Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials

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CRD summary
The authors concluded that hydrochlorothiazide (12.5mg to 25mg daily dose) lowered blood pressure significantly less well than other drug classes used to treat hypertension (measured by 24-hour ambulatory blood pressure monitoring). The reliability of the authors' conclusion is uncertain given potential error and bias in the review process and reliance on only a few high-quality trials.

Authors' objectives
To evaluate the antihypertensive efficacy of hydrochlorothiazide as assessed by ambulatory blood pressure monitoring.

Searching
PubMed, the Cochrane Library and EMBASE were searched (from inception to March 2010) with no language restrictions. Search terms were reported. Reference lists of identified articles were handsearched. Articles available in abstract-only formats were excluded.

Study selection
Randomised controlled trials (RCTs) that assessed 24-hour ambulatory blood pressure treated with hydrochlorothiazide compared with other antihypertensive drugs, in patients with hypertension, were eligible for inclusion. Trials had to assess hydrochlorothiazide as a monotherapy and of at least four weeks duration.

The outcome measure was blood pressure (systolic/diastolic) reduction from baseline to follow-up.

In included trials, the severity of hypertension in participants was varied. The mean age of included patients was 58 years; 54% were men (where reported). Hydrochlorothiazide doses varied from 12.5mg to 25mg in most trials; in other trials the dose was 50mg. Comparator antihypertensive drugs were varied including: amlodipine, atenolol, bisoprolol, candesartan, enalapril, felodipine, indapamide, irbesartan, isradipine, lacidipine, lisinopril, losartan, nifedipine, perindopril, pinacidil, quinapril, ramipril, spirapril, telmisartan and zofenopril. Baseline ambulatory blood pressure ranged from 135/93mmHg to 161/85mmHg.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
Components of trial quality assessed included: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Trials with high or unclear risk for bias for sequence generation, allocation concealment, and blinding were classified as low quality.

The authors did not state how many reviewers assessed study quality.

Data extraction
Two reviewers independently extracted data to enable calculation of mean differences (MDs) and corresponding 95% confidence intervals (CIs). Disagreements were resolved by discussion or by involvement of other reviewers. Authors of primary trials were contacted to clarify unclear data.

Methods of synthesis
Pooled weighted mean differences (WMDs) with 95% confidence intervals were calculated using random-effects (DerSimonian and Laird) meta-analysis where some evidence of heterogeneity ($I^2 > 25\%$) was found. Heterogeneity was assessed using $I^2$. Analysis was performed on an intention-to-treat basis.

Subgroup analysis was performed for hydrochlorothiazide doses (12.5mg, 25mg and 50 mg). Sensitivity analysis was
performed for blood pressure reduction in hydrochlorothiazide dose 12.5mg to 25mg based on trial quality, trial design, and blinding.

Publication bias was assessed using funnel plots, Begg's and Egger's tests.

**Results of the review**

Nineteen RCTs (n=1,463 patients, range 12 to 354) were included in the review. The quality of four of 14 trials with hydrochlorothiazide dose 12.5mg to 25 mg were classified as low risk of bias; the rest were classified as high risk of bias. The results of quality assessment for five trials with hydrochlorothiazide dose 50 mg were not reported. Follow-up duration ranged from four to 95 weeks.

**Antihypertensive efficacy (14 RCTs)**

Hydrochlorothiazide treatment of 12.5mg to 25mg reduced systolic ambulatory blood pressure by 6.5mmHg (95% CI 5.3 to 7.7; I\(^2\)=0%) and diastolic ambulatory blood pressure by 4.5mmHg (95% CI 3.1 to 6.0; I\(^2\)=56%).

Hydrochlorothiazide treatment of 12.5mg to 25mg was associated with less reduction in 24-hour ambulatory blood pressure compared with the 24-hour blood pressure reduction of angiotensin-converting enzyme inhibitors (mean blood pressure reduction 12.9/7.7mmHg), angiotensin-receptor blockers (mean blood pressure reduction 13.3/7.8mmHg), beta-blockers (mean blood pressure reduction 11.2/8.5mmHg), and calcium antagonists (mean blood pressure reduction 11.0/8.1mmHg).

**Head-to-head comparisons**

Hydrochlorothiazide (12.5mg to 25mg) was less efficacious in lowering systolic 24-hour ambulatory blood pressure compared with angiotensin-converting enzyme inhibitors (WMD 4.45, 95% CI 1.75 to 7.16; I\(^2\)=0%; five RCTs), angiotensin-receptor blockers (WMD 5.13, 95% CI 1.73 to 8.54; I\(^2\)=69%; seven RCTs), beta-blockers (WMD 6.19, 95% CI 5.07 to 7.32; I\(^2\)=0%; three RCTs), calcium antagonists (WMD 4.47, 95% CI 0.85 to 8.08; I\(^2\)=39%; five RCTs).

Hydrochlorothiazide (12.5mg to 25mg) was less efficacious in lowering diastolic 24-hour ambulatory blood pressure compared with angiotensin-converting enzyme inhibitors (WMD 3.74, 95% CI 1.34 to 6.14; I\(^2\)=26%; five RCTs), angiotensin-receptor blockers (WMD 2.89, 95% CI 1.10 to 4.68; I\(^2\)=57%; seven RCTs), beta-blockers (WMD 6.71, 95% CI 5.96 to 7.45; I\(^2\)=0%; three RCTs), calcium antagonists (WMD 4.16, 95% CI 2.06 to 6.26; I\(^2\)=41%; five RCTs).

**Dose response**: There were no significant differences in ambulatory blood pressure reductions between hydrochlorothiazide 12.5mg and 25mg doses. Hydrochlorothiazide dose of 50mg was associated with significant reduction in 24-hour systolic ambulatory blood pressure (WMD 12.0mmHg, 95% CI 8.2 to 15.9; five RCTs) compared with 25mg dose (diastolic blood pressure WMD was 5.4mmHg, 95% CI 3.2 to 7.7).

Results remained unchanged in sensitivity analyses.

No evidence of publication bias was found.

The authors also reported on office blood pressure monitoring, which was not part of the review objective.

**Authors' conclusions**

Hydrochlorothiazide in its commonly used dose of 12.5mg to 25mg had clinically significant inferior antihypertensive efficacy compared with other drug classes used to treat hypertension, as measured using 24-hour ambulatory blood pressure monitoring.

**CRD commentary**

The review question was clearly stated. Three relevant databases were searched, with no language limitations, which minimised potential language bias. Data extraction was carried out in duplicate to reduce the risk of error and bias, but it was unclear whether similar processes were used in study selection and quality assessment.

Trial quality was assessed using appropriate criteria but the results were incompletely reported. Trial details were
adequately reported. Statistical heterogeneity was taken into account in the choice of synthesis. The basis of the decision to include comparisons of office blood pressure monitoring was unclear.

The reliability of the authors' conclusion is uncertain given potential error and bias in study selection and quality assessment processes, and reliance on only a few high-quality trials.

**Implications of the review for practice and research**

**Practice:** The authors stated that the lack of evidence that hydrochlorothiazide commonly used dose of 12.5mg to 25 mg reduced myocardial infarction, stroke, or death, together with the poor antihypertensive efficacy, should strongly motivate physicians to refrain from prescribing hydrochlorothiazide as initial therapy in hypertension.

**Research:** The authors did not state any implications for research.

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