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Review

Effects of different antihypertensive medication groups on cognitive function in older patients: A systematic review

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ABSTRACT

Background: Chronic hypertension has been associated with an increased risk of cognitive decline. Although a link between hypertension and cognitive decline has been established, there is less evidence supported by systematic reviews. The main aim was to compare different antihypertensive drug groups in relation to their effect on cognition in older patients without established dementia using a systematic review.

Method: A systematic search in Medline and Embase through to January 2017 was used to identify randomized controlled clinical trials (RCTs) studying the impact of different antihypertensives on cognition in older patients without dementia. Angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACE-Is), beta-blockers (BBs), diuretics, and calcium channel blockers (CCBs) were included in this review.

Results: The systematic search identified 358 studies. The full text of 31 RCTs was reviewed and a total of 15 RCTs were included in the review. Most studies reported an improvement in episodic memory in patients treated with ARBs versus placebo or other types of antihypertensive drugs. No study showed an improvement in cognition in patients who received diuretics, BBs, or CCBs. Heterogeneity was high in most trials (predominantly in the blinding of participants and investigators).

Conclusion: This review suggests that ARBs can improve cognitive functions in the elderly, especially episodic memory. ACE-Is, diuretics, BBs and CCBs did not seem to improve cognitive function in the elderly but were similarly effective in blood pressure lowering as ARBs.

1. Introduction

Hypertension is a long-term medical condition in which the arterial blood pressure is elevated. Chronic hypertension, particularly midlife high blood pressure, has been associated with an increased risk of cognitive decline and dementia [1]. In a meta-analysis published in 2015 antihypertensive drugs, particularly calcium channel blockers and renin-angiotensin system blockers, were beneficial in preventing cognitive decline and dementia. Thirty-eight relevant publications, corresponding to 18 longitudinal studies, 11 randomized controlled trials, and nine meta-analyses were identified from the 10,251 articles. Antihypertensive medication could decrease the risk of not only vascular dementia but also of Alzheimer's disease. Four randomized controlled trials showed a potentially preventative effect of antihypertensive drugs on the incidence of dementia or cognitive decline [1]. In a network meta-analysis where the authors compared the effects of different classes of antihypertensive drugs on the incidence of dementia and on cognitive function (19 randomized trials (18,515 individuals) and 11 studies (831,674 individuals)), the results showed that antihypertensive treatment had beneficial effects on cognitive decline and prevention of dementia, and indicated that these effects may differ between drug classes, with Angiotensin II receptor blockers (ARBs) possibly being the most effective. ARBs were more effective than Beta-blockers (BBs) (0.67 ± 0.18, $P = 0.01$), diuretics (0.54 ± 0.19, $P = 0.04$) and angiotensin-converting enzyme inhibitors (ACE-Is) (0.47 ± 0.17, $P = 0.04$) in rank [2]. The mean change in blood pressure did not differ significantly between the different antihypertensive drug classes [2]. In another review published by Birns et al., the authors analyzed the effects of blood

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pressure reduction on cognitive function based on pooled data from clinical trials. Sixteen studies with 19,501 subjects were identified. Modest reductions in blood pressure (< 5/3 mmHg) in 13,860 subjects were associated with improvements in Mini-Mental State Examination score [weighted mean difference (WMD) = 0.19; 95% confidence interval (CI) = 0.19–0.19] and performance on immediate (WMD = 0.62; 95% CI = 0.21–1.02) and delayed (WMD = 0.67; 95% CI = 0.23–1.11) logical memory tasks. The authors suggested that blood pressure lowering may have a heterogeneous effect on different aspects of cognitive function [3].

It is known that hypertension is a direct risk factor for vascular dementia (VaD) and recent studies have suggested that hypertension impacts upon the prevalence of Alzheimer's disease (AD) too. A Cochrane's systematic review and meta-analysis included four trials including 15,936 hypertensive subjects, in which only randomized, double-blind, placebo-controlled trials where pharmacological or non-pharmacological interventions to lower blood pressure were given for at least six months, were included [4]. The combined result of the four trials reported that the incidence of dementia was not significantly different between the treatment and placebo groups (236/7767 versus 259/7660, Odds Ratio (OR) = 0.89, 95% CI 0.74–1.07) [4]. There was no convincing evidence from the trials identified that blood pressure lowering in late-life prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease [4]. There were, however, significant problems identified in the data analysis due to the number of patients lost to follow-up and the number of placebo patients who received active treatment. The authors suggested, that more robust results may be obtained by conducting a meta-analysis using individual patient data [4]. This Cochrane's meta-analysis was an upgrade on the previous meta-analysis published by the same authors in 2006 [5].

