ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of the Association of Nimodipine and Choline Alphoscerate in the Treatment of Cognitive Impairment in Patients with Cerebral Small Vessel Disease. The CONIVaD Trial

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Abstract

Background No approved treatment is available for patients with vascular cognitive impairment (VCI) due to cerebral small vessel disease (SVD).

Objective The CONIVaD (Choline Alphoscerate and Nimodipine in Vascular Dementia) study aimed to investigate the feasibility, efficacy, and safety of a combined treatment with choline alphoscerate and nimodipine in patients with SVD and mild-to-moderate cognitive impairment.

Methods Within this pilot, single-center (university hospital), double-blinded, randomized clinical trial, patients were randomized to two arms: 1-year treatment with nimodipine 30 mg three times a day (TID) plus choline alphoscerate 600 mg twice a day (BID) (arm 1) or nimodipine 30 mg TID plus placebo BID (arm 2). Patients underwent an evaluation at baseline and after 12 months. Cognitive decline, defined as a ≥ 2-point loss on the Montreal Cognitive Assessment, was the primary endpoint. Functional, quality of life, other cognitive measures, and safety were secondary endpoints. Treatment adherence was measured by the count of medicine bottles returned by patients.

Results Sixty-two patients were randomized (31 each arm). Fourteen patients (22%) dropped out for reasons including consent withdrawal ($n = 9$), adverse reactions ($n = 4$), and stroke ($n = 1$). Forty-eight patients (mean ± SD age 75.1 ± 6.8 years), well balanced between arms, completed the study. Regarding adherence, of the prescribed total drug dose, > 75% was taken by 96% of patients for choline alphoscerate, 87.5% for placebo, and 15% for nimodipine. No statistically significant differences were found between the treatment groups for the primary cognitive outcome, nor for the secondary outcomes. Eight patients had non-serious adverse reactions; five presented adverse events.

Conclusion Patients' adherence to treatment was low. With this limitation, the combined choline alphoscerate–nimodipine treatment showed no significant effect in our cohort of VCI patients with SVD. The safety profile was good overall.

Trial Registration Clinical Trial NCT03228498. Registered 25 July 2017.

1 Introduction

Vascular cognitive impairment (VCI) encompasses a wide range of possible etiologies, among which cerebral small vessel disease (SVD) is one of the most relevant due to its impact in terms of social and economic burden [1–3]. Several efforts have been made to identify a drug effective in VCI, but evidence is inconclusive, and at present, no approved pharmacological treatment exists [4, 5].

Key Points

The association of choline alphoscerate and nimodipine showed no efficacy in improving cognitive abilities in patients with cerebral small vessel disease.

Treatment safety was adequate, while patients' adherence was not optimal, thus reducing the rate of patients treated as per protocol.

Further efforts are needed to find a specific treatment for patients with cognitive impairment and cerebral small vessel disease.

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Acetylcholinesterase inhibitors, approved for the treatment of Alzheimer's disease, have been tested in VCI patients according to the hypothesis of a functional disconnection in subcortical–cortical pathways, and thus in the cholinergic cortical network [6]. In the several controlled trials on the efficacy of acetylcholinesterase inhibitors in VCI patients, an overall positive effect on cognitive functions was found, but the treatment's efficacy regarding functional and global status was limited or absent [7–17]. Other cholinergic drugs, such as the choline precursors cytidine diphosphate-choline and choline alphoscerate (semisynthetic derivative of phosphate choline), have been tested in VCI patients, showing some positive effects on cognitive performances and a good tolerability profile [18–21].

Also, the vasoactive and neuroprotective mechanisms possibly induced by the dihydropyridinic calcium-antagonist nimodipine have been tested in VCI, with preliminary evidence of some positive effects on cognitive functions, good tolerability, and few side effects [22–29].

Taking into account the overall evidence from pharmacological studies, the statement of the American Heart Association/American Stroke Association (AHA/ASA) on VCI highlighted the need for further clinical trials designed according to a homogeneous case selection and an outcomes definition based on measures sensitive to executive function [17].

Considering the previous evidence of some beneficial cognitive effects of choline alphoscerate and nimodipine, we tested the hypothesis that a combined treatment with these two drugs could act synergistically on different targets, and thus induce a superior effect in comparison with single-treatment with nimodipine in patients affected by VCI related to SVD. We thus designed a pilot trial in patients with SVD and mild-to-moderate cognitive impairment with the aim of investigating the (1) feasibility and patient adherence, (2) efficacy, and (3) safety of the combined treatment.

