with RH. In the review, a moderate-certainty of evidence suggested that renal denervation significantly reduced systolic 24-hour ambulatory blood pressure monitoring (ABPM) (MD= -5.29 mmHg, 95% CI -10.46 to -0.13); diastolic 24-hour ABPM (MD= -3.75 mmHg, 95% CI -7.10 to -0.39) and office diastolic BP (MD= -4.61

mmHg, 95% CI -8.23 to -0.99) compared with sham/standard therapy. However, renal denervation showed no difference in office systolic BP in the same comparison (MD -5.92 mmHg, 95% CI -12.94 to 1.10). Renal denervation had no tangible effects on serum creatinine levels (MD 0.03 mg/dL, 95% CI -0.06 to 0.13) and renal function as estimated by eGFR or creatinine clearance (MD -2.56 mL/min, 95% CI -7.53_to 2.42) when compared with controls with moderate-certainty evidence. Low-certainty evidence showed that renal denervation was also not significantly associated with a lower risk of; myocardial infarction (RR=1.31, 95% CI 0.45 to 3.84); ischaemic stroke (RR=0.98, 95% CI 0.33 to 2.95) and unstable angina (RR=0.51, 95% CI 0.09 to 2.89) compared with controls. The authors concluded that moderate-certainty evidence exists that renal denervation may improve 24h ABPM and diastolic office-measured BP in patients with RH. However, there is low-certainty evidence that renal denervation does not improve major cardiovascular outcomes (myocardial infarction, ischaemic stroke, unstable angina) and renal function.[11]

A systematic review and meta-analysis by Agasthi P et al. looked at the efficacy of renal denervation on blood pressure and renal function in patients with RH as compared with medical therapy ±sham procedure six months post-randomisation. Fifteen RCTs were included in the meta-analysis in which two third of the included studies were open-label clinical trials with control group treated with optimal medical therapy while the remaining five studies were double blinded RCTs with sham controls. The overall quality of the included studies was high based on the Jadad scale except for one study. The results showed that renal denervation in patients with RH did not significantly change both the systolic and diastolic blood pressure (office) at six month as compared with control groups (medical therapy ± sham control). They also found there was no significant changes in renal function (estimated glomerular filtration rate) between renal denervation group and controls.[12]

A recently published RCT by Kario K et al. (REQUIRE trial) was the first trial of ultrasound renal denervation in Asian patients. It was a multicentre, single-blind trial conducted in Japan and South Korea. The inclusion criteria were adults aged 20 – 75 years and had RH with maximum tolerated dosages of at least three antihypertensive drugs including a diuretic in the period between 17 January 2017 and 31 March 2020. There were no standardisation of regimen or requirement for a fixed drug combination. A total of 143 patients were randomised (72 in the renal denervation group; 71 in the sham control group). However, only 69 patients in the renal denervation group and 67 patients in the sham control group were included in the final analysis. The participants were blinded to treatment until six months after the procedure, but the treating physicians and coordinators were not blinded. They found no statistical significance change in 24-hour ambulatory systolic BP (MD= -0.1, 95% CI -5.5 to 5.3) and office systolic BP (p=0.488) between catheter-based ultrasound renal denervation and sham procedure in patients with RH at three months follow-up. It is worth mentioning that medication adherence was not measured objectively in this trial and there was no standardisation of medications which may cause variability in BP outcomes. These issues in the setting of RH may cause confounding of results.[13]

An RCT published in 2021 compared ultrasound renal denervation with a triple medication pill (RADIANCE-HTN TRIO) in patients with RH. The trial took place at 28 tertiary centres in the USA and 25 in Europe. The inclusion criteria were adults aged 18 - 75 years with RH (BP >140/90 mmHg despite on ≥ three antihypertensive medications including a diuretic). Selected participants were switched to a single-pill, fixed-dose, daily combination of amlodipine (or 5 mg in the event of severe leg oedema), valsartan 160 mg (or olmesartan 40 mg) and hydrochlorothiazide 25 mg. No other antihypertensive medications were allowed except β blockers for chronic coronary syndrome or heart failure. Both patients and clinicians involved in follow-up care were masked to treatment allocation for six months after random assignment. Renal denervation significantly reduced daytime ambulatory systolic blood pressure (p=0.022) and 24-hour ambulatory systolic blood pressure (p=0.016) at two months compared with sham controls.[14]

