Effectiveness of Renal Denervation for Treatment of Resistant Hypertension: an Evidence-based Case Report

Minarma Siagian¹, Aldo Ferly², Arinna Irianti², Arky Kurniati², Florence Low², Ras A. Riza²

¹ Department of Physiology, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
² Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

Correspondence mail:
Department of Physiology, Faculty of Medicine Universitas Indonesia. Jl. Salemba 6, Jakarta 10430, Indonesia.
email: minarma2001@yahoo.com.

ABSTRACT

Aim: to determine whether the renal sympathetic – nerve ablation method is more effective compared to multiple anti – hypertensive drug among patients with resistant hypertension. Methods: a search was conducted on PubMed. The selection of title and abstract was conducted using inclusion and exclusion criteria, which led to five relevant articles. The selected studies were critically appraised for its validity, importance and applicability. Results: one of studies showed that renal denervation is not effectively reduced blood pressure in patients with resistant hypertension; nevertheless other studies showed significant results. Conclusion: literature with strongest evidence showed that there is no relationship between renal sympathetic-nerve ablation procedure and reduction of blood pressure. However, as there is still some methodological flaw on the literature, we recommend doing another study that may find the appropriate results.

Key words: renal denervation, resistant hypertension.
INTRODUCTION

The increasing rate of the aging population in Indonesia leads to an increase in the number of hypertensive patients. In clinical practice, it is estimated that 10% of hypertensive patients are suffering from resistant hypertension. Resistant hypertension is defined as systolic blood pressure that is higher than 140 mmHg even though they consume three maximally tolerated antihypertensive medication class, including diuretics at an appropriate dose. There are many complications of resistant hypertension such as left ventricular hypertrophy, increased incidence of retinal hemorrhage and kidney damages.

Pharmacological treatment for resistant hypertension is currently available. However, the effectiveness of pharmacological treatment for resistant hypertension is low. Many failure of this pharmacological therapy is mainly attributed to low-adherence of pharmacological therapy. In which patient do not realize the seriousness of this asymptomatic disease and do not consume anti-hypertensive drug routinely. New approach in form of therapeutic intervention may be needed.

Renal denervation is based on a hypothesis that essential hypertension is caused by an elevated rate of norepinephrine spillover, the number of norepinephrine that is not taken by neuronal uptake and distributed to general circulation. The first proof-of-concept experiment involving ablation of sympathetic nerve was done by Schlaich in 2009. This experiment reduced blood pressure from 161/107 mmHg to 127.81 mmHg.

CASE ILLUSTRATION

A 57 years old man came to our clinic for a general medical check up. He did not have any complaints. However, during physical examination we found that his blood pressure is 152/94. From his medical records, he has consumed three different hypertensive drugs: captopril 25 mg 3 times a day, hydrochlorothiazine 25 mg twice a day and amlodipine 10 mg once a day. At first, we thought that this patient has a compliance problem. However, his wife reassured us that he was compliant in consuming his anti-hypertensive drugs. Having heard renal denervation procedure that can reduce blood pressure in patient with resistant hypertension, we were wondering whether this procedure can be done in patient.

CLINICAL QUESTION

In a population with resistant hypertension, does renal sympathetic-nerve ablation effective in reducing blood pressure compared to people that only get combined- anti-hypertensive drugs?

METHODS

A search of PubMed® was performed on May 29th, 2014 using the key words “renal denervation”, “resistant hypertension”, “treatment” with its synonyms and related terms. A search Cochrane® was also attempted using the same key words. The results were not included since only 2 articles were found, which were already on the PubMed® list.

Search strategy, results, the inclusion and exclusion criteria are shown in the flowchart. They were articles on clinical trials, systematic reviews, published within 5 years, and performed on humans. After literature selection, critical appraisal was done using several aspect based on Center of Evidence-Based Medicine, University of Oxford for therapy study (Table 1 and Table 2).

