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Impact of alternative therapies in the treatment of resistant systemic arterial hypertension

Impacto de las terapias alternativas en el tratamiento de la hipertensión arterial sistémica resistente

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ABSTRACT

Resistant arterial hypertension has been defined as a condition where a patient is being treated with an antihypertensive regimen with ≥ 4 drugs or ≥ 3 drugs that include a diuretic and still has blood pressure figures ≥ 140/90 mmHg. Given that the prevalence of resistant arterial hypertension is high, clinicians should be aware of its potential risk of not handling this condition. This review aims to discuss contributors and clinical recommendations to help clinicians better understand and treat resistant arterial hypertension within all care settings. We also demonstrate data from randomized placebo-controlled trials and conclude that renal denervation significantly reduces ambulatory and office blood pressure. Moreover, it was similar between patients on and off background antihypertensive medications. Furthermore, a novel therapy named baroreceptor stimulation therapy has shown promising data in both experimental and clinical experiments to handle resistant arterial hypertension. Both approaches may be highly relevant in patients who are intolerant to medications.

RESUMEN

La hipertensión arterial resistente se ha definido como una condición en la que un paciente está siendo tratado con un régimen antihipertensivo con ≥ 4 fármacos o ≥ 3 fármacos que incluyen un diurético y todavía tiene cifras de presión arterial ≥ 140/90 mmHg. Dado que la prevalencia de la hipertensión arterial resistente es alta, los clínicos deben ser conscientes de su riesgo potencial de no manejar esta condición. Esta revisión tiene como objetivo discutir las contribuciones y las recomendaciones clínicas para ayudar a los clínicos a entender y tratar mejor la hipertensión arterial resistente dentro de todos los entornos de atención. También se muestran datos de ensayos aleatorios controlados con placebo y se concluye que la denervación renal reduce significativamente la presión arterial ambulatoria y en el consultorio. Además, fue similar entre los pacientes que tomaban o no medicamentos antihipertensivos de fondo. Asimismo, un nuevo tratamiento denominado terapia de estimulación de barorreceptores ha mostrado datos prometedores tanto en experimentos como en la clínica para manejar la hipertensión arterial resistente. Ambos enfoques pueden ser muy relevantes en pacientes que no toleran la medicación.

INTRODUCTION

Systemic arterial hypertension is the number one risk factor for mortality worldwide. The burden of the disease relies on its contribution to cardiovascular morbidity and mortality. Nevertheless, resistant arterial hypertension stands for a highly risk condition that could exacerbate diverse complications and outcomes of the disease. According to international guidelines, resistant arterial hypertension has been defined as a condition where a patient is being treated with an antihypertensive regimen with ≥ 4 drugs or ≥ 3 drugs that include a diuretic and still has blood pressure figures ≥ 140/90 mmHg.[1] Usually, patients classified with resistant arterial hypertension trend to had target organ lesions, hence, it is highly recommended to perform an immediate referral with a trained specialist of to a qualified clinical center that could deal with the optimal management of the disease. Moreover, it has

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been shown that patients living with persistent arterial hypertension trend to have an adverse cardiovascular risk profile. A recent report from Daugherty et al. declared that patients with resistant hypertension display a 47% increase in cardiovascular events compared with patients without this condition.[2] Therefore, persistent arterial hypertension is a condition that should be promptly detected and in consequence, appropriately treated to prevent associated complications to the disease. In this review, we discuss the epidemiology, contributors and clinical recommendations that could help clinicians to better understand and treat resistant arterial hypertension within all care settings.

Prevalence of resistant arterial hypertension. Although resistant arterial hypertension is a condition that has been associated with mixed factors related to therapeutic and clinical management, diverse epidemiological reports have pointed out that its prevalence is properly high. According to the American National Health and Nutrition Surveys (NHANES) from 2008, the estimated prevalence of adults that classified with resistant arterial hypertension was of 12.8%.[3] A similar prevalence has been reported in the 2011 Spanish Registry of Ambulatory Blood Pressure, where 14.8% of its participants were classified with resistant arterial hypertension.[4] Moreover, results from ASCOT, ALLHAT and ACCOMPLISH studies reported an estimated prevalence of resistant arterial hypertension of 25% up to 35% on threatened patients.[5] These epidemiological reports shown that the estimated prevalence of patients that had resistant arterial hypertension criteria ranges from 15 to 35%.

