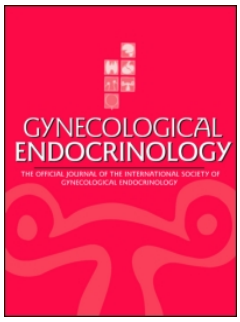

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REVIEW ARTICLE

Effect of combined drospirenone with estradiol for hypertensive postmenopausal women: a systemic review and meta-analysis

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Abstract

Postmenopausal hypertensive is associated with estrogen deficiency. This meta-analysis was performed to assess the efficacy and safety of drospirenone combined with 17-β-estradiol (DRSP/E2) in postmenopausal hypertensive women. A systemic literature search of PubMed, Embase, Cochrane Library, Web of Science (up to Oct. 2015) was performed. Studies were screened independently by two researchers according to the inclusion and exclusion criteria which included only the randomized controlled trials (RCT) about the drospirenone with 17-β-estradiol for postmenopausal women with hypertension. The methodological quality was evaluated by Cochrane handbook 5.1.0 and meta-analysis was conducted using RevMan 5.3.0 software. Five randomized controlled trials involved 1121 patients who met the eligibility criteria. Overall, DRSP/E2 group was superior in reducing clinical blood pressure (BP) and 24-h mean BP. There was no significant change in potassium levels on DRSP/E2 group versus control group, suggesting probability potassium sparing effect of this hormone therapy. The incidences of adverse events were low and similar. The current evidences indicate that DRSP 3 mg/E2 2 mg can significantly lower both systolic and diastolic blood pressure in postmenopausal hypertensive women.

Keywords

Drospirenone, estrogen, hypertension, meta-analysis, postmenopausal

History

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Introduction

Hypertension is a growing global health concern. The prevalence of hypertension shows a marked increase incidence after menopause in epidemic studies [1–3]. As a major risk factor of cardiovascular disease and stroke [3–6], the shortcoming of medical treatment results in an unexpected morbidity and mortality [2,5]. The decline of estrogen production after menopause shows a strong association with an increase in blood pressure and cardiovascular risk. Nowadays, loss of estrogens had been regarded as the main cause of promoting postmenopausal hypertension in women. Thus, it has been suggested that estrogen replacement can protect postmenopausal women from hypertension and cardiovascular system; most of the randomized controlled trials using the conventional hormonal replacement therapy (HRT) have not confirmed in reducing cardiovascular risk [7–11]. The mechanisms of this controversy are not clarified.

There is evidence that DRSP/E2 can relief climacteric symptoms and decrease extracellular water (ECW) and body weight (BW), which have negative effect on postmenopausal hypertension [12]. Besides, DRSP/E2 play important role in protecting endothelial function and modifying the lipid parameters that concentrations of total cholesterol, triglycerides, and LDL cholesterol were lowered significantly, especially in postmenopausal women with metabolic syndrome [13,14]. Whether DRSP/E2 have positive role in preventing cardiovascular diseases remained to be further clarified. At present, DRSP combined with 17-β-estradiol (E2) has been developed as a new and effective therapy for the relief from postmenopausal symptoms [15–18].

Current evidences have demonstrated the beneficiary actions of aldosterone antagonist effect in improving cardiovascular and renal functions [19–22]. Therefore, drospirenone (DRSP), a derivative of 17-spirolactone, a novel progestin with anti-aldosterone effect, has a potential role in lowering blood pressure and enhances cardiovascular and renal functions.

DRSP/E2 has also showed a significant antihypertensive effect in clinical trials [23,24] and also has shown an additive effect on blood pressure when combined with traditional antihypertensive drugs [25–27]. Considering the anti-aldosterone effect of DRSP, it mustn't be forgotten that it is capable of inducing hyperkalemia. So we have been focusing on the change of serum potassium levels carefully. In general, we would like to look for a new therapy that could be used in prevention and control of blood pressure in postmenopausal women with serious postmenopausal symptoms.

The objective of this meta-analysis is to assess the efficacy and safety of drospirenone/17-estradiol (DRSP/E2) which has a high potential for the lowering blood pressure of postmenopausal women.

Methods

Search strategy and data sources

We searched the databases of PubMed, Embase, Cochrane Library, Web of Science (up to Apr. 2015) with the following

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term of ''drospirenone'' and ''postmenopausal'' and ''hypertension''. We supplemented lists of all papers by manual retrieval references. Two authors independently screened the study by reading the title and abstract. Studies which met the inclusion criteria were checked full text in detail. Disagreements were resolved by discussion.

Inclusion and exclusion criteria

We only included clinical trials and study design that had met the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [28] statement criteria: (1) random, double, and controlled trial using DRSP/E2 treatment; (2) participants were postmenopausal women with hypertension; (3) at least two weeks follow-up duration. Randomized crossover trials had to include the period of washout. Women of 40 to 75 years of age at postmenopausal with hypertension were included and those with secondary hypertension and history of unstable medical illness were excluded.

