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Article

The efficacy and safety of nimodipine in acute ischemic stroke patients with mild cognitive impairment: a double-blind, randomized, placebo-controlled trial

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ABSTRACT

Nimodipine might be effective in subcortical vascular dementia (VaD). Its benefit in preventing further cognitive decline in patients with acute ischemic stroke (AIS) and vascular mild cognitive impairment (VaMCI) remains to be established. In this multicenter, double-blind trial, we randomly assigned 654 eligible patients to nimodipine 30 mg three times a day or placebo. The primary outcome was any cognitive decline defined by the changes on the Mini-Mental State Examination (ΔMMSE ≤ -3) or vascular AD assessment scale cognitive subscale (ΔADAS-cog ≥ 4) at 6 months. Secondary outcomes included any distribution shift of ΔADAS-cog, ΔMMSE or cognitive improvement defined by ΔADAS-cog ≤ -2, or ΔMMSE ≥ 0. The primary outcome in the nimodipine group and placebo group were similar for ΔMMSE ≤ -3 (4.18% and 7.22%, respectively, $P = 0.15$) and ΔADAS-cog ≥ 4 (8.36% and 8.93% respectively, $P = 0.88$). The distribution shift of ΔADAS-cog and ΔMMSE differed significantly between the two groups ($P = 0.03$ and $P = 0.05$ respectively). Cognitive improvement occurred in 55.4% in the nimodipine group and 43.6% in the placebo group measured by ΔADAS-cog ≤ -2 (Odds Ratio, 1.54; 95% confidence interval [CI] 1.10–2.14, $P < 0.01$) or 84.0% and 74.6% respectively by ΔMMSE ≥ 0 (Odds Ratio, 1.79; 95% CI 1.18–2.70, $P < 0.01$). Nimodipine was associated with better cognitive function in the memory domain. The adverse events rate was similar in two groups. This study is registered with ClinicalTrials.gov, NCT01220622. Nimodipine did not show benefit to prevent cognitive decline in AIS patients with VaMCI, but improved cognition moderately, especially measured in the memory domain.

1. Introduction

Vascular mild cognitive impairment (VaMCI), caused by cerebrovascular disease, is a predementia stage. VaMCI patients often demonstrated objective symptomatic cognitive impairment but are independent in their routine activities of daily living [1].

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VaMCI is common in stroke patients and more than half of them develop VaMCI during the first 3 months after stroke onset [2]. About 30%–50% of patients with VaMCI will develop dementia in 5 years [3]. Vascular dementia (VD), as well as VaMCI, are independently associated with lower Quality of Life (QoL) after stroke [4]. The risk for recurrent stroke and for the mortality will double in long term follow up in stroke patients with VD, after adjustment for the significant covariates [5–7]. The annual cost of dementia and care givers' support has been estimated at $818 billion globally in 2015, and was expected to exceed $1 trillion in 2020 [8]. Hence, the prevention of cognitive decline from VaMCI into VD is urgent. Currently, there is no effective therapy to prevent the cognitive decline in patients with VaMCI [9–11].

Several preclinical studies implied that calcium channel blockers (CCBs) may improve patient's cognitive function by blocking the influx of calcium [12].

Nimodipine, a selective calcium channel blocker, may have beneficial effects on patients with symptoms of dementia as reported in a recent meta analyses [13]. It showed benefit in patients with subcortical VD in a subgroup analysis [14,15]. Other than that, nimodipine might prevent cognitive decline in VD patients in a secondary outcome analysis by MMSE [16]. However, the efficacy of nimodipine on treating VaMCI has not been investigated [9–11].

Thus, we hypothesized that acute stroke patients with VaMCI may benefit from early nimodipine treatment. We conducted a randomized, double-blind, placebo controlled trial to study the efficacy and safety of Nimodipine in treating patients with AIS and VaMCI.

2. Methods

2.1. Study design and patients

The study design was described previously [17]. NICE was an investigator-initiated, multicenter, prospective, randomized, double-blind, placebo-controlled trial [5]. Eligible patients were 30–80 years old with vascular mild cognitive impairment (VaMCI), had AIS within 7 days before enrollment. International Classification of Diseases–10 (ICD–10) was used to code the diagnosis of AIS, plus the verification on the Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) of brain [18,19]. MCI was screened by the Montreal Cognitive Assessment (MoCA) and Mini-mental State Examination [20–23] and diagnosed according to the ASA guideline [1]. A vascular cognitive impairment was identified by the Hachinski Ischemic Score (HIS) [24]. Exclusion criteria included a history of mental diseases, dementia diagnosed before the index stroke, cognitive impairment or dementia of other causes.