Contributors of resistant arterial hypertension. The contributors to resistant arterial hypertension highlight a therapeutic non-compliance within two main axes: fail in appropriated pharmacotherapy and lack of appropriate non-pharmacological measures. Both conditions could be further combined with secondary commodities that aggravate arterial hypertension, such as obstructive sleep apnea or renal artery stenosis. Hence, it is endorsed that the first actions to perform within resistant arterial hypertension is to assess adequate therapeutic compliance and then, rule-out secondary causes of arterial hypertension. Additionally, a high percentage of these patients will require a combined multi-antihypertensive regime, some of which are understudied drugs in randomized clinical trials. In this context, spironolactone is a recent promising antihypertensive that has been studied to treat resistant arterial hypertension due to primary and secondary causes. A randomized clinical trial performed in 2015 revealed that spironolactone succeeded in decreasing blood pressure within patients living with resistant arterial hypertension.[6] Since then, spironolactone has been considered a potential pharmacological approach to treat the disease.[7]

INTERVENTIONAL TREATMENT OF RESISTANT HYPERTENSION: RENAL SYMPATHETIC DENERVATION

Potential benefits of renal denervation. For several decades, increased hyperactivity within the sympathetic nervous system has been described as the leading cause of the physiopathology of resistant arterial hypertension.[8] Therefore, renal sympathetic denervation has been studied as an approach to handle the disease. The method consists of a minimally invasive percutaneous intervention based on the ablation of afferent and efferent renal nerves using a catheterism approach through arterial access (E.g., right femoral artery). The technique is based on forming a low dose of radiofrequency or ultrasonographic energy within the adventitia of the renal artery to create a thermic ablation, interrupting large portions of the nervous system fibers. Alternative ways to accomplish renal nerve ablation include applying nerve agents, cryotherapy, or brachytherapy, which are currently under clinical investigation.

Conversely, for what happened with similar techniques that failed to improve outcomes (E.g., lumbar sympathectomy), renal sympathetic denervation has consistently improved blood pressure control by decreasing renal adrenergic nerve stimulation. Furthermore, this procedure have shown pleiotropic benefits in improving glycemic levels, sleep apnea, arrhythmias, and oxidative stress since other cardiometabolic conditions such as congestive heart failure,

atrial fibrillation, sleep-disordered breathing, and diabetes mellitus are also found within these patients.[9,10] Nevertheless, the efficacy of renal denervation has been the subject of broad discussions. Pragmatic and observational studies showed a completely different effect on lowering blood pressure than those observed in early clinical trials.[11,12] Moreover, a recent placebo-controlled clinical trial using ultrasonographic renal denervation failed to give increased benefit against conventional triple antihypertensive treatment in patients with resistant arterial hypertension.[13]

Efficacy of renal denervation. To elucidate the controversies, a recent published meta-analysis of randomized, blinded, placebo-controlled clinical trials sought to assess the overall effect of renal denervation compared with concomitant antihypertensives in patient living with resistant arterial hypertension.[14] The main endpoints of the selected studied were changes in 24-hour ambulatory systolic blood pressure or changes in office measure diastolic blood pressure compared to baseline. The authors found seven clinical trials that randomized 1,368 patients (782 in renal denervation and 586 to placebo) during a mean time follow-up of 4.5 months.[13,15-20] We summarize the main findings of the meta-analysis as follows:

1. Renal denervation achieved a statistically significant reduction of 3.61 and 1.85 mmHg of ambulatory systolic and diastolic blood pressure, respectively.
2. Renal denervation was associated with a decrease of 5.86 and 3.65 mmHg office systolic and diastolic blood pressure.
3. The overall benefit was consistent in both patients taking baseline antihypertensive medications and those naïve-treated subjects.