Data extraction

Two reviewers extracted all date including baseline characteristics and endpoints. Change from baseline in clinical blood pressure was the primary endpoint and the change in baseline of the 24 h mean ambulatory blood pressure was the secondary endpoint. Change in serum potassium and other adverse events were evaluated.

Assessment of methodological quality

The Cochrane Handbook was applied to assess the quality of include trials [29]. We evaluated seven aspects for studies quality as following: randomized sequence generation; allocation concealment; blinding of participants; outcome assessors; incomplete outcome data; selective outcome reporting; and other potential threats to validity. The risk of bias was graded as high, low, or unclear bias for all the included trials.

Statistical analysis

We preformed meta-analysis to compare DRSP/E2 with placebo. Heterogeneity between trial results was tested using the I^2 statistic where percentages greater than 50% were taken to indicate significant heterogeneity. If heterogeneity existed, random-effect model was used to combine data from included trials, meanwhile, we further conducted sensitivity analysis to find the possible explanation for heterogeneity. The effect of a single study on overall risk factors was investigated by sensitivity analysis. Cochrane Review Manager Software, RevMan 5.3.0 was used for all data syntheses and analyses. A value of $p<0.05$ was defined as statistically significant.

Results

Selection flow and study characteristics

The search strategy found 214 references in PubMed, Embase, Cochrane Library and Web of Science (Figure 1). After removal of duplicates, 93 references were included and the remaining 10 articles were assessed by detailed evaluation. On detailed assessment, we excluded 5 articles for the following reasons: on-going study (1 trial); healthy people (1 trial); repeated data (1 trial); only published abstract (2 trials).

In five included trials, three studies [25–27] used anti-hypertension drug controlling the baseline of blood pressure, one study used 10 mg enalapril [27], one other used ACE inhibitors or angiotensin II receptor antagonist [26] and another used 25 mg hydrochlorothiazide [25] considering potassium-sparing effect. The duration of follow-up was between 2 and 12 weeks. The doses of DRSP/E2 were 3 mg/1 mg. The included studies and patient characteristics are shown in Table 1.

All trials reported data on BP, serum potassium levels and adverse events during treatment were noted. Data from included trials were aggregated in a meta-analysis. Forest plots of these results are showed in Figure 2.

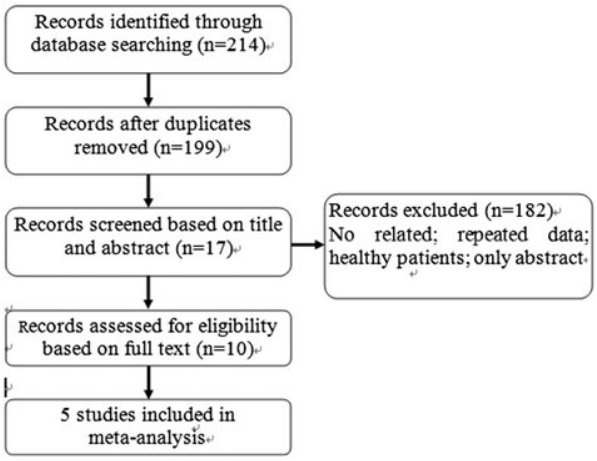

Figure 1. Study flow diagram summarizing trials selection process.

Table 1. Description of the studies included in the meta-analysis.

Author (refer. no)	Study type	SS EG	SS CG	Age (years)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	Dose of DRSP/E2	Duration treatment (week)
Preston 2002 [27]	RCT	12	12	57 ± 6	–	139 ± 19	80 ± 7	3 mg/1 mg	2
				62 ± 6	–	139 ± 12	83 ± 8		
Preston 2005 [26]	RCT	74	74	59.6	29	134 ± 15	82 ± 8	3 mg/1 mg	4
				58.1	29	131 ± 12	82 ± 8		
Preston 2007 [25]	RCT	72	72	61.2 ± 6.6	31.1 ± 5.6	138 ± 7.08	84.6 ± 4.07	3 mg, 2 mg, 1 mg/1 mg	4
White 2005 [24]	RCT	102	111	56 ± 5	29 ± 4	145 ± 7	89 ± 6	3 mg/1 mg	12
				57 ± 5	28 ± 4	146 ± 7	89 ± 5		
White 2006 [23]	RCT	446	146	57 ± 6	30.6 ± 5.8	151 ± 9	94 ± 5	3 mg, 2 mg, 1 mg/1 mg	8
				57 ± 6	30.0 ± 5.2	151 ± 9	94 ± 5		

RCTs: randomized controlled trails. SS: sample size. EG: experimental group. CG: control group.