The protocol and all amendments were approved by the Ethics Committee at each site. Written informed consent was provided by all the patients or by their legal representatives.

2.2. Randomization and masking

A statistical programmer generated the randomization codes and did not participate in patient enrollment or statistical analysis. Treatment was allocated on a 1:1 ratio with a randomization envelope. We used a block randomization design and four treatment packs were allocated in each block within the same study site. Study drugs were tablets identical in appearance for nimodipine and placebo. Patients, investigators, staff, and the sponsor were blinded to the treatment assignment. Statisticians analyzed outcomes after blinding was broken on the basis of a statistical analysis plan finalized before blinding was broken.

2.3. Procedures

The eligible patients were given nimodipine 30 mg three times daily (tid) or placebo tid orally with randomization for 6 months. Secondary prevention therapy for stroke was prescribed according to the ASA Guideline [25]. Baseline examinations included demographic information, medical history, educational background, National Institutes of Health Stroke Scale (NIHSS), and imaging characteristics (Alberta Stroke Program Early CT Score (ASPECTS)/Fazekas Scale/CHIPS). MMSE, ADAS-Cog, MoCA and Frontal Assessment Battery (FAB) were performed at baseline and 6 months after stroke onset. Concomitant Medications and adverse events were recorded during the study period.

2.4. Study outcomes

The primary and secondary efficacy outcomes and safety outcomes were defined according to the published results from previous studies (Table S1 online). In brief, the primary efficacy outcome was the proportion of patients with cognitive function decline defined by at least 3 points decline on the MMSE total score or 4 points increase on the ADAS-cog score at 6 months follow-up compared to baseline [16,26,27]. The secondary efficacy outcome included the distribution shift of the change of cognitive function scores from baseline to 6 months follow-up. The cognitive improvement was defined by ΔADAS-cog change of ≤ -2 or ΔMMSE change ≥ 0 [28], the change of ≥ 2 on MoCA [20,29] or FAB of ≥ 2.5 from the baseline to 6 months follow-up [30,31].

Safety outcomes included any adverse events and abnormalities in clinical assessment or laboratory testing (hematologic and serum chemical testing, urinalysis, assessment of vital signs, physical and neurologic examinations). An independent external data and safety monitoring committee reviewed the safety data.

2.5. Statistical analysis

All statistical analyses were performed as outlined in the protocol. Analysis was done in the intention-to-treat population. Baseline characteristics were compared between the two treatment groups. χ^2 test was used for categorical variables and t test for continuous variables. Last-observation-carried-forward (LOCF) was used to impute missing values for cognitive function tests at follow-up at 6 months. Logistic regression was used to evaluate the effect of nimodipine as compared to placebo. Shift analysis was performed to evaluate the changes of distribution in the ADAS-cog and MMSE scores from baseline to follow up at 6 months in both groups. Prespecified subgroup analysis was performed in patient strata according to their baseline characteristics including age, sex, diabetes, education level, Vit B12, NIHSS score, baseline MoCA score, FAB score, Fazekas and CHIPS score. All statistical tests were two-sided hypothesis tests done at the 5% level of significance; CIs were two-sided at 95% through out. The statistical software used was SAS, version 9.4. NICE is registered with ClinicalTrials.gov, number NCT01220622.

3. Results

Between October 2010 and August 2013, a total of 5,028 patients with stroke were screened at 23 study sites in China. Most of the study sites were tertiary care hospitals (21/23) and/or teaching hospitals (20/23), and 2 were comprehensive secondary care hospitals. Of all screened, 654 patients were enrolled into this trial. Among them, 329 received nimodipine, and 325 received matching placebo. Fig. 1 showed the profile of all patients enrolled in this