RESULTS

This evidence-based case report will review the effectiveness of renal denervation in reducing blood pressure of patients with resistant hypertension. The primary endpoint was reduction of blood pressure compared to baseline at 6 months follow-up.

From the search criteria mentioned above, 13 journals met the inclusion and exclusion criteria. Through further selection process, five studies, which included two RCTs, two cohorts, and one systematic review, were eligible for this evidence-based case report. All included trials were appraised for its validity and relevance (Table 1 and Table 2). The summary of all included studies are depicted in Table 3.

Four articles discussed populations with resistant hypertension while Ott et al investigated patients with moderate-resistant hypertension.
Online database searching using key words "renal denervation", "resistant hypertension", and "treatment"

Addition of filters
- clinical trial
- systematic review
- published within 5 years
- study on human

359 articles found from PubMed

38 articles found

13 fulltext studies assessed for eligibility

26 of records were excluded

1 article is excluded due to trial is still ongoing

11 studies assessed for validation

6 articles excluded

5 studies included

Figure 1. Flow chart of search strategy

Table 1. Critical appraisal of the 10 studies based on criteria by centre of evidence medicine University of Oxford

<table>
<thead>
<tr>
<th>Articles</th>
<th>Year</th>
<th>Study design</th>
<th>Number of Patients</th>
<th>Randomization</th>
<th>Similarity &amp; Treatment &amp; Control</th>
<th>Blinding</th>
<th>Comparable Treatment to Intention to Treat</th>
<th>Domain</th>
<th>Determinant</th>
<th>Measurement of Outcome</th>
<th>Levels of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatt et al⁶</td>
<td>2014</td>
<td>RCT</td>
<td>535</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Krum et al⁷</td>
<td>2014</td>
<td>cohort</td>
<td>88</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Ott et al⁸</td>
<td>2013</td>
<td>cohort</td>
<td>54</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Esler et al⁹</td>
<td>2010</td>
<td>RCT</td>
<td>106</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>2</td>
</tr>
</tbody>
</table>

+ stated clearly in the article; - not being done; ? not stated clearly; * levels of evidence based on The Oxford Center of Evidence Based Medicine 2011

Table 2. Critical appraisal of a systematic review

<table>
<thead>
<tr>
<th>Authors</th>
<th>PICO</th>
<th>Appropriate searching</th>
<th>Relevant study included</th>
<th>Quality assessment of trials</th>
<th>Heterogeneity</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al¹⁰</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3</td>
</tr>
</tbody>
</table>

