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Original Study

Excessive Lowering of Blood Pressure Is Not Beneficial for Progression of Brain White Matter Hyperintensive and Cognitive Impairment in Elderly Hypertensive Patients: 4-Year Follow-Up Study



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A B S T R A C T

Keywords:

Systolic blood pressure
excessive old age
cognitive impairment
brain white matter lesions

Objectives: This study was designed to explore the appropriate blood pressure (BP) target required to reduce cognitive decline and brain white matter lesions (WMLs) in elderly hypertensive patients.

Methods: Elderly patients ($n = 294$, ≥ 80 years of age) being treated for hypertension were enrolled in a longitudinal study examining cognitive impairment after an initial assessment and a period of 4 years. All patients underwent neurological and cognitive assessment, laboratory examination, and magnetic resonance imaging of the brain.

Results: The 4-year follow-up examination revealed that body mass index, alcohol consumption, systolic blood pressure (SBP), diastolic blood pressure, and Mini-Mental State Examination (MMSE) all showed a significant decline, whereas fasting plasma glucose, white matter hyperintensities (WMH) volume, and the WMH/total intracranial volume (TIV) ratio were significantly increased when compared with baseline observations. Interestingly, the decline in MMSE, as well as the increment of WMH and WMH/TIV ratio was smaller in patients with SBP ranging from 140 to 160 mm Hg than in those whose SBP was lower than 140 mm Hg or higher than 160 mm Hg ($P < .05$). Furthermore, we observed that a 15 to 35 mm Hg targeted lowering of SBP in the elderly patients was more beneficial to our cognitive analysis than treatments that achieved less than 15 mm Hg or greater than 35 mm Hg ($P < .05$).

Conclusions: In elderly hypertensive patients, there exists a beneficial target for SBP lowering beyond which treatment may not be beneficial for improving or delaying the progression of cognitive impairment and WMLs.

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This study was funded by the National Basic Research Program of China (973 Program, Grant 2013CB530700), the National Natural Science Foundation of China (81070192, 81070141, 81100605, 81270352, and 81270287), the Natural Science Foundation of Shandong Province (BS2013YY017), Independent Innovation Foundation of Shandong University (2012JC034), and the Cardiovascular Exploration Research Foundation of Chinese Medical Doctor Association (DFCMDA201320).

The authors declare no conflicts of interest.

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1525-8610/© 2014 AMDA – The Society for Post-Acute and Long-Term Care Medicine.
<http://dx.doi.org/10.1016/j.jamda.2014.07.005>

As life expectancy is steadily increasing, the number of individuals reaching an age of 80 years or older represents a rapidly growing segment of the population, imposing new health and economic challenges in dealing with a geriatric population. As a result, age-related disease, such as cognitive impairment, represents an important factor affecting quality of life for the elderly. Epidemiological analysis has shown that¹ cognitive decline is highest in the most elderly individuals, with more than half showing signs of dementia.^{2,3} Understanding the reasons for this cognitive impairment and formulating treatment are crucial for coping with the impact resulting from an increasingly aging population.

Brain white matter lesions (WMLs), also known as leukoaraiosis, are commonly observed on structural brain scans using magnetic

resonance imaging (MRI) in older adults.⁴ WMLs may be indicated by the appearance of white matter hyperintensities (WMH) on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences of MRI.^{5,6} WMH is a common indicator of cerebrovascular disease and one of the pathologic changes that emerges early in the pre-symptomatic phase leading to cognitive decline in older people.^{5,7,8} Increased accumulation of WMH volume over time is closely associated with cognitive impairment and increased risk of dementia.⁸

Although the pathogenesis of leukoaraiosis is not completely elucidated, WMLs are more common with advancing age, hypertension, diabetes mellitus, and where there is a history of stroke.⁹ Recently, a large prospective study reinforced the hypothesis that hypertension is a strong predictor of WMLs, and that adequate treatment may reduce the course of WML progression.¹⁰ Other studies also have found that antihypertensive treatment is associated with a reduced risk of dementia and cognitive decline.^{11,12} However, these studies mainly involved older or middle-aged (younger than 80 years) populations. In these populations, hypertension has detrimental effects on cognitive impairment and WMLs.^{13,14} As the elderly (≥ 80 years of age) represent the fastest growing population segment, and they also have a high prevalence of hypertension,¹⁵ an evaluation of the impact of antihypertensive treatment in these frail patients is warranted, especially with regard to efficacy of treatment and cognitive decline.

The main goal and novel aspect of our study was to explore the effect of antihypertensive treatment on cognitive decline, and determine the most appropriate blood pressure (BP) target that is beneficial for limiting cognitive decline and WMLs in elderly hypertensive patients.

