Journal of Clinical Neuroscience 33 (2016) 32–38

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

The association of renin-angiotensin system blockade use with the risks of cognitive impairment of aging and Alzheimer's disease: A meta-analysis

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ARTICLE INFO

Article history:
Received 30 October 2015
Accepted 14 February 2016

Keywords:
Alzheimer disease
Angiotensin-converting enzyme inhibitor
Angiotensin receptor blocker
Cognitive impairment of aging
Meta-analysis
Renin-angiotensin system

ABSTRACT

A quantitative meta-analysis was performed to evaluate the association of renin-angiotensin system blockade (RASB) use with the incidence of cognitive impairment of aging and Alzheimer's disease (AD). Pubmed, Embase, and Cochrane Library databases were searched up to October 2015. Ten studies that assessed the relationship between RASB use and the incidence of cognitive impairment of aging or AD were included. When randomized trials and observational studies were combined, the use of RASB was significantly associated with a reduced risk of AD (risk ratio [RR], 0.80; 95% confidence interval [CI] 0.68–0.92) and cognitive impairment of aging (RR, 0.65; 95% CI 0.35–0.94) compared no use of RASB. Meanwhile, in an analysis of subgroups, both subjects with angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) use were lower incidence of AD (RR, 0.87; 95% CI 0.74–1.00; RR, 0.69; 95% CI 0.44–0.93, respectively) than those without, whereas, indirect comparison between ACEI and ARB revealed no significance in the risk of AD (RR, 1.27, 95% CI 0.85–1.89, $p = 0.245$). In an analysis of cognitive impairment of aging, ARB use (RR, 0.40; 95% CI 0.02–0.78), rather than ACEI use (RR, 0.72; 95% CI 0.36–1.09), was shown to decrease the risk of cognitive impairment of aging. In conclusion, RASB treatments, regardless of the drug class, have benefits on prevention of AD, and the effects of ACEI may analogous to ARB. However, the benefit differs according to drug classes for cognitive impairment of aging, with ARB use, rather than ACEI use, being a potential treatment for reducing the incidence of cognitive impairment of aging.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive and behavioral abnormalities, and is the most common cause of dementia and exerts tremendous burdens on patients and families around the world [1]. The greatest risk factor of AD is advancing age, with multiple memory functions decline [2], as a result of more severe Aβ aggregation [3]. As the burden of AD is increasing, prevention and delay of cognitive impairment of aging are becoming a priority. Therefore, early identification and prevention of cognitive impairment of aging may provide a unique opportunity to protect against the occurrence of overt AD.

Antihypertensive medication use could decrease the risk of the development of dementia [4–7]. Some evidence indicate that renin-angiotensin system blockade (RASB) drugs may be more beneficial than other classes of antihypertensive drugs in the prevention of cognitive decline [8] and dementia [9], independent of their blood pressure lowering properties [10]. Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) both belong to RASB and target the renin-angiotensin system (RAS) in different ways [11]. The RAS involves in the cholinergic pathways [12,13], amyloid-β (Aβ) production and clearance as well as the vascular and inflammatory factors [14], which may contribute to AD [15]. Related studies found Aβ is a potential substrate for angiotensin-converting enzyme (ACE) mediated degradation in both mouse and human brain homogenates [16,17], and this might be of great importance to the pathogenesis of AD. However, ACEI could contribute to increased Aβ burden by interfering with degradation of Aβ [8,18,19], potentially accelerating the severity of AD and the rate of cognitive decline [20].

Additionally, according to several clinical studies, the effects of RASB on cognitive impairment and AD have been discussed controversially. A network meta-analysis [21] found that both the ACEI

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http://dx.doi.org/10.1016/j.jocn.2016.02.036
0967-5868/

and ARB had beneficial effects on cognitive decline and prevention of dementia, with ARB possibly being the most effective. And centrally acting ACEI (CACEI), which cross the blood-brain barrier, had a significantly lower risk of AD versus peripheral angiotensin-converting enzyme inhibitor (PACEI) [22]. However, one meta-analysis showed that antihypertensive medication use could not decrease the risks of AD and cognitive impairment [4]. Another meta-analysis [23] observed that a slower rate of cognitive decline in AD patients with RASB antihypertensive drug, and both ACEI and ARB could decrease the incidence of AD, but an important study [24] was not included and the classes of ACEI were not analyzed. No meta-analysis has concerned about the association of RASB use with the risk of cognitive impairment of aging. Here we conduct an updated and extended meta-analysis to evaluate the association of RASB use on cognitive impairment of aging and AD incidence and to examine the association by type of RASB (e.g., all RASB, ACEI, and ARB).

