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TREATMENT OF RESISTANT ARTERIAL HYPERTENSION

Summary

Metaanalyses have demonstrated a linear relationship between level of blood pressure (BP) and risk for cardiovascular events. The prevalence of resistant hypertension in the general population is unknown and vary in the range of 1,9 to 30%. More established approaches, such as low dietary salt and mineralocorticoid receptor blockers are indicated for these patients. New technologies, such as renal denervation and carotid stimulation, may be used in the management of patients with resistant hypertension.

Key words: treatment, resistant arterial hypertension.

Introduction

Hypertension is the most common chronic disease in developed societies, affecting >25% of adults. Metaanalyses have demonstrated a linear relationship between level of blood pressure (BP) and risk for cardiovascular events. Suboptimal BP control is, consequently, the most common attributable risk for death worldwide, being responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease as well as an estimated 7.1 million deaths a year [1].

The Joint National Committee 7 defines resistant hypertension as failure to achieve goal BP (<140/90 mm Hg for the overall population and <130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) when a patient adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic [2]. According to 2013 ESH/ESC Guidelines for the management of arterial hypertension, hypertension is defined as resistant to treatment when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses (but not necessarily including a mineralocorticoid receptor antagonist) fails to lower SBP and DBP values to <140 and 90 mmHg, respectively [3].

The risk of clinical complications, including stroke, acute aortic dissection, myocardial infarction, congestive heart failure and renal failure, is higher in patients with RH compared with other types of hypertensive patients, including not only well-controlled subjects, but also those with false resistant and masked hypertension [4].

Epidemiology of resistant hypertension

The prevalence of resistant hypertension in the general population is unknown because of an inadequate sample size of published studies as well as the feasibility of doing a large enough prospective study that would answer the question. However small studies, demonstrate a prevalence of resistant hypertension that ranges from ~5% in general medical practice to >50% in nephrology clinics [1].

It was difficult to find published official information about situation in Kazakhstan. In June of 2013 at the third Physicians Congress and at fifth Congress of Cardiologists of Kazakhstan there was reported that according to calculations based on data from the European Society of Cardiology, the total number of patients with arterial hypertension in Kazakhstan may reach 600,000 people - about 65% of the adult population of the country (at age above 59 years). Among them, about 10-12% of patients have a resistant form. Another source indicates about 6% of patients with resistant hypertension in Kazakhstan [5].

An analysis of US National Health and Nutrition Examination Survey data suggests that among hypertensive adults treated with medications, approximately 13% have RH. A recent study of RH in Spain found a similar rate of 12% [6]. Data from the BP-CARE study provided evidence that the prevalence of true resistant hypertension in Central and East European countries is similar to that found in Western Europe and USA [7]. From the 2013 ESH/ESC Guidelines for the management of arterial hypertension the prevalence of resistant hypertension has been reported to range from 5–30% of the overall hypertensive population, with figures less than 10% probably representing the true prevalence. The HOT-CHINA study revealed only 1.9% resistant hypertension in Chinese individuals with hypertension [8]. The prevalence of RH in Japan was reported in J-HOME study is 13% [9]. So, the prevalence of RH is in the range of 1,9 to 30%, and I think it is due to incorrect diagnostic algorhythm, exclusion of secondary forms of arterial hypertension, small amount of studies, etc.

Treatment of resistant hypertension

In spite of the progressive and considerable improvements achieved in diagnostic options and therapeutic interventions, recent observational surveys continue to show persistently low rates of BP control in the general population of hypertensive patients [10].

Management of RH includes lifestyle modifications as well as antihypertensive medications, and both can be suboptimal. For patients with resistant hypertension, lifestyle modifications should be re-emphasized. Patients may not realize that the eating plan combined with low sodium intake can be as effective in lowering BP as a single antihypertensive medication. The importance of weight loss (for overweight patients) should be reiterated. An important principle of antihypertensive therapy is that greater BP reduction is achieved by combining drugs from different classes rather than by maximally increasing the dose of a single medication [6].