Methods

Study Population and Design

This study was conducted in compliance with the Declaration of Helsinki and approved by the medical ethics committee of Shandong Academy of Medical Sciences. Written informed consent was obtained from each participant. The participants were recruited from community-dwelling individuals in Shandong, China. The inclusion criteria were (1) aged 80 or older, (2) a sitting systolic blood pressure (SBP) of 160 mm Hg or higher and a standing SBP of 140 mm Hg or higher,^{16,17} or known treatment for hypertension. Exclusion criteria for this study included (at baseline) secondary hypertension, diabetes mellitus, stroke, end-stage heart disease, dementia, seizures, Parkinson disease, bipolar disorder, schizophrenia, claustrophobia, contra-indication to MRI, or those unwilling to provide informed consent.

This study was a longitudinal observational study. From May 2006 to September 2006, 294 eligible persons were enrolled in this study. All patients underwent a clinical visit to determine body mass index (BMI), BP, cholesterol and blood glucose, a neurological and cognitive assessment, and an MRI of the brain. The assessors were blinded to clinical and imaging outcomes. Eligible participants receiving tailored treatment had been advised by a cardiologist to take measures to treat hypertension during a home interview. As our study was to observe the effect of BP for cognitive function and brain white matter in elderly hypertensive patients, the therapeutic schedule was according to the subject's intention, hence no unified treatment was made. The antihypertensive agents included hydrochlorothiazide, β -adrenoceptor blockers, calcium channel blockers, and so on. Thereafter, clinical BP was measured at baseline and every 6 months. Cognitive performances were assessed at baseline and during the annual visit. Brain MRI scans were performed at baseline and the last follow-up visit.

Clinical Visit

Age, sex, education level, medical history, medication use, and personal health habits (physical activity, smoking, alcohol consumption) and other clinical data were assessed by questionnaire. Education level was categorized into 4 levels (level 1 indicates <5 years of education; level 2, 6–8 years; level 3, 9–11 years; level 4, ≥ 12 years) by the number of years at school. Smoking habits and smoking status were classified as current, former, or never. Alcohol intake was quantified as units per week.

BP Measurements

At every visit, after at least 5 minutes of quiet rest, BP was measured 3 times on the right arm with a 2-minute interval at the sitting position using a fully automatic digital BP monitor (HEM-7071, OMRON [Omron Life Science, Kyoto, Japan]). The average of the 3 measurements was used as the representative clinical BP value. To obtain a more robust measure of BP, 4-year mean of BP measures was calculated. Changes in BP were calculated as the BP difference between the 4-year means and the baseline measurements.

Laboratory Examination

Venous blood samples were obtained from all participants after fasting for at least 12 hours for biochemical determination, performed at the central laboratory of the city hospital by standard and quality-controlled procedures. Concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and fasting plasma glucose (FPG) were determined enzymatically using an autoanalyzer (Type 7600; Hitachi Ltd, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation,¹⁸ when the triglyceride level was less than 4.5 mmol/L.

MRI Scanning Protocol and Processing

At baseline and end follow-up visit, the MRI data were acquired using a 3T Siemens Allegra scanner (Erlangen, Germany) for each patient, according to the follow sequences: T1-weighted magnetization prepared rapid gradient echo sequence (repetition time = 2300 ms; echo time = 3 ms; inversion time = 900 ms; flip angle 9°; matrix 256 $\times$ 240 with 160 slices yielding 1 mm³ isotropic voxels; sagittal acquisition with field of view 256 $\times$ 240 mm² and 1-mm-thick slices), T2-weighted 3-dimensional fast spin-echo, and a FLAIR. Total intracranial volume (TIV) was computed as the sum of gray matter, white matter, and cerebrospinal fluid volumes using the BET and FAST tools from the FSL 4.1 software package (FMRIB, Oxford, UK).¹⁹ WMH volume was computed from an automated subcortical segmentation routine with T1 scan using Freesurfer (version 4.5.0, Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA).²⁰ To account for brain size variability, the total volume of WMH was evaluated using a fraction of the TIV: WMH fraction = (total WMH [mL]/TIV [mL]) $\times$ 100%.²¹

Assessment of Cognitive Function

Assessment of cognitive function was evaluated using the Mini-Mental State Examination (MMSE), which is a validated and powerful tool for diagnosis in the advanced stages of cognitive impairment.²² It is a 30-point test that consists of 5 areas of possible cognitive impairment: orientation, registration, attention and calculation, and language. Possible scores on the MMSE range from 0 to 30 points, with lower scores indicating impaired global cognitive functioning. To ensure methodological reliability, the evaluators attended a training session conducted by neuropsychologists who were experts in cognitive function measurements. Certification required

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