2 Methods

The CONIVaD (Choline Alphoscerate and Nimodipine in Vascular Dementia) study is a 2-year, single-center, double-blinded, randomized clinical trial carried out at Careggi University Hospital in Florence, Italy. Its rationale and methodology, including sample size and statistical power estimation, have been extensively reported elsewhere [30].

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the local ethics committee, and each patient provided written informed consent. The study is registered in the ClinicalTrials.gov registry (identifier number NCT03228498, registration date 25 July 2017).

Included patients were diagnosed as affected by cognitive impairment and SVD according to the following criteria: (1) cognitive impairment of mild-to-moderate degree defined by a Clinical Dementia Rating (CDR) score ranging between 0.5 and 2.0 [31] and (2) white matter hyperintensities (WMH) on brain magnetic resonance imaging (MRI) of moderate or severe degree according to the modified Fazekas scale (score 2 or 3) or moderate to severe white matter hypodensities on computed tomography according to van Swieten scale (score > 2) [32, 33]. When MRI was available, the degree of WMH severity was rated on fluid attenuated inversion recovery (FLAIR) sequences, taking into account only deep and subcortical white matter lesions. The modified Fazekas scale is a visual scale based on three severity classes: grade 1 (mild WMH) = single lesions smaller than 10 mm, areas of 'grouped' lesions smaller than 20 mm in diameter; grade 2 (moderate WMH) = single lesions between 10 and 20 mm, areas of 'grouped' lesions more than 20 mm in diameter, no more than 'connecting bridges' between individual lesions; and grade 3 (severe WMH) = single lesions or confluent areas of hyperintensity 20 mm or more in diameter [32].

Exclusion criteria were as follows: (1) diagnosis of major depression, schizophrenia, major anxiety syndrome, or bipolar disorder; (2) diagnosis of cognitive impairment related to Alzheimer's disease, Parkinson's disease, Huntington's disease, and frontotemporal lobar degeneration based on clinical and neuroimaging findings in line with the standard diagnostic criteria [34, 35]; (3) diagnosis of cognitive impairment of other origin (i.e., vitamin B_{12} and folic acid deficiency, thyroid disorders, metabolic diseases, head trauma, tumor or infections of the central nervous system, normal pressure hydrocephalus); (4) medical conditions expected to progress, recur, or change to such a degree as to interfere with the assessment of the clinical and mental status; (5) vision, hearing, or language impairments severe enough to interfere with cognitive assessment; (6) clinically relevant heart failure, respiratory insufficiency, electrocardiographic abnormalities (bradycardia or tachycardia); (7) myocardial infarction within the past 6 months; (8) stroke still requiring neurological rehabilitation; (9) severe/untreated hypertension; (10) clinically relevant liver function impairment; (11) insulin-dependent diabetes mellitus; (12) idiopathic epilepsy and anti-epileptic treatment; (13) severe anemia, gastrointestinal disease, or renal failure; (14) cancer; (15) known intolerance to study drugs; and (16) expected poor compliance or coexistent serious illnesses that would likely imply the patient would drop out before the end of the trial.

At baseline, according to the study protocol, each patient underwent an extensive clinical (medical history, standard

cardiovascular parameters, and neurological examination), functional, quality-of-life, mood, and neuropsychological assessment [30].

After baseline assessment, participants were randomly assigned to one of the two arms of treatment: (1) oral nimodipine 30 mg three times a day (TID) plus oral choline alphoscerate 600 mg twice a day (BID) (arm 1) and (2) nimodipine 30 mg TID plus placebo BID (arm 2). Both drugs were administered as oral solutions: nimodipine was taken by means of a dropper bottle in the morning, early afternoon, and evening at least 1 h before or 2 h after meals, while choline alphoscerate was taken by means of a phial in the morning and in the afternoon.

Treatment was designed to last for 12 months. The study protocol comprised two follow-up visits: (1) at 6 months, with evaluation of standard cardiovascular parameters, side effects, routine blood tests, and compliance with and adherence to treatment, and (2) at 12 months, with evaluation of side effects and compliance with and adherence to treatment and an extensive clinical and neuropsychological assessment performed according to the baseline protocol.