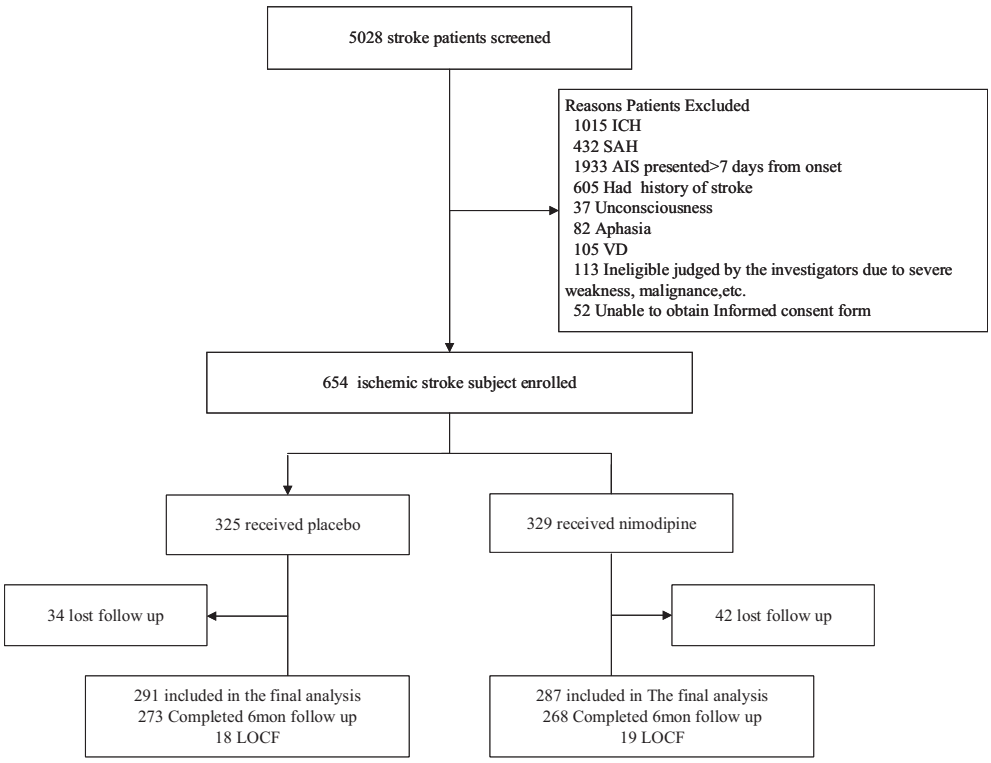

Fig. 1. The trial profile. LOCF, last observation carried forward.

trial. Forty-two in the treatment group and 34 in the placebo group were lost to follow-up. In the end, a total of 578 patients (287 in the treatment group and 291 in the placebo group) were included in the final analysis.

The two study groups were well balanced with their baseline characteristics (Table 1). Overall, 75.1% of the patients were male; the mean age was 60.5 years (SD 9.4). The baseline cognitive function scores were: 20.83 ± 3.49 on MoCA, 26.80 ± 2.22 on MMSE, 9.42 ± 3.89 on ADAS-cog-11, and 13.94 ± 2.38 on FAB.

There was no significant difference in the primary efficacy outcome between the two treatment groups in the proportion of cognitive decline (Table 2). The frequency of having a $\Delta MMSE \leq -3$ (the change from baseline to 6 months follow-up) was 4.18% (12/287) in the nimodipine group, compared to 7.22% (21/291) in the placebo group (OR = 0.56, 95% CI 0.27–1.16, $P = 0.15$). The frequency of $\Delta ADAS\text{-}cog$ of ≥ 4 (the change from baseline to 6 months) was 8.36% (24/287) in the nimodipine group, compared to 8.93% (26/291) in the placebo group (OR = 0.93, 95% CI 0.52–1.66, $P = 0.88$).

However, significant differences in the distribution of $\Delta ADAS\text{-}cog$ ($P = 0.03$) and $\Delta MMSE$ ($P = 0.05$) scores (Fig. 2) between the two treatment groups was present. The cognitive improvement occurred more frequently in the nimodipine group than in the placebo group when the secondary efficacy endpoint was defined by the changes from baseline to 6 months on $\Delta ADAS\text{-}cog \leq -2$ or $\Delta MMSE \geq 0$. In the nimodipine group, 55.4% (159/287) of the patients had an improved cognitive function, compared to 43.6% (127/291) in the placebo group measured by $\Delta ADAS\text{-}cog \leq -2$ (OR = 1.54, 95% CI 1.10–2.14, $P < 0.01$). About 84.0% (241/287) of the patients in the nimodipine group had an improved cognitive function, compared to 74.6% (217/291) in the placebo group by $\Delta MMSE \geq 0$ (OR = 1.79, 95% CI 1.18–2.70, $P < 0.01$) (Table 2). The frequency of the cognitive improvement