Based on the literature, resistant hypertension is defined as systolic blood pressure of at least 160 mmHg, to be taking maximally tolerated doses, one of which had to be a diuretic at an optimum dose, while moderate-resistant hypertension is defined as office BP ≥140/90 mmHg and <160/100 mmHg with at least 3 anti-hypertensive drugs, including a diuretic, in adequate dose.⁶-¹⁰ Studies by Bhatt et al, Esler et al, Ott et al, and Davis et al had a follow-up period for 6 months, whereas Krum et al assessed the trials for 36 months.
### Table 3. Results of all studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Primary Endpoint</th>
<th>Result</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatt et al</td>
<td>Reduction of blood pressure compared with baseline at 6 months</td>
<td>Decrease in SBP* of -14.13±23.93 mmHg in the denervation group compared to -11.74</td>
<td>Reduction of blood pressure after 6 months post-renal denervation is neither clinically significant nor statistically significant.</td>
</tr>
<tr>
<td>Krum et al</td>
<td>Reduction of blood pressure from baseline within 36 months</td>
<td>Mean reduction (95% CI) in systolic and diastolic blood pressure from baseline, p&lt;0.01:</td>
<td>Significant reduction of blood pressure of blood pressure within 36 months.</td>
</tr>
</tbody>
</table>
| Ott et al    | Blood pressure reduction in moderate hypertension patient after 6 months post renal denervation therapy | 1. Office BP  
   - At baseline in 54 patients: Systolic (151 ± 6 mmHg), Diastolic (83 ± 11 mmHg)  
   - Three months post RDN: Systolic (146 ± 23 mmHg, p = 0.164), Diastolic (79 ± 12 mmHg, p = 0.011)  
   - Six months post RDN: Systolic (138 ± 21 mmHg, p < 0.001); Diastolic (75 ± 11 mmHg, p < 0.001)  
2. 24-h ABPM (n = 36)  
   - at baseline: Systolic (151 ± 5 mmHg); Diastolic (84 ± 10 mmHg)  
   - Three months post RDN: Systolic (142 ± 20 mmHg, p = 0.012); Diastolic (79 ± 11 mmHg, p = 0.003)  
   - Six months post RDN: Systolic (133 ± 19 mmHg, p < 0.001); Diastolic (75 ± 11 mmHg, p < 0.001) | Significant reduction of office and 24-h ambulatory BP in patients with moderate treatment of resistant hypertension after 6 months post RDN. |
| Esler et al  | Reduction of blood pressure compared to non treated patient with baseline at 6 months | 1. 3 months: therapy group → Office BP was reduced from baseline by 32/12 mm Hg (SD 23/11, p<0.0001); Control group → Office BP was reduced from baseline by 1/0 mm Hg [21/10], p=0.77 systolic and p=0.83 diastolic | Reduction of blood pressure of blood pressure after 6 months. This randomised controlled trial is statistically significant |
| Davis et al  | Reduction of blood pressure in controlled and uncontrolled studies at 6 months   | 1. 12 studies included: 4 controlled studies, uncontrolled studies  
2. MA* of controlled study showed significant decrease in both systolic and diastolic blood pressure (SBP and DBP): Mean difference of SBP at 3 month follow-up → -20.82 (95%CI -26.41, -15.24), Mean difference of SBP at 6 month follow-up → -28.90 (95%CI -37.20, -20.60)  
3. MA of uncontrolled studies also showed significant decrease in both SBP and DBP: Mean difference of SBP at 3 month follow-up → -22.79 (95%CI -26.83, -18.76), Mean difference of SBP at 6 month follow-up → -25.01 (95%CI -29.92, -20.09) | Renal denervation therapy resulted in substantial reduction in mean BP at 6 months in patient with resistant hypertension |

*Abbreviations: ABPM (Ambulatory Blood Pressure Monitoring); SBP (Systolic Blood Pressure); DBP (Diastolic Blood Pressure); MA (Meta Analysis)
Study by Bhatt showed no significant reduction of blood pressure in post renal denervation therapy, however, other studies concluded the contrary results.6-10

DISCUSSION

Since the inception of renal denervation, this method has been hailed as a novel way to combat resistant hypertension.4 It is a relatively new finding, in which proof of concept study was done in 2009 by Schlach.5 Even though it is a relatively new study, as many as 4 RCT and cohort studies and one systematic reviews (Table 2) were found in this topic. This may be caused by high prevalence and morbidity that may be caused by resistant hypertension.2

From five studies that we analyzed in this EBCR, we found two cohorts and one RCT that found that renal denervation procedure effectively reduce both systolic and diastolic blood pressure. The reduction of systolic blood pressure ranged from 10 mmHg to 32 mmHg.7,8 Whereas the reduction of diastolic blood were more modest ranged from 10 mmHg to 17 mmHg.7,11 Two studies showed decreased blood pressure of >10mmHg however both these studies were more aimed at the safety hence limited number of participant and heterogeneity and no randomization performed.12,13

One study that begs to differ from the consensus is done by Bhatt et al.6 This study found renal denervation did not significantly reduce blood pressure. The different conclusions between these studies were explained by superior methods that were applied by Bhatt et al.6 This study has the most number of patients, which were 535. In this study, we found randomization between treatment and control groups, which are lacking in all other studies. In addition, Bhatt et al used sham procedure as control in this study.6 Even though many researchers consider sham surgery as unethical, it is found to be more effective in testing effectiveness of procedure by performing randomized comparison.14