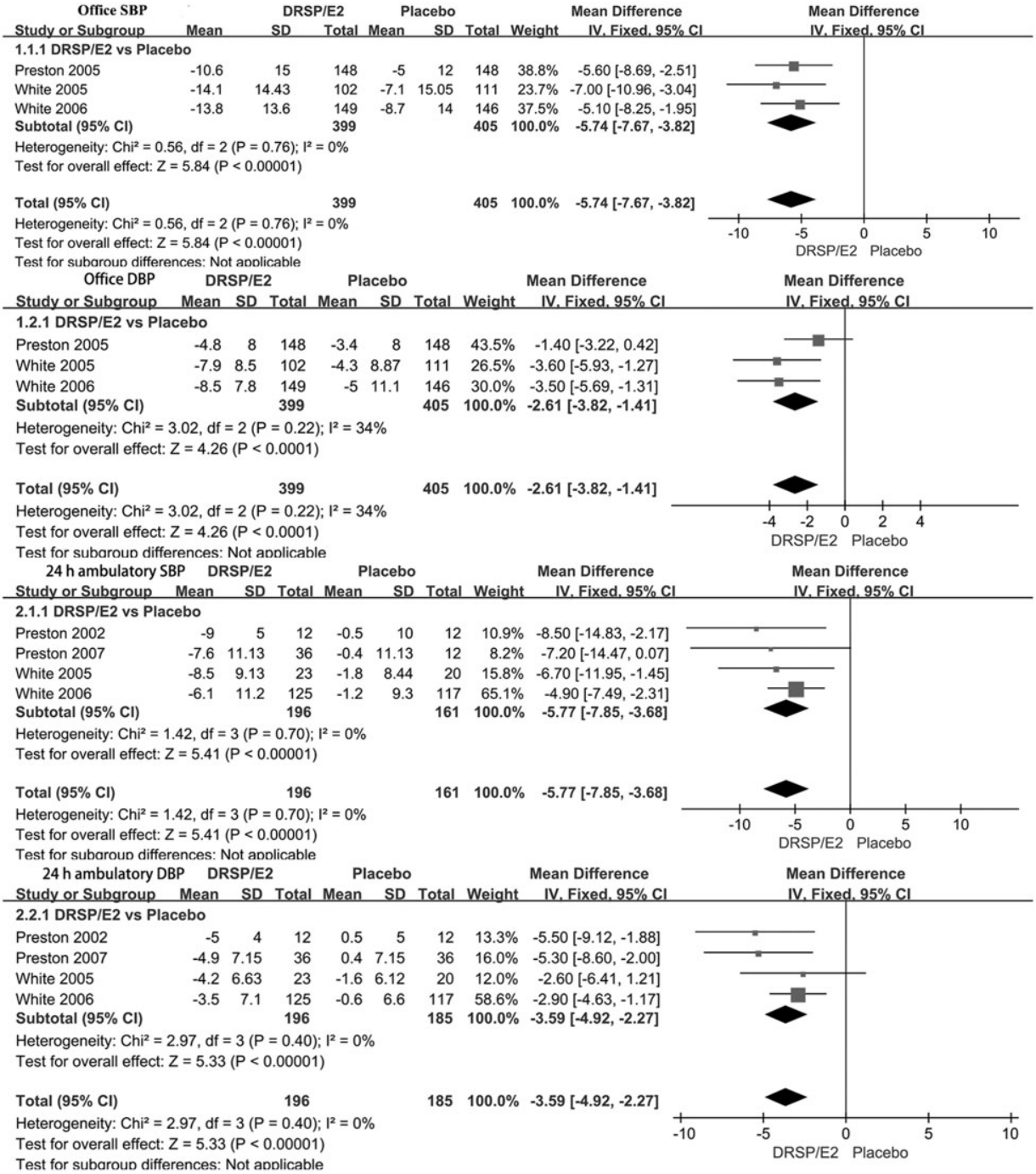

Figure 2. Forest plot of comparison DRSP/E2 versus Placebo on blood pressure.

Main results

For the Primary outcome clinical blood pressure regimen analysis, the meta-analysis of included trials showed that clinical SBP of DRSP/E2 group reduced by −5.74 mm Hg (95%CI −7.67 to −3.82, $p<0.00001$), which was statistically significant difference compared with placebo group. No significant heterogeneity ($I^2=0\%$) was observed. We analyzed results by comparing DRSP/E2 only with placebo, which the results (95% CI −8.30 to −3.73, $p<0.00001$) were consistent with DRSP/E2 plus anti-hypertensive treatment. The analysis of in DBP found that clinical DBP decreased by −2.61 mm Hg (95%CI −3.82 to −1.41, $p<0.00001$), which was statistically difference. The results from meta-analysis had supported evidences for lowering both clinical SBP and DBP, as shown in Figure 2.