After seven years, the randomised Oslo study that investigated the efficacy of renal denervation vs antihypertensive drug adjustments in patients with RH showed that there was no difference between the groups in office systolic blood pressure over time. However, the number of participants included in the analysis were small numbers [renal denervation (n=9), drug adjustments (n=10)]. The results were analysed using per protocol approach; hence introducing potential bias due to exclusion of patients.[15]

Types of renal denervation

A recent three-arm RCT of different renal denervation devices and techniques demonstrated that ultrasound-based renal denervation showed significant improvement in blood pressure as compared with combined approach of radiofrequency ablation of the main arteries, accessories, and side branches in patients with resistant hypertension three months post-intervention. However, there was no significant difference in blood pressure reduction between resistant hypertension patients treated with ultrasound-based ablation and radiofrequency ablation of the main renal arteries.[16]

SAFETY

Meta-analysis of two RCTs in a review by Silverwatch J et al. showed that there were no significant differences on serious adverse events between renal denervation (radiofrequency of main renal artery ± branches, radiofrequency of main renal artery + antihypertensive therapy) vs sham control.[10]

Pooled data from three RCTs in a Cochrane systematic review revealed that renal denervation was significantly associated with higher risk of bradycardia symptoms than sham/standard treatment (RR=6.63, 95% CI 1.19 to 36.84). In a separate meta-analyses, renal denervation was not statistically associated with a higher risk for femoral artery pseudoaneurysm, plank pain, hypotensive episodes, hypertensive crisis and hyperkalaemia than sham/standard therapy.[11]

Kario et al. reported that there was no procedure-/device-related major adverse events. The most common clinical events reported were procedure-related pain lasting for >2 days (e.g. back pain, puncture site pain etc.).[13]

An RCT by Azizi M et al. showed no significant difference in safety outcomes between renal denervation and sham controls in resistant hypertension patients.[14]

The randomised Oslo study found that there were no long-term complications of the renal denervation procedure, and no functional or anatomical renal injury in both intervention and control groups.[15]

COST-EFFECTIVENESS

There was no local evidence retrieved on the cost-effectiveness of renal denervation in RH. However, there were two cost-effectiveness study conducted in Netherlands and Australia in 2015 and 2018 respectively.

Chowdhury EK et al. constructed a Markov model to simulate cardiovascular events over a lifetime among 60-year-old patients with RH without prior cardiovascular disease. The effect on lowering blood pressure was based on findings from previous renal denervation clinical trials, and the expected subsequent change in cardiovascular risk was derived from a published meta-regression. The cost and utility data were obtained from publicly available sources. Using the Australian health care perspective, with a willingness-to-pay threshold of AUD 50,000, the model predicted that renal denervation would be cost-effective only if it was targeted to patients with a 10-year predicted cardiovascular risk of at least 13.2% (AUD 9531/€6573, 1€ = 1.45 AUD) over a lifetime horizon.[17]

Henry TL et al. conducted cost-effectiveness study using Markov state-transition model relevant to Dutch setting for catheter-based renal denervation in the treatment of RH from the perspective of the healthcare payer in The Netherlands. The efficacy of renal denervation was modeled as a reduction in the risk of cardiovascular events (stroke, myocardial infarction, coronary heart disease, heart failure, end-stage renal failure, cardiovascular mortality, and all-cause mortality) associated with a lower systolic BP. An existing cost-effectiveness model based on data from the HTN-2 trial was used to examine the cost-effectiveness of renal denervation in this study. The results showed that treatment with renal denervation gave an incremental quality-adjusted life year (QALY) gain of 0.89 at an additional cost of €1315 over a patient's lifetime when compared with standard care. The incremental cost effectiveness ratio (ICER) was €1474. Treatment with renal denervation was demonstrated to be cost-effective at traditional willingness-to-pay levels (E10,000-80,000/QALY) using deterministic and probabilistic sensitivity analyses (PSA).[18]

CONCLUSION

The evidence retrieved showed some inconsistency in terms of improving blood pressure in patients with RH with some showed modest improvement while others showed no difference when compared with sham/standard therapy (pharmacological therapy). There is moderate-certainty evidence suggesting that renal denervation in RH have some effects on both systolic and diastolic 24-hour ABPM, however, there were no difference in terms of cardiovascular outcomes and renal function between the two groups. The renal denervation procedures are safe as there were no significant side effects of renal denervation as evident in the studies before this.

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