The randomization list was generated prior to the enrollment start using the procedure PROC PLAN of SAS 9.4 for Windows by the statistician of the pharmaceutical company providing the drugs. The statistician was blind to patients' characteristics. In order to cover any potential loss of product for any given reason during the trial, the randomization list was stratified into 12 blocks of six treatment kits each, for a total of 72 treatment kits. The principal investigator and the relevant personnel involved in the study were blinded to the allocation until the end of study, thus allowing a double-blind trial to be conducted.

2.1 Outcome Measures

2.1.1 Primary Outcome

The primary outcome was the reduction of cognitive decline, defined as the loss of ≥ 2 points on the Montreal Cognitive Assessment (MoCA) [36] test 12 months after baseline, in patients treated with the combination of oral nimodipine and choline alphoscerate (arm 1) compared to patients treated with the combination of nimodipine and placebo (arm 2).

2.1.2 Secondary Outcomes

Secondary outcomes included the effects of treatments on:

1. Functional status measured by means of each of three scales administered to the caregiver: the Activities of Daily Living (ADL) scale (score range 0–6; higher scores represent less disability), Instrumental Activities of Daily Living (IADL) scale (score range 0–8; higher scores represent more disability), and Disability Assessment in Dementia scale (total score as a percentage; higher scores represent less disability) [37–39].

2. Mood and quality of life measured respectively by means of two questionnaires administered to the patient: the Stroke Adapted-Sickness Impact Profile 30 (SA-SIP30) (total score as a percentage; higher scores represent worse health status) and Center for Epidemiologic Studies Depression Scale (CES-D) (score range 0–60; higher scores represent greater presence of depressive symptoms) [40, 41].

3. Cognitive performance on neuropsychological tests evaluating the following: maintained attention (Symbol Digit Modalities Test; score range 0–110; higher scores represent better performance), selective attention (Color Word Stroop Test; total score is time to complete; higher scores represent worse performance), psychomotor speed and divided attention (Trail Making Test parts A and B; total score is time to complete; higher scores represent worse performance), and memory (Rey Auditory-Verbal Learning Test immediate and delayed recall; score ranges 0–75 and 0–15, respectively; higher scores represent better performance) [42].

The tolerability of treatment and the incidence of adverse reactions and events were also studied. The distinction between adverse reactions and adverse events was based on the fact that a causal relationship was suspected for the former, but was not required for the latter [43].

Treatment adherence was measured indirectly by the count of medicine bottles returned by patients, i.e., the number of empty phials for choline alphoscerate and the decrease in drug solution in dropper bottles for nimodipine. Adherence to treatment was evaluated in patients who completed the study, taking into account the total doses of choline alphoscerate, placebo, or nimodipine taken in 12 months and dividing patients into four categories according to the ratio between the taken and the theoretical total dose of treatment: $\leq 25\%$, 26–50%, 51–75%, and > 75%.

2.2 Statistical Analysis

Sample size estimation was determined a priori based on the MoCA performances in a sample of patients with SVD and mild cognitive impairment who had been evaluated longitudinally in the observational V-MCI Tuscany study [44]. Taking into account the five-point standard deviation of the MoCA score at 12 months and the correlation between baseline and follow-up MoCA scores equivalent to 0.70, for a treatment-arm assignment equivalent to 1:1, a sample size of 60 patients was estimated to guarantee 80% equal power to the study in comparison to the alternative hypothesis, with

a 20% significance level according to the exploratory nature of this study.

Descriptive analyses were used to illustrate the clinical characteristics and the distributions of the rates of adherence to the treatments and of adverse reactions and events. To search for possible systematic biases either in patients' withdrawal of consent or treatment allocation, independent sample *t* tests and chi-square tests were used to compare baseline characteristics between patients who completed the study and those who dropped out, and between the two treatment arms.

The MoCA score changes were analyzed according to different approaches:

- Rates of patients presenting a loss of ≥ 2 points on the MoCA test between baseline and 12-month visits were computed and then compared between the treatment groups using a chi-square test (primary outcome).
- Repeated measures factorial analysis of variance (ANOVA): Introducing into the statistical model the MoCA test scores at baseline and at 12 months as dependent variables and the arm of treatment as independent variable.
- Changes in scores (Δ) approach: MoCA delta scores (Δs) were calculated by computing the difference between baseline and 12-month scores for each patient (a positive score indicated an improvement). Delta scores were analyzed using independent sample *t* tests, with treatment as an independent variable.
- Clinical significance approach: After the classification of each patient's performance as 'normal,' 'borderline,' or 'abnormal' at each visit according to national norms, variations in performance categories between baseline and 12 months were dichotomized as 'stable or better' or 'worst.' Variations in performance categories were analyzed using Chi-square tests.

