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ORIGINAL ARTICLE

Efficacy and Safety of Spironolactone in Patients with Resistant Hypertension: A Meta-analysis of Randomised Controlled Trials

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Background The treatment of resistant hypertension (RH) is challenging. Several observational studies have suggested that the addition of spironolactone to triple-drug therapy might have a promising anti-hypertensive effect on RH. To provide more definite evidence for the benefit of spironolactone, we performed a meta-analysis of randomised controlled trials (RCTs) to evaluate the efficacy and safety of spironolactone in RH patients.

Methods Articles were searched from PubMed, EMBASE and Cochrane Library. Randomised controlled trials investigating the effect of additional spironolactone on office blood pressure (BP), ambulatory BP or adverse events in RH patients were included for analysis. Then quality assessment, subgroup, sensitivity, and publication bias analyses were performed.

Results Five RCTs involving a total of 553 patients were eligible for inclusion. Compared with control therapies, additional spironolactone treatment in RH patients significantly decreased 24-h ambulatory systolic BP (ASBP, weight mean difference [WMD] = -10.50, 95% confidence interval [CI] = -12.30 to -8.71, $P < 0.001$), 24-h ambulatory diastolic BP (ADBP, WMD = -4.09, 95% CI = -5.28 to -2.91, $P < 0.001$), daytime ASBP (WMD = -10.20, 95% CI = -12.41 to -7.99, $P < 0.001$), daytime ADBP (WMD = -4.14, 95% CI = -5.50 to -2.78, $P < 0.001$), night-time ASBP (WMD = -10.02, 95% CI = -12.63 to -7.41), night-time ADBP (WMD = -3.21, 95% CI = -4.84 to -1.58, $P < 0.001$), office systolic BP (WMD = -16.99, 95% CI = -25.04 to -8.95, $P < 0.001$) and office diastolic BP (WMD = -6.18, 95% CI = -9.30 to -3.05, $P < 0.001$). However, serum potassium might be slightly elevated by additional spironolactone (WMD = 0.181, 95% CI = 0.042 to 0.319, $P = 0.011$).

Conclusion Spironolactone combined with triple-drug therapy may be an effective and relatively safe strategy for the management of RH patients.

Keywords Resistant hypertension • Spironolactone • Meta-analysis • Efficacy • Safety

Introduction

Resistant hypertension (RH) is defined as a failure to reduce the blood pressure (BP) lower than 140/90 mmHg despite the concurrent use of three or more antihypertensive drugs, including one diuretic, at optimal dosages [1]. The exact prevalence of RH is not well documented, but based on the data from large clinical trials, about 10% to 15% of

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hypertensive patients are suffering from RH [2,3]. In comparison with controlled hypertension, RH could greatly increase the risk of cardiovascular morbidity and mortality [4,5]. Pharmacological treatment is still the mainstay for the management of RH, however, a substantial proportion of patients remain uncontrolled with the use of the first three recommended drugs including calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) and thiazide diuretics [6]. Hence, it is necessary to develop new strategies to improve the BP control rates and outcomes in patients with RH.

Spironolactone is a mineralocorticoid receptor antagonist which has a promising effect on lowering BP in hypertensive patients [7,8]. Several previous observational studies have demonstrated that addition of spironolactone to triple-drug therapy in patients with RH could significantly decrease the office systolic BP (SBP) and diastolic BP (DBP) with relatively rare adverse events including gynecomastia, breast discomfort and biochemical abnormalities [9–11]. However, it has also been reported that spironolactone is effective for lowering SBP, but not lowering DBP in patients with RH [12]. Consequently, to provide more definite evidence for the anti-hypertensive benefit of spironolactone, we performed a meta-analysis of RCTs to evaluate the efficacy and safety of spironolactone as an add-on treatment in patients with RH, compared with placebo or other anti-hypertensive agents.

Method

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Literature Search Strategy

Two reviewers systematically searched the pertinent studies in PubMed, EMBASE and Cochrane Library until December, 2015. These search strategies were restricted to articles published in English. The following search strategy was used: (spironolactone or aldactone or mineralocorticoid receptor antagonists) AND (resistant hypertension or refractory hypertension). We also performed backward snowballing to obtain potentially relevant articles from the reference lists of retrieved RCTs and review articles.

Research Strategy in PubMed as follows: ((''spironolactone''[MeSH Terms] OR ''spironolactone''[All Fields]) OR (''spironolactone''[MeSH Terms] OR ''spironolactone''[All Fields] OR ''aldactone''[All Fields]) OR (''mineralocorticoid receptor antagonists''[Pharmacological Action] OR ''mineralocorticoid receptor antagonists''[MeSH Terms] OR (''mineralocorticoid''[All Fields] AND ''receptor''[All Fields] AND ''antagonists''[All Fields]) OR ''mineralocorticoid receptor antagonists''[All Fields])) AND ((resistant[All Fields] AND (''hypertension''[MeSH Terms] OR ''hypertension''[All Fields])) OR (refractory[All Fields] AND (''hypertension''[MeSH Terms] OR ''hypertension''[All Fields]))).

Study Selection

Titles and abstracts of all retrieved articles were independently scanned by two reviewers and obviously irrelevant studies were excluded at this stage. The eligibility of the remaining articles was further assessed with full-text evaluation by the same two reviewers. Disagreements between reviewers were resolved by discussion. Studies were eligible for inclusion if they met the following criteria: (1) clinical trial with RCT design; (2) patients with RH; (3) addition of spironolactone to a triple-drug antihypertensive treatment; (4) reporting any relevant outcomes including mean changes of 24-h, daytime, night-time ambulatory BP, office BP and serum potassium from baseline.

Data Extraction and Assessment of Risk of Bias

Two reviewers independently extracted the relevant data from included studies and the third reviewer was responsible for repeated checking, with divergences resolved by discussion. The extracted information was as follows: characteristics of included studies (title, the first author, publication year, journal, country, corresponding address, study design, inclusion and exclusion criteria, RH definition), characteristics of RH patients (number of patients, sex, average age), intervention and control treatment (dose and duration) and pertinent outcomes (mean changes of 24-h, daytime, night-time ambulatory BP, office BP and serum potassium from baseline). If several articles reported the same study, the one with most complete data was included in our meta-analysis.

Risk of bias for included RCTs was independently evaluated by two reviewers in accordance with the Cochrane risk of bias tool. Disagreements were resolved by discussion. The quality evaluation was judged on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.

Statistical Analysis

All the statistical analyses were completed using Stata 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Heterogeneity was evaluated using chi-square test ($P \leq 0.10$ indicating significant heterogeneity) and I^2 test ($I^2 > 50\%$ indicating significant heterogeneity). To assess the effect of spironolactone on the mean changes of 24-h, daytime, night-time ambulatory BP, office BP and serum potassium, inverse variance (IV) fixed-effect model was utilised to calculate the weight mean difference (WMD) and 95% confidence interval (CI) if there was no significant heterogeneity among the included studies; otherwise, random-effects model was chosen. Sensitivity analysis was used to identify the stability of statistical results by exclusion of each study one by one. In addition, publication bias was also evaluated with the use of funnel plots and Egger's test. Statistical significance was defined as $P < 0.05$.