Although evidence so far about this important question suggests that some systematic reviews and meta-analyses have been available, there is an urgent need for further research within this field that takes into account more recent trials. The main aim of this review was to determine whether antihypertensive drugs have a positive effect on cognition in the elderly. A non-sponsored systematic review was carried out comparing the impact of different antihypertensive therapies on cognitive functioning in older adults with hypertension.

2. Methods

2.1. Search strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines-review protocol were used to conduct this review and is summarized in detail in the Appendix 1 [6]. A comprehensive search of databases was performed in PubMed/Medline and Embase (no limit- February 15, 2017), limited to human studies. The keywords 'Antihypertensive AND Cognition' were searched for in both databases. In addition, references from meta-analyses on this topic were checked. Congress abstracts which were not published as regular articles were excluded. A protocol for the literature search is presented as a flow chart (Fig. 1), and a systematic search was conducted in tandem with a medical research librarian (MI). The included RCTs were also checked manually (whole text) after the first search.

2.2. Inclusion/exclusion criteria

For inclusion in the systematic review, studies had to meet predefined PICOS + E requirements: specified population, intervention, comparator(s), outcome(s), study design, and exclusion criteria, for study inclusion [6]. A filter for randomized controlled trials (RCTs) was applied. Through a screening process, eligible papers were selected, and papers with a population aged on average less than 65 years (without defined standard deviation) as well as those with patients on no antihypertensive medication were excluded. RCTs including patients with any type of dementia (including patients treated with cognitive enhancers) and other cognitive problems except mild cognitive impairment were also excluded. RCTs with any type of cardiovascular problems excluding stroke were not excluded. The results were not divided according to the dosage regime. Study duration was not limited and the minimum number of included patients was not limited. Only papers in English were included in the final analysis. Only papers with an RCT design were included. Both RCT designs including open-label RCTs and"head-to-head" were included in this analysis. RCTs in which the authors did not specify effect values were excluded. RCTs where it was not clear what happened to the patients who withdrew from the study were also excluded (e.g. no information about possible adverse events). We also excluded RCTs where the methodology was not clear enough to obtain final results with appropriate differences. Non-RCTs (prospective cohort, retrospective cohort, and controlled before-and-after) were also excluded from this review. The final findings are presented in a Table 1.

2.3. Study selection and data extraction

A dual review was undertaken for study inclusion and extraction. All findings and extracting was done by M.S. and J.K. independently. When an agreement between M.S. and J.K. had not been established, J.S.M. undertook a third review. We extracted the following from each RCT: title of the paper (full title); name of the authors; publication year; study design (double-blind; single-blind; open-label); inclusion/exclusion criteria; interventions; outcomes (primary and secondary); main conclusions. The following outcomes were assessed: incidence of dementia, cognitive change from baseline, blood pressure level, incidence and severity of side effects. The final results were presented in a Table 1.

To assess the risk of bias, the Cochrane RoB 1.0 tool was used to determine different sources of bias; i.e. random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting, and other biases [7]. The results of the biases are presented in the Table 2. For each RCT the risk of bias was divided into 3 different categories (ratings): – (high risk of bias), + (low risk of bias) and ? (unknown risk of bias). Two reviewers (J.K. and M.S.) independently assessed risk of bias and resolved differences through consensus. RevMan-style Risk of Bias Graphs for systematic reviews were also used (Fig. 2).

2.4. Outcomes, data synthesis, and analysis

Primary outcomes were identified and used for this review. For trials, where a specific primary outcome was not clearly stated (e.g. no comparison to usual care made, and/or when more than one outcome was listed as being primary) the most relevant outcome with a comparison to usual care was identified and reported in the final review. In those RCTs where more outcomes were reported, a hierarchy was made: primary outcome on cognition > secondary outcome on cognition etc. Where primary outcome was not measured in terms of cognition a secondary outcome was used if measured regarding impact on cognition, etc.

Intervention component types and targeted population categories were generated to standardize reporting. A meta-analysis was not performed.