The secondary cognitive and functional outcomes have been analyzed according to the repeated measures factorial ANOVA and delta scores approaches. The clinical significance approach was further used only for cognitive tests.

3 Results

Enrolment started on May 2, 2017 and was completed on July 23, 2018.

Patient selection and attrition from the screening phase to follow-up assessments are shown in Fig. 1. Among the 263 screened patients, 201 (76%) were excluded from the study. Main reasons for exclusion were refusal ($n = 42$), not fitting the cognitive criteria ($n = 41$ normal, $n = 24$ demented), expected low compliance ($n = 29$), functional

deficit or clinical complications ($n = 24$), and not fitting the neuroimaging criteria ($n = 15$). Sixty-two Caucasian patients (24%) [30 males (48%), mean ($\pm$ SD) age and years of education 75.8 $\pm$ 7 and 8.3 $\pm$ 4.6, respectively] were finally enrolled. As shown in Table 1, the vascular risk factors distribution and the cognitive and functional test profiles were those expected in a sample of patients with SVD and cognitive impairment of mild-to-moderate degree. Out of the 62 enrolled patients, 31 were randomized to arm 1 (combination of nimodipine and choline alphoscerate) and 31 to arm 2 (combination of nimodipine and placebo).

The rate of drop-out among the 62 enrolled patients was 22% ($n = 14$; 12 occurred within the first 3 months, and two occurred between the 6th and 9th month), and was equally balanced between the two arms (Fig. 1 and Table 1). Reasons for drop-out were treatment interruption due to consent withdrawal ($n = 4$ in arm 2, $n = 5$ in arm 1) or symptoms compatible with an adverse reaction or event ($n = 3$ in arm 2, $n = 2$ in arm 1) (Fig. 1).

Comparison between patients who completed the study and those who dropped out showed no statistically significant differences in baseline characteristics, except for education level, which was significantly higher in patients who completed the study (Table 1).

The final study cohort included 48 patients well balanced between the two treatment groups. As shown in Table 2, the two treatment arms had no significant differences in baseline characteristics, except for education, which was significantly higher in arm 1.

Distributions of adherence to the treatments are shown in Fig. 2. Among the 48 patients who completed the study, considering the total doses of drug taken in 12 months, an adherence level of $> 75\%$ was reached by 23 patients (96%) for choline alphoscerate (arm 1), 21 patients (87.5%) for placebo (arm 2), and only by seven patients (15%) for nimodipine (arm 1 and arm 2) (Fig. 2).

Data on the primary cognitive outcome are shown in Table 3. No statistically significant difference was found between the treatment groups in performances on the MoCA test in any of the different statistical approaches. Also, comparisons for the secondary cognitive, functional, and mood and quality-of-life outcomes did not show any statistically significant difference between the treatment arms (Table 3).