2. Methods

2.1. Search strategy

A computerised literature search was carried out using the Pubmed, Embase, and the Cochrane library from their commencement to October 2015 with the terms (cogniti* or cognitive impairment of aging or Alzheimer disease) and (antihypertensi* or renin-angiotensin system or angiotensin converting enzyme inhibitor or angiotensin receptor blockade or *pril or *sartan) in title/abstract/keywords. The references of selected papers were manually searched for potentially relevant new papers. Next, the full text of each selected study was screened using the inclusion criteria.

2.2. Eligibility criteria

The inclusion criteria for the analysis were randomized controlled trials (RCTs) or observational studies reporting the effects of ACEI or ARB on cognitive impairment of aging or AD in hypertensive population without neurological disorders. Meanwhile, the RCTs with fatal flaws in their study design or data analysis process and the observational studies with a quality assessment score below five were excluded.

2.3. Quality assessment

The quality of included observational studies was appraised with the Newcastle-Ottawa Scale (NOS) criteria. The NOS is an 8-item instrument, and the NOS grading standard was as follows: (1) selection, total score: 4; (2) comparability, total score: 2; (3) exposure (case-control studies)/outcome (cohort studies), total score: 3. A high score out of a total of 9 points, and a score greater than or equal to 5 indicates high methodological quality. As for RCTs, the methodological quality was assessed according to the guidelines of the Cochrane Collaboration's tool for assessing the risk of bias [25]. The detail of the tool was listed as follows: random sequence generation, allocation concealment, blind, incomplete outcome data, selective reporting, and other possible sources of bias.

2.4. Data abstraction

The following data were extracted from each study: first author, study location, year of publication, study design, number of participants, sex (male), age at baseline, outcome definition, exposure definition, follow-up years, effect estimates and 95% CIs (or information required to compute these), and information required to complete the NOS questionnaire. When multiple effect estimates were reported, maximally adjusted estimates were extracted. When results were presented with and without lag periods, with multiple lag periods, or with multiple periods of exposure ascertainment, the estimates based on the longest time between exposure and disease onset were chosen. If more than one study used the same study population during the same time period, only one study with the highest quality score was included. Two investigators extracted the data and evaluated the study quality independently. Conflicting results were resolved through consultation.

2.5. Statistical analysis

Primary analyses evaluated the association between AD or cognitive impairment of aging and RASB. Subgroup analyses were conducted to examine the differences by study design and RASB classes (ACEI and ARB). Moreover, analyses compared exposed with unexposed for each of the three RASB exposures of interest: all RASB, ACEI, and ARB. For all analyses, we used the random-effects or fixed-effects model with an inverse variance method to calculate the pooled RRs and 95% CIs according to the heterogeneity between studies [26]. The hazard ratios (HRs) and odds ratios (ORs) were considered to be approximations of the relative risks (RRs). The heterogeneity across all of the eligible comparisons was assessed using the Cochrane Q test and quantified using the I^2 test [27]. An error $p \leqslant 0.10$ and an $I^2 > 50\%$ were considered to be indicators of the significant heterogeneity of the outcomes. When the heterogeneity was insignificant, the RR from a fixed-effect model was chosen. If heterogeneity was present, subgroup analysis was adopted for the classified variable and a random-effect meta-regression was performed for continuous variables to explore the potential sources of heterogeneity. Sensitivity analyses were conducted to assess the robustness of the primary analyses for each exposure type, and to exclude studies of poor quality or those with the greatest weight. The RR from a random-effect method was adopted, if the heterogeneity was still significant in spite of subgroup analysis, meta-regression or sensitivity analysis. Publication bias was assessed via visual inspection of the Begg's funnel plot. A two-tailed p-value <0.05 was considered significant for all the analyses (with the exception of heterogeneity). All analyses were performed with STATA12.0 software. Additionally, in order to compare the efficacy between ACEI and ARB, we conducted adjusted indirect comparisons employing the method proposed by Altma et al. [28]. A two-tailed p-value <0.05 was considered significant, if the effect between ACEI and ARB exhibited a statistically significant difference.

3. Results

3.1. Literature search findings and characteristics of the included trials

The search strategy identified 4729 citations. Afterwards, 84 publications were included in the full-text after screening according to titles and abstracts, and 74 were excluded for the reasons shown in Figure 1. Eventually, 10 studies, including one RCT, seven cohort studies, and two case-control studies met our inclusion criteria. Among these included studies, seven reported the association between ACEI use and AD incidence, five reported the association between ARB and AD, three reported specifically the association between ACEI and cognitive impairment, and one reported the association between ARB and cognitive impairment. The characteristics of the 10 studies included in the meta-analysis are shown in Table 1. Furthermore, we assessed the