Pharmacological treatment should be based on the most common causes of resistant hypertension and focused on blocking all the physiological pathways to blood pressure elevation [11]. Antihypertensive agent doses should be titrated upward until blood pressure is controlled or the maximum recommended dosage is reached, unless the patient experiences dose related adverse effects. It is then appropriate to add a drug from another class that has additive or synergistic effects with the first drug. In general, a typical regimen should include a diuretic, an ACE inhibitor or angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and a β-blocker [12]. Subgroup

analyses of large scale trials and observational studies have provided evidence that all drug classes with mechanisms of action partially or totally different from those of the existing three drug regimens can lower BP in at least some resistant hypertensive individuals. A good response has been reported to the use of mineralocorticoid receptor antagonists, i.e. spironolactone, even at low doses (25–50 mg/day) or eplerenone, the alpha-1-blocker doxazosin and a further increase in diuretic dose, loop diuretic replacing thiazides or chlorthalidone if renal function is impaired [3].

It is known the role of the RAAS in the pathogenesis of hypertension, on this basis in clinical practice known drug alisikren. Aliskiren, the first orally active direct renin inhibitor, was approved by the US Food and Drug Administration in March 2007. It has demonstrated effective blood pressure (BP) control and is generally well tolerated as monotherapy or in combination with other antihypertensive drugs [13]. Extra advantages can be reached when it is used in combination therapy. The data from 7 randomized clinical trials for a total of 6074 participants in meta-analysis report that the aliskiren/amlodipine combination therapy had a stronger effect in lowering blood pressure as compared with the monotherapy using aliskiren [14].

In March 2012 was published results of investigation about the combination of aliskiren, amlodipine and hydrochlorothiazide is a rational choice for combination therapy and recent studies suggest that it is safe and effective in lowering blood pressure in patients who fail dual combination therapy [15].

But the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-renal Disease Endpoints) trial was stopped on the recommendation of its Data Monitoring Committee (DMC) due to increased adverse events, including nonfatal stroke, renal dysfunction, hyperkalemia and hypotension, with no apparent benefit. The major concern was increased stroke with aliskiren in comparison to placebo (2.6% versus 2%, unadjusted p = 0.04) [16]. This trial studied the effects of aliskiren in addition to ACEI or ARB therapy in patients with diabetes and renal disease (glomerular filtration rate < 60 ml/min per 1.73 m2 or microalbuminuria). The primary endpoints of the study were time to first event for the composite endpoint of CV death, resuscitated death, myocardial infarction, stroke, unplanned hospitalization for HF, onset of end-stage renal disease or doubling of baseline serum creatinine concentration [17]. Based on these findings, dual aliskiren and ACEI/ARB therapy is not recommended in patients with hypertension and diabetes or at least moderate renal dysfunction [13].

Nonpharmacological methods of therapy of resistant hypertension

The role of the sympathetic nervous system in modulating blood pressure has been extensively investigated during the last century, and some drugs have already been proven to efficiently act on adrenergic apparatus such as α-metildopa in the 1950 s, β-blockers in the 1960 s, α-blockers in the 1970 s, angiotensin-converting enzyme inhibitors in the 1980 s, and moxonidine in the 1990 s. None of them, however, has turned out to be as effective as renal denervation. The proof of concept for applying such a therapeutic strategy mainly derives from the assumption that sympathetic nerves enter the kidneys in the walls of the renal arteries, thus affecting renal function in 3 different ways: (1) increasing the renin secretion rate through the β1-adrenergic receptors; (2) enhancing sodium and water reabsorption through α2B-adrenergic receptors; and (3) inducing renal vasoconstriction with renal blood flow and glomerular flow rate reductions through α1A-adrenergic receptors.

Therapeutic renal denervation has been explored in preclinical models and in humans since the 1950 s, when surgical renal denervation was shown to be a highly effective treatment for resistant hypertension in the clinical setting. Unfortunately, the procedure was abandoned because of intolerable side-effects, but gave rise to other promising surgical techniques, such as carotid baroreceptor surgery for resistant hypertension, which showed encouraging results.