Table 1
Patient characteristics of the trial participants.[a)]

	Total (n = 578)	Nimodipine (n = 287)	Placebo (n = 291)
Male-no. (%)	434(75.1)	222(77.4)	212(72.9)
Age (a)	60.5 ± 9.4	60.9 ± 9.5	60.1 ± 9.4
Education (a)	9.4 ± 3.6	9.5 ± 3.7	9.2 ± 3.5
Tobacco-no. (%)	282(48.8)	135(47.0)	147(50.5)
Alcohol-no. (%)	224(38.8)	109(38.0)	115(19.9)
Dyslipidemia-no. (%)	140(24.2)	71(24.7)	76(26.1)
Diabetes mellitus-no. (%)	147(25.4)	71(24.7)	76(26.1)
Hypertension-no. (%)	415(71.8)	198(69.0)	217(74.6)
Coronary disease-no. (%)	85(14.7)	39(13.6)	46(15.8)
Baseline NIHSS (median, IQR)	10(9–12)	10(9–12)	10(9–12)
≤5	3(0.5)	1(0.4)	2(0.7)
6–10	323(55.9)	155(54.0)	168(57.7)
≥11	252(43.6)	131(45.6)	121(41.6)
Time from onset to Randomize			
≤72 h	166(28.7)	80(27.9)	86(29.6)
>72 h	412(71.3)	207(72.1)	205(70.4)
ASPECT score (median, IQR)	12(11–13)	12(11–13)	12(11–13)
>10	465(81.0)	238(82.9)	227(79.1)
8–10	96(16.7)	42(14.6)	54(18.8)
5–7	13(2.3)	7(2.5)	6(2.1)
<5	0	0	0
Fazekas score (median, IQR)	2(1–3)	2(1–3)	2(1–3)
0–2	354(61.9)	178(62.2)	176(61.5)
3	218(38.1)	108(37.8)	110(38.5)
CHIPS score (median, IQR)	16(7–23)	16(8–24)	15(6–23)
MoCA	20.8 ± 3.5	20.84 ± 3.7	20.8 ± 3.3
MMSE	26.8 ± 2.2	26.8 ± 2.3	26.8 ± 2.2
ADAS-cog	9.42 ± 3.9	9.28 ± 3.6	9.55 ± 4.2
FAB	13.9 ± 2.4	13.9 ± 2.3	14.0 ± 2.4

[a)] Qualitative variables were presented as no and percentage (%). Quantitative variables were presented as means ± SD ($\bar{\chi}$±s) or median (interquartile range, IQR).

Table 2
Primary and secondary outcomes, according to treatment group.

Outcome	Nimodipine (n = 287)	Placebo (n = 291)	OR (95% CI)	P value
Primary outcome				
MMSE ≤ -3 change from baseline to 6 mon (n, %)	12(4.2)	21(7.2)	0.56(0.27–1.16)	0.15
ADAS-Cog ≥ 4 change from baseline to 6 mon (n, %)	24(8.4)	26(8.9)	0.93(0.52–1.66)	0.88
Secondary outcome				
ADAS-Cog ≤ -2 change from baseline to 6 mon (n, %)	159(55.4)	127(43.6)	1.60(1.16–2.23)	<0.01
MMSE($\geq$0, change from baseline to 6 mon (n, %)	241(84.0)	217(74.6)	1.79(1.18–2.70)	<0.01
MoCA ≥ 2, change from Baseline to 6 months (n, %)	160(56.1)	160(55.8)	1.02(0.73–1.41)	0.92
FAB ≥ 2.5, change from Baseline to 6 months (n, %)	47(16.4)	48(16.5)	0.99(0.64–1.54)	0.97
Mortality (n, %) 6 months	0	0	–	–