The authors concluded that there is consistent evidence that renal denervation is a useful strategy to handle resistant arterial hypertension demonstrated by randomized clinical trials. Furthermore, it could be a useful alternative rather than increasing the number of medications in patients who are already taking three or more antihypertensives. The results from this study could lead to further research to even consider renal denervation as first-line therapy for naïve-treatment patients living with arterial hypertension. Limitations to be mentioned from this metanalysis is the inclusion of two trials that were conducted in patients without concomitant antihypertensives, and five trials that were performed with concomitant antihypertensives. Additionally, the short duration of all the clinical trials still is unable to assess the long-term benefits of denervation or even the adverse effects related to this technique, which could only be assess using long-term blinding. The latter point has been only tested in animal models, but the long-term effects of renal denervation on humans continuous to be an area of further research.[21] Nevertheless, there are still limitations regarding randomized clinical trials as these studies makes impractical the long-term follow up and the real-life assessment of cost-effectiveness of renal denervation. Some authors have mentioned that within subjects ≥ 60 years of age with a 13.2% initial 10-year predicted risk of cardiovascular disease, it would be a cost-effective strategy.[22] Finally, it is unknown whether renal denervation is superior to aggressive antihypertensive schemes with spironolactone, which will need to be further assess with clinical trials.

Final considerations of renal denervation. The evidence from all the previously mentioned randomized placebo-controlled clinical trials makes us conclude that renal denervation has consistently shown to provide a significant reduction of both ambulatory and office blood pressure. Although the crude benefit is of 4 to 2 mmHg, it has been proven to be similar between patients with a background of use of antihypertensives. Therefore, it has been mentioned that the real beneficiaries of renal denervation would be those patients that could be adequately manage with oral antihypertensives of which may be completely intolerant to the adverse effects caused by the medication. Within these cases, renal denervation could be the last resource to reduce all-cause mortality and mayor cardiovascular events similarly to what has been demonstrated for conventional antihypertensive approaches.[23,24]

STIMULATION OF CAROTID BARORECEPTORS FOR THE TREATMENT OF REFRACTORY HYPERTENSION

Baroreceptor stimulation therapy (BAT) has been described as an invasive approach to managing resistant arterial hypertension in patients in whom conventional and even invasive treatments have failed to control blood pressure. The BAT is based on the activation of carotid baroreceptors through an implant that modulates autonomic activity; hence, its capacity to reduce blood pressure. A recent meta-analysis of seven observational and two randomized clinical trials found a significant reduction in systolic blood pressure after applying ventricular stimulation therapy in carotid baroreceptors. The study found a reduction of 36 mmHg (30-42 mmHg) systolic blood pressure.[25] Another meta-analysis demonstrated a significant reduction of 21 mmHg (17-26 mmHg) and 38 mmHg (30-46 mmHg) of systolic blood pressure at short-term (1-6 months) and long-term (> 12 months) effects, respectively.[26] Although both meta-analyses suggest BAT's beneficial effect on blood pressure management, the results should be interpreted with great care. The current evidence from controlled clinical trials is scarce. Therefore, there is a need for further research in this area. Nevertheless, these results provide promising evidence for continuing performing experimental and clinical trials to evaluate the long-term benefit of BAT further.

CONCLUSIONS AND TAKE A HOME MESSAGES

Renal sympathetic denervation offers the most consistent and robust evidence to be considered an alternative to handle resistant arterial hypertension. Overall, renal sympathetic denervation offers a consistent reduction in blood pressure for at least three years with a good safety profile and infrequent need for reintervention. However, the is still unknown evidence whether it could be superior to aldosterone antagonists as the first choice in resistant arterial hypertension. Renal sympathetic denervation may be considered whether the use of aldosterone antagonists is impossible. Further research is needed regarding novel therapies that could be implemented to reduce the cardiovascular risk profile in patient who are intolerant to traditional antihypertensive medications.

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