There are several reasons that may explain the results of the clinical trial that is conducted by Bhatt et al.15 The first explanation is that renal denervation may not be effective in human. As mentioned before, this study is the most rigorous study that have been conducted in analyzing the efficacy of renal denervation. There may be regression-to-the-mean phenomenon that can be observed in this large sample.16 The second possible explanation is the lack of statistical power in this trial. This study’s sample size is calculated based on previous study that may have overestimated clinical effect of renal denervation. This overestimation may be possible because of different baseline characteristics with other studies that have been discussed in this article: in Bhatt et al paper, the baseline hypertension in this study is 159.1 mmHg in denervation group and 159.5 mmHg in sham group. Different from other studies that have baseline blood pressure of 180 mmHg in other studies. There is evidence that renal denervation is much more effective in higher baseline blood pressure.16

The third reason is doubt that the procedure can be performed effectively in Bhatt et al trial. In this paper, it is stated that there are 88 centers of study with 535 patients participated in this trial.15 As in the supplementary section of the study it is said that all of the cardiothoracic surgeon that participated in this trial have no previous experience in doing renal denervation.15,16 It is likely that this procedure were not done properly. Moreover, there are no tools to assess whether renal nerve destructions has already happened. The fourth reason is the high consumption rate of vasodilators in this study.16,17 Vasodilators are found to be a predictor for non-response in renal denervation procedure.17

For the patient in case illustration, we cannot yet recommend renal denervation to solve his persistent high blood pressure. Even though all of the studies were conducted in patients with similar characteristics to the case: high blood pressure that is resistant with at least three drugs that includes thiazide, the lack of single conclusion between these studies prevent us to recommend this procedure. Moreover, the study that has different results was superior in term of methodology.

In addition, safety of this procedure and long-term effect of renal denervation procedure on kidney function must be also considered. Even though individual trials have explored safety profile of renal denervation procedure. A more
robust systematic review must be implemented to find the definitive results.\textsuperscript{18}

Currently, renal denervation is available at the National Cardiovascular Center, Harapan Kita and Hasan Sadikin Hospital, Bandung. However, it is not yet available to the general public. So, we do not know the economical cost of this procedure in Indonesia. An analysis by Geisler et al on the cost-effectiveness of renal denervation procedure may give us some glimpse on the cost of renal denervation.\textsuperscript{19} In the analysis, the cost of renal-denervation procedure costs Rp 150,000,000.00 (assuming that 1 US$=Rp 12,000,00) compared to Rp 10,416,000.00 of yearly combined antihypertensive drugs. According to the economic model, the cost of this procedure is US$ 3,071 per quality-adjusted-life year.\textsuperscript{19} This expensive procedure may limit the applicability of this procedure in Indonesian society.

We should also consider genetic variations that may influence the results. A study by Dimsdale et al found that there’s a significant racial difference between race and it’s vascular response to norepinephrine. In this study, we found that blacks are more sensitive to autonomic nervous system changes compared to whites.\textsuperscript{20} No study has found the comparison of autonomic changes in Asian population compared to white which is the subject of this research. However, as study from Asian-American showed that ACE inhibitor is less effective compared to calcium channel blocker, renal denervation may be less effective in Asian population compared to white.\textsuperscript{21}

**CONCLUSION**

In conclusion, results of studies concerning the practice of renal denervation on patient with resistant hypertension are inconclusive. Randomized trials with large number of participants with intention-to-treat analysis of data will be required before an evidence-based recommendation can be provided on the benefits of this procedure.

**RECOMMENDATION**

As there’s still conflicting results on the efficacy of renal denervation procedure we should conduct other randomized controlled trials. The trial that we recommend should be:
- Has experienced operator, which at least have done twenty renal denervation procedure
- Has clear method to measure success of renal denervation procedure
- Baseline in lower range of blood pressure: 150-160 mmHg
- Revise calculation of sample size
- Reduce the consumption of vasodilator drug in the treatment group

**REFERENCES**