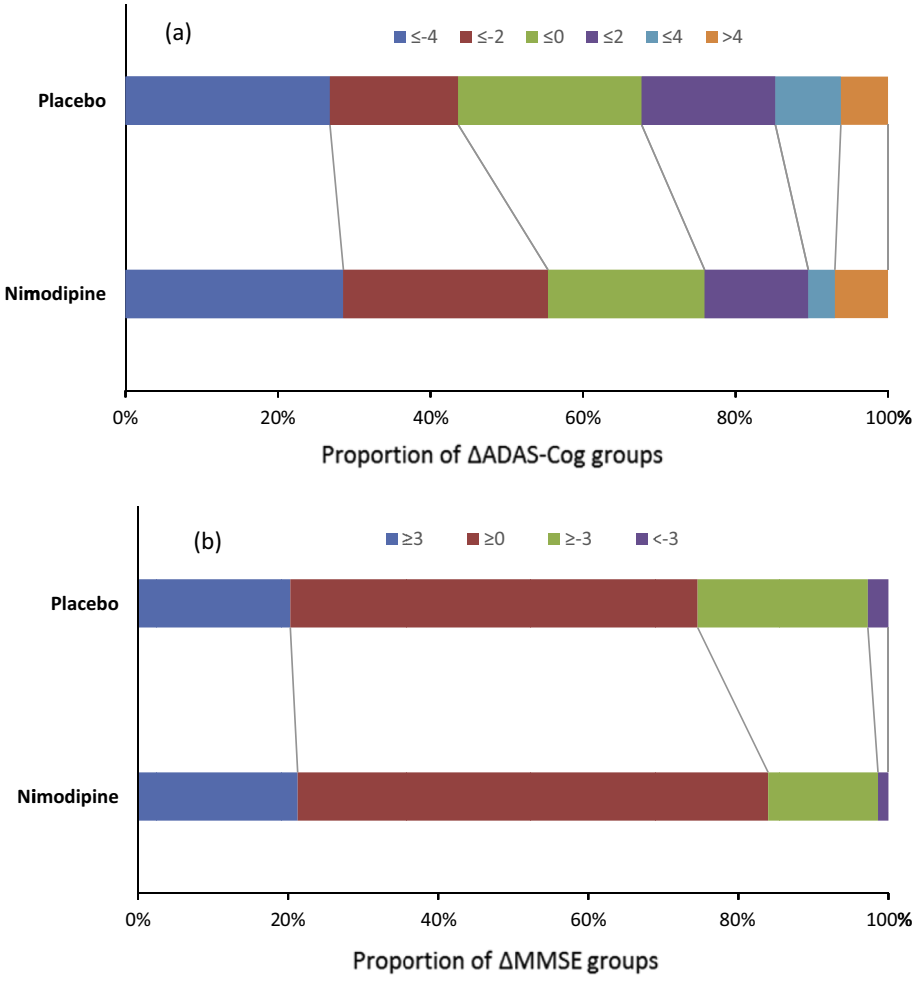

Fig. 2. Cognitive function change from baseline to 6 months. (a) Change of ADAs-cog (P = 0.03); (b) change of MMSE (P = 0.05). ADAs-cog, AD assessment scale cognitive subscale; MMSE, Mini-Mental State Examination.

defined by the changes from baseline to 6 months on ΔMoCA ≥ 2 or ΔFAB ≥ 2.5 was not significantly different between the two groups (Table 2).

Cognitive domains were examined separately. There was a significant improvement in the orientation domain of ADAS-cog in the nimodipine group compared to the control group. Both MMSE and MOCA scores revealed the same trend, but the difference was not significant. The registration domain in ADAS-cog or the recall domain in MMSE of the patients was also better in the nimodipine group (Table 3).

In the subgroup analysis, no treatment effects were detected in the prespecified subgroups of age, sex, diabetes, educational level, Vit B12, NIHSS score, baseline MoCA score, FAB score, Fazekas and CHIPS score (Figs. S1, S2 online, $P > 0.05$ for all comparisons).

Results of safety analysis were listed in Table S2 (online). There was no significant difference in the number of adverse events or serious adverse events. No serious adverse event or study medication discontinuation was associated with the treatment assignment.

Table 3
Cognitive domains change from baseline to 6 months in both treatment groups [a)].