Recently, percutaneous renal denervation has emerged as a potential mini-invasive strategy to treat resistant hypertension. It is a localized procedure, minimally invasive, and has no systemic side-effects. Moreover, procedure and recovery times are very short compared to the surgical procedure.

The main studies of renal denervation are the Symplicity HTN-1 and the randomized controlled Symplicity HTN-2 trial. In both trials, this approach was shown to successfully reduce blood pressure, without serious adverse events in patients with resistant hypertension [18].

Another target for the interventional treatment of resistant hypertension is **carotid baroreceptors.** Baroreceptors are stretch-sensitive fibers located primarily in the aortic arch and each of the carotid sinuses near the area where the common carotid artery bifurcates [19]. The Rheos device (CVRx, Maple Grove, Minn) stimulates the carotid baroreceptors for better blood pressure control by taking advantage of chronic electrical activation of the afferent limb of the carotid baroreflex. The device consists of a pulse generator and bilateral perivascular carotid sinus leads that are implanted under narcotic anesthesia. According to the findings from the Device-Based Therapy of Hypertension (DEBuT-HT) study that were recently presented, after four years of treatment, Rheos reduced systolic blood pressure by an average of 53mmHg (193mmHg versus 140mmHg). Blood pressure was reduced significantly each year, with the largest decrease occurring in year four. Many of these patients were able to reach their blood pressure goal and reduce the number of medications that patients were taking to treat their hypertension from an average of 5 at baseline to 3.4 medications at 4 years. Baroreflex activation therapy also improved functional capacity and reduced left ventricular mass without any evidence of carotid injury or stenosis [12].

Conclusion

Resistant hypertension is an increasingly common medical problem and patients with this condition are at a high risk of cardiovascular events. Because secondary hypertension may be the underlying cause of resistant hypertension, and sometimes a specific and definite treatment is available, a thorough investigation is mandatory in patients with resistant hypertension. However, in the majority of these patients, an underlying cause cannot be found. More established approaches, such as low dietary salt and mineralocorticoid receptor blockers are indicated for these patients. New technologies, such as renal denervation and carotid stimulation, may be used in the management of patients with resistant hypertension.

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Резюме
ЛЕЧЕНИЕ РЕЗИСТЕНТНОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ
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Многочисленные мета анализы показали линейную зависимость между уровнем артериального давления (АД) и риском сердечно-сосудистых осложнений. Распространенность резистентной артериальной гипертонии в общей популяции неизвестна и варьирует в диапазоне от 1,9 до 30%. Таким пациентам показаны наиболее изученные и доказанные подходы, такие как низкий уровень соли в пище и применение блокаторов рецепторов минералокортикоидов. Новые технологии, такие как почечная денервация и стимуляция барорецепторов сонных артерий, также могут быть использованы в лечении пациентов с резистентной АГ.

Ключевые слова: *:лечение, резистентная артериальная гипертония.*

Тұжырым
РЕЗИСТЕНТТІ АРТЕРИАЛДЫ ГИПЕРТОНИЯНЫ ЕМДЕУ
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Көптеген мета талдаулар артериалды қысым (АҚ) және жүрек-тамырдың асқынуы деңгейі арасындағы сызықтық тәуелділігін көрсетті. Резистентті артериалды гипертонияның таралуының жалпы популяциясы белгісіз және 1,9 -дан 30%-ға диапазонында басым. Мұндай науқастарға көбінесе зерттелген және дәлелденген тәсілдер көрсетілген, асқа тұздың аз деңгейі және минералокортикоидты блокатор рецепторларын қолдану ұсынылады. Резистентті артериалды гипертониямен ауыратын науқастарды емдеуде үйқы артериясындағы барорецепторларының стимуляцисын және бүйрек денервация сияқты жаңа технологияларды қолдануға болады.

Негізгі сөздер: *емдеу, резистентті артериалды гипертония.*