As for the secondary outcomes of the 24-h ambulatory blood pressures regimen analysis in all single trials showed significant reduction in mean 24-h blood pressure in DRSP/E2 group versus control group. The meta-analysis of comparative studies (Figure 2) found that the 24-h mean systolic blood pressure reduced −5.77 mm Hg (95%CI −7.85 to −3.68, $p<0.00001$) and the 24-h mean diastolic blood pressure reduced −3.59 mm Hg (95%CI −4.92 to −2.27, $p<0.00001$), which was a

statistically significant difference. No heterogeneity ($I^2 = 0\%$) was observed.

The change of serum potassium over time was reported in all included trials. There was no statistical difference of change in serum potassium baseline levels as compared to placebo group. The analysis of overall mean difference in serum potassium showed that change from its baseline was −0.04 mEq/L (95%CI −0.18 to 0.11, $p = 0.60$, $I^2 = 84\%$).

All parallel trials [23–27] reported adverse events. One crossover trial described adverse events respectively in detail. The meta-analysis of five trials showed that there was no statistically significant difference between DRSP/E2 group and placebo group in the incidence of overall adverse events (RR = 0.59, 95%CI: 0.37 to 1.65, $p = 0.25$, $I^2 = 59\%$). Hyperkalemia is serious adverse event and all trials showed that hyperkalemia incidences caused by DRSP/E2 were low and similar compared with placebo.

Publication bias

In general, the methodological quality of included studies was moderate. The detailed randomization process was described only in forty (40%) of the five trials. All included trials did not conduct allocation concealment. Five trials reported double blind, but the detail of blind was not clearly reported and all losses to follow-up were reported in studies.

Discussions

The meta-analysis results demonstrated that 3 mg DRSP with 1 mg E2, a novel therapy with aldosterone blocking activity, was effective in reducing clinical blood pressure and 24-h ambulatory blood pressure for postmenopausal women. Also DRSP/E2 combination anti-hypertensive treatment reduced clinical BP and 24-h ambulatory BP. Although the change from baseline of serum potassium in meta-analysis was not statistically significant and hyperkalemia incidence did not demonstrated differences when compared with placebo, serum potassium still should be kept in mind during treatment. The incidences of adverse events between DRSP/E2 and placebo were low and similar.

Postmenopausal hypertension is complex cardiovascular disease which is accompanied by various other cardiovascular risks. Traditional anti-hypertensive treatment is insufficient in controlling blood pressure of postmenopausal women with hypertension when estrogen deficiency plays an important role in prevalence of hypertension. More importantly, menopausal symptoms have negative effects for lowing blood pressure in postmenopausal women with hypertension [30]. DRSP/E2 also showed to improve the postmenopausal symptoms [15]. Furthermore, the anti-aldosterone activity of DRSP/E2 has confirmed the favorable effect on cardiovascular disease and renal function by improving endothelial function and nitric oxide bioactivity [22,31,32].

In one included study, postmenopausal women with type 2 diabetes mellitus using DRSP/E2 did not reach statistical significance in SBP; however, the reduction of DBP had statistical significance [26]. Further studies should be done to clarify this mechanism. The reason for change of potassium from baseline was inconsistent [25], we checked the details of included trials and found that 0.21 mEq/l could not be important at 3.2–3.3 mEq/l level of serum potassium. The change of heart rate and ECG abnormality were identical between two groups [24,27]. Besides, significant reduction in total and low-density lipoprotein cholesterol occurred on DRSP/E2 treatment [23]. The improvement of lipid profile is positive for cardiovascular protection. This shows that hormone therapy with a combination of DRSP and E2 may provide a potential advantage in preventing and treating postmenopausal hypertension.

This meta-analysis comes with a few limitations. It included randomized trials where sample sizes were small and duration of follow-up was variable between 2 weeks to 12 weeks. Almost all published trials included limited data. We need to explain cautiously, the outcomes, which were observed with significant heterogeneity. It is necessary to conduct larger sample size randomized controlled trials to prove the effect and safety of drospirenone with 17-β-estradiol with more precision.

In conclusions, this meta-analysis demonstrates that a new hormone therapy with aldosterone receptor-blocking activity, DRSP/3 mg combined E2/1 mg is effective for lowering clinical BP and 24-h ambulatory blood pressure in postmenopausal hypertensive women. All included participants could well tolerate this hormone therapy. In conclusion, data from recurrent studies support that DRSP/E2 is an effective and safe hormone combination therapy that could be used in postmenopausal hypertension.

Declaration of interest

No interest conflicts were declared. This study was supported by the National Natural Science Foundation of China (NSFC-81270332), Gansu Province Natural Science Foundation (1104FKCA150, 1205TCYA042), and the Gansu Administration of Traditional Medicine Foundation (GZK-2010-Z-1).

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