Outcome	ΔMMSE subtest scores			ΔADAS-cog subtest scores			ΔMoCA subtest scores		
	Nimodipine (n = 287)	Placebo (n = 291)	P value	Nimodipine (n = 287)	Placebo (n = 291)	P value	nimodipine (n = 287)	placebo (n = 291)	P value
Memory									
Orientation	0.28 ± 1.09	0.20 ± 1.15	0.06	−0.14 ± 0.75	−0.004 ± 0.82	0.01	0.26 ± 0.80	0.12 ± 0.81	0.06
Z-score	0.03 ± 0.98	−0.03 ± 1.02	0.06	−0.09 ± 0.95	0.09 ± 1.04	0.01	0.08 ± 0.99	−0.08 ± 1.00	0.06
Registration	0.02 ± 0.35	0.004 ± 0.41	0.33	−0.71 ± 1.43	−0.41 ± 1.62	0.02	–	–	–
Z-score	0.02 ± 0.92	−0.02 ± 1.08	0.33	−0.10 ± 0.93	0.10 ± 1.06	0.02			
Recall	0.26 ± 0.84	0.09 ± 0.94	0.05	−0.61 ± 2.26	−0.61 ± 2.51	0.64	0.73 ± 1.46	0.59 ± 1.55	0.28
Z-score	0.09 ± 0.94	−0.09 ± 1.05	0.05	0.001 ± 0.95	−0.001 ± 1.05	0.64	0.05 ± 0.97	−0.05 ± 1.03	0.28
Attention									
Attention	–	–	–	−0.18 ± 1.10	−0.23 ± 1.40	0.50	0.36 ± 1.01	0.24 ± 1.10	0.38
Z-score				0.02 ± 0.87	−0.02 ± 1.11	0.50	0.06 ± 0.96	−0.05 ± 1.04	0.38
Language									
Language	0.28 ± 1.22	0.26 ± 1.10	0.86	0.48 ± 1.04	0.44 ± 1.00	0.65	0.24 ± 1.01	0.14 ± 0.97	0.14
Z-score	0.01 ± 1.05	−0.01 ± 0.95	0.86	0.02 ± 1.02	−0.02 ± 0.98	0.65	0.05 ± 1.02	−0.05 ± 0.98	0.14
Naming	0.22 ± 0.83	0.14 ± 0.78	0.38	−0.23 ± 0.82	−0.22 ± 0.68	0.62	0.09 ± 0.50	0.17 ± 0.60	0.12
Z-score	0.05 ± 1.03	−0.05 ± 0.97	0.38	−0.01 ± 1.09	0.01 ± 0.90	0.62	−0.07 ± 0.90	0.07 ± 1.09	0.12
Visuoexecutive									
Constructional praxis	0.00 ± 0.09	0.004 ± 0.11	0.66	−0.09 ± 0.69	−0.08 ± 0.77	0.45	0.61 ± 1.10	0.54 ± 1.21	0.24
Z-score	−0.02 ± 0.90	0.02 ± 1.09	0.66	−0.01 ± 0.94	0.01 ± 1.05	0.45	0.03 ± 0.96	−0.03 ± 1.04	0.24
Ideational praxis	0.12 ± 0.46	0.09 ± 0.56	0.57	–	–	–	–	–	–
Z-score	0.03 ± 0.90	−0.03 ± 1.09	0.57						
Abstraction	–	–	–	–	–	–	0.25 ± 0.84	0.17 ± 0.80	0.25
Z-score							0.05 ± 1.02	−0.05 ± 0.98	0.25

[a)] Cognitive domain change showed different results among the three tests, which is reasonable. Average *Z*-score is recommended to cluster the similar tests for each domain.

4. Discussion

In this double-blind, placebo-controlled trial, treatment with nimodipine was not beneficial in AIS patients with MCI based on the designated primary outcomes: the changes of scores of MMSE of ≤ -3 or ADAS-cog ≥ 4 from the baseline.

Our results were similar to the previous studies for nimodipine in VD patients. The Scandinavian Multi-Infarct Dementia Trial failed to show a significant effect of nimodipine on cognitive assessment in patients with multi-infarct dementia [6], although in the subgroup analysis of those with small vessel subcortical VaD, nimodipine was associated with less cognitive decline [12]. In another trial treating patients with subcortical VD, the primary outcome, evaluated by the Sandoz Clinical Assessment Geriatric scale 5-point variation, did not differ between the nimodipine group and the placebo group, but the patients in the nimodipine group had less cognitive deterioration ΔMMSE ≤ -3 (28.1% versus 50.5%, $P < 0.01$) [16].

