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Featured Article

# The effects of DL-3-n-butylphthalide in patients with vascular cognitive impairment without dementia caused by subcortical ischemic small vessel disease: A multicentre, randomized, double-blind, placebo-controlled trial

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**Abstract**

**Background:** Vascular cognitive impairment without dementia is very common among the aged and tends to progress to dementia, but there have been no proper large-scale intervention trials dedicated to it. Vascular cognitive impairment without dementia caused by subcortical ischemic small vessel disease (hereinafter, subcortical Vascular cognitive impairment without dementia) represents a relatively homogeneous disease process and is a suitable target for therapeutic trials investigating Vascular cognitive impairment without dementia. Preclinical trials showed that dl-3-n-butylphthalide (NBP) is effective for cognitive impairment of vascular origin.

**Methods:** In this randomized, double-blind, placebo-controlled trial, we enrolled patients aged 50–70 years who had a diagnosis of subcortical Vascular cognitive impairment without dementia at 15 academic medical centers in China. Inclusion criteria included a clinical dementia rating $\geq$0.5 on at least one domain and global score $\leq$0.5; a mini-mental state examination score $\geq$20 (primary school) or $\geq$24 (junior school or above); and brain magnetic resonance imaging consistent with subcortical ischemic small vessel disease. Patients were randomly assigned to NBP 200 mg three times daily or matched placebo (1:1) for 24 weeks according to a computer-generated randomization protocol. All patients and study personnel were masked to treatment assignment. Primary outcome measures were the changes in Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog)

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and clinician's interview-based impression of change plus caregiver input (CIBIC-plus) after 24 weeks. All patients were monitored for adverse events (AEs). Outcome measures were analyzed for both the intention-to-treat (ITT) population and the per protocol population.

**Results:** This study enrolled 281 patients. NBP showed greater effects than placebo on ADAS-cog (NBP change −2.46 vs. placebo −1.39; $P = .03$; ITT) and CIBIC-plus (80 [57.1%] vs. 59 [42.1%] patients improved; $P = .01$; ITT). NBP-related AE were uncommon and primarily consisted of mild gastrointestinal symptoms.

**Conclusions:** Over the 6-month treatment period, NBP was effective for improving cognitive and global functioning in patients with subcortical vascular cognitive impairment without dementia and exhibited good safety.



*Keywords:* DL-3-n-Butylphthalide; Vascular cognitive impairment without dementia; Cerebral small vessel disease; Randomized controlled trial; Multicentre study

## 1. Introduction

Vascular cognitive impairment without dementia refers to cognitive disorders that arise from underlying vascular causes in patients who do not meet the criteria for vascular dementia (VaD) [1,2]. It is a very common form of cognitive impairment among the aged globally. The Canadian Study of Health and Aging (CSHA) reported that vascular cognitive impairment without dementia was the most prevalent form of vascular cognitive impairment among those aged 65–84 years, with an estimated prevalence of 2.6% [3,4]. The American Aging, Demographics, and Memory Study reported that the prevalence of vascular cognitive impairment without dementia among those aged ≥71 years was 5.7%, accounting for 25.6% of the total cases, second only to the prodromal AD subtype (34.2%) [5]. With a high prevalence of cerebral vascular disease in China, vascular cognitive impairment without dementia might be relatively more common. The China Cognition and Aging Study found that vascular cognitive impairment without dementia is the most common subtype of mild cognitive impairment (MCI) in China, accounting for 42.0% of the total cases. The prevalence of vascular cognitive impairment without dementia is 8.7% among Chinese people over the age of 65 years, overwhelming that of amnestic MCI (6.1%) [6]. Patients with vascular cognitive impairment without dementia are at high risk for developing dementia. The CSHA study found that 50% of those patients with vascular cognitive impairment without dementia progressed to dementia over 5 years of follow-up, and the rate of institutionalization and mortality among individuals with vascular cognitive impairment without dementia is similar to that of those with VaD [1,3]. These results emphasize the importance of vascular cognitive impairment without dementia and call for more attention and greater effort toward addressing this relatively neglected patient population. Early intervention of vascular cognitive impairment without dementia holds the potential to delay or even reverse the cognitive deterioration, and from a public health viewpoint, may lead to a global decrease of incident dementia. However, there has been no effective treatment specifically for vascular cognitive impairment without dementia to date. Due to the significant heterogeneity in the pathogenesis, clinical features, and prognosis of vascular cognitive impairment without dementia, clinical drug trials evaluating this disorder may need to focus on a particular subtype to obtain an accurate efficacy evaluation. Vascular cognitive impairment without dementia caused by subcortical ischemic small vessel disease (hereinafter, subcortical vascular cognitive impairment without dementia) is a common subtype of vascular cognitive impairment without dementia and is considered relatively homogeneous in terms of its clinical and neuroimaging features. Therefore, it is suitable as a specific target for therapeutic trials investigating vascular cognitive impairment without dementia [7].

DL-3-n-butylphthalide (NBP) (Fig. 1) is a synthetic chiral compound containing L- and D-isomers of butylphthalide. It is developed from L-3-n-butylphthalide, which was initially isolated as a pure component from seeds of *Apium graveolens* in 1978 by researchers of Institute of Medicine of Chinese Academy of Medical Sciences. Studies in the past several decades have demonstrated that NBP is effective in protecting against ischemic cerebral injury, including inhibiting platelet aggregation, alleviating oxidative damage and mitochondria dysfunction in middle cerebral artery occlusion rats, improving microcirculation in focal cerebral ischemia rats, and reducing neurologic deficit after stroke in spontaneously hypertensive rats [8–13]. NBP was approved by the State Food and Drug Administration of China (SFDA) as a therapeutic drug for treatment of ischemic stroke in 2005 based on the results of the multicentre phase 2 and 3 randomized controlled clinical trials, which consistently reported that NBP was effective in improving neurologic function after stroke, with a good safety and tolerability [14,15]. Not only for ischemic stroke, NBP has been reported to increase the expression of NR2B and synaptophysin in hippocampus of aged rats after chronic cerebral hypoperfusion and increasing brain acetylcholine level, which are important processes involved in learning and memory [16,17]. It could alleviate the learning and