VaMCI is a prodromal stage of dementia. In our trial in VaMCI, the percentage of the patients with cognitive decline were much lower than those in the previous studies in the VD patients. Both the nimodipine and the placebo group showed cognitive improvement instead of cognitive decline in AIS patients in our trial (Table S3 online). In the previous trials for VD patients with subacute or chronic stroke, both the nimodipine group and the placebo group showed cognitive decline [14–16]. Our study had a low statistic power because of a relatively minor percentage of cognitive decline.

Nimodipine may have improved the cognitive function as defined by the change of scores of ADAS-cog of ≤ -2 or MMSE ≥ 0 in the VaMCI patients from baseline to 6 months. There was a significant shift of the distribution of ΔADAS-cog and ΔMMSE scores in nimodipine group compared to the placebo group.

The effect size of nimodipine in VaMCI patients showed in this trial is similar to that of cholinesterase inhibitors or NMDA receptor antagonist on VD as previously reported [28]. The benefit for cholinesterase inhibitors or NMDA receptor antagonists in VD patients was small but significant cognitive improvement was seen. The difference on ΔADAS-cog from baseline to 6 months showed about 2 points decrease between the treatment group and the placebo group in VD patients, nearly half of the effect reported in AD trials. Some guidelines recommend cholinesterase inhibitors or NMDA receptor antagonist for patients with vascular dementia [1,10], although the benefit was moderate. By now, no robust evidence exists as to improve the cognitive function in AIS patients with MCI. In our trial, nimodipine did improve cognition moderately in these patients, especially measured in the memory domain. Our trial indicate that nimodipine might benefit the patients with VaMCI. Further trials are needed to test the tendency. The cognitive decline was less frequent in AIS with MCI, so the power for the primary endpoints in our trial was low. We suggest cognitive improvement be the primary endpoints instead of cognitive decline in the trials on VaMCI.

The mechanism of vascular cognitive impairment is very complex, including inflammation, chronic hypoperfusion, deposition of β amyloid, apoptosis, cytokines release, excitotoxicity, the breakdown of BBB, etc [7]. Such complexity may explain why the benefit of nimodipine, cholinesterase inhibitors or NMDA receptor antagonist was small for patients with VCI. Due to multiple mechanisms in the development of dementia, nimodipine failed to show efficacy in patients with subcortical dementia in the former trial. We can not excluded mixed (vascular and neurodegenerative) MCI, because no Positron Emission Tomography (PET) or biomarker. Perhaps in patients with VCI, those related to cholinergic mechanisms should be excluded and the effect of nimodipine could be larger in patients without cholinergic mechanisms.

In this clinical trial, we found that nimodipine might improve cognitive function in domains such as memory when measured by both ADAS-cog and MMSE. Memory impairment was an independent predictor of poor long-term survival and death in previous study [7]. Whether memory improvement can lead to better outcome need to be studied further. There were certain discrepancy

for cognitive domains comparation in different scales. The sensitivity and specificity for the ADAS-cog, MoCA and MMSE in vascular cognitive impairment need to be discussed further.

The NICE trial has several strengths. To the best of our knowledge, this is the largest trial to test the efficacy and safety of nimodipine in AIS with VaMCI. And this is the first trial that only recruited patients with AIS and cognitive impairment without dementia. These participants could more likely benefit from nimodipine than those already developed dementia after AIS. In addition, cognitive function was evaluated by several scales at baseline and during the follow up period to better understand the possible effect of nimodipine.

Our study also has several limitations. The TOAST classification for stroke subtype was not collected, and therefore any effect of nimodipine in patients with different subtypes of stroke could not be studied. In addition, other functional outcome was not evaluated in this trial. Finally, participants enrolled were all Chinese and thus the findings in the NICE trial may not apply to other stroke population with VaMCI.

5. Conclusion

Nimodipine did not show benefit to prevent cognitive decline as defined by the study primary outcomes in patients with AIS and VaMCI. However, these patients had moderate cognitive improvement from nimodipine, especially in the memory domain.

Conflict of interest

The NICE trial received funding from Bayer HealthCare Pharmaceuticals China.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scib.2018.12.006.

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