Distributions of adverse reactions and events in the baseline sample are shown in Table 4. Eight patients referred a total of 14 symptoms compatible with an adverse reaction, of which 13 fell within those known for the drugs; none was classified as serious; five were referred from two patients in arm 1 (one patient interrupted the treatment) and nine from six patients in arm 2 (three patients interrupted the treatment and one decided to decrease the treatment dose). The total number of adverse events was five (two in arm 1 and three in arm 2); four of them were classified as serious,
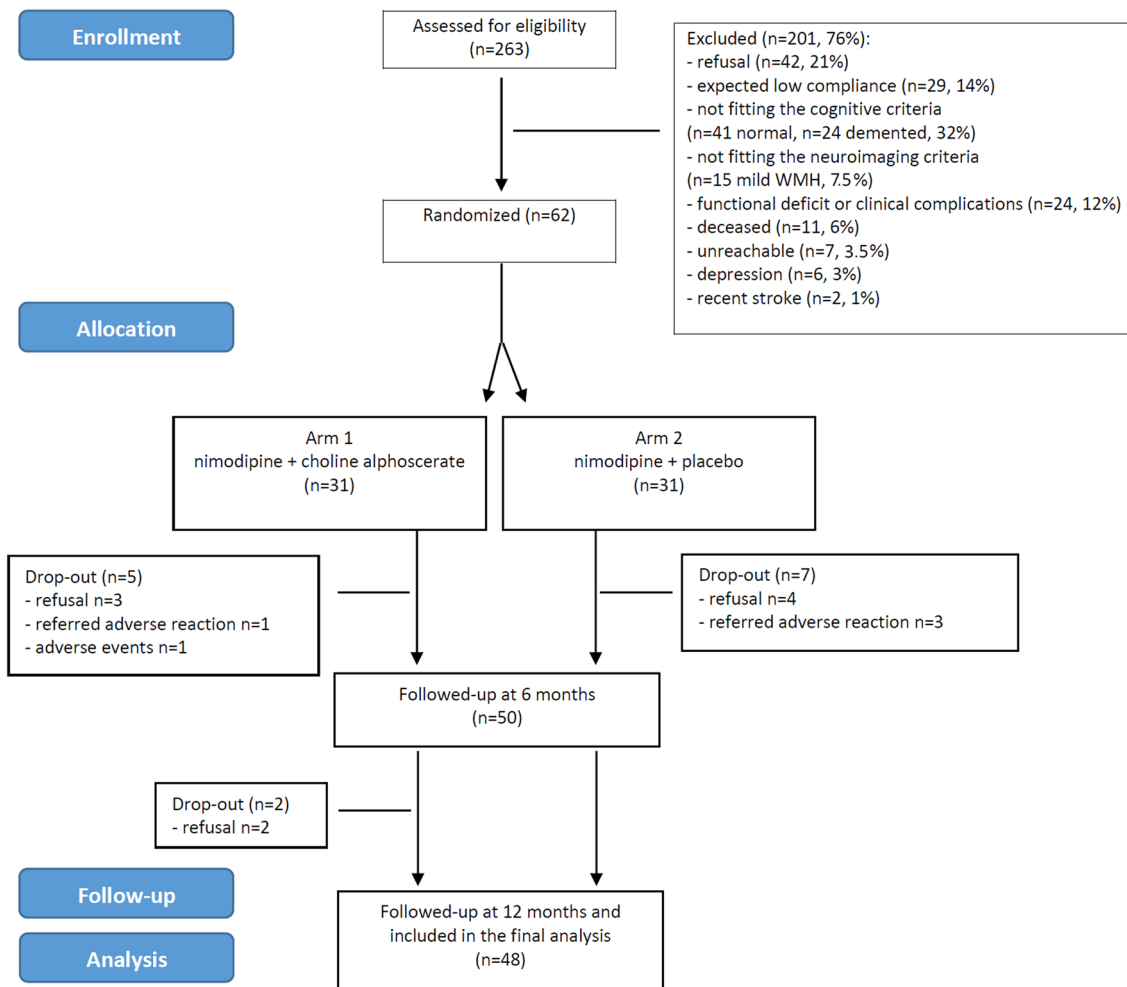
Fig. 1 Patients' selection and attrition from the screening phase to follow-up assessments (CONSORT flow diagram). *CONSORT* Consolidated Standards of Reporting Trials, *WMH* white matter hyperintensities

and one patient in arm 1 interrupted the treatment (cerebral hemorrhage).

4 Discussion

In the CONIVaD trial, we were not able to show any efficacy of the association of choline alphoscerate and nimodipine in improving cognition in patients with cognitive impairment and SVD. No safety or tolerability concerns were identified, but the trial also generates some considerations regarding the adherence of patients to the proposed treatment approach. In particular, the taking of nimodipine represented an issue in our pilot experience because only a very small proportion of patients took the prescribed dosage. As a consequence, only a few patients could be considered as really having been treated as per protocol. At present, we have no clear explanation for this.

We can hypothesize that one reason was the trial protocol requirement of three doses a day, which was derived from the typical regimen for nimodipine, while choline alphoscerate requires two doses a day. Moreover, administration via dropper and the requirement of avoiding mealtimes could have further reduced patients' adherence. Another possible issue is the fact that the trial was set to last for 12 months, a duration longer than that of many other trials, which was deliberately chosen because chronic therapies in cognitively impaired patients should be tested using a long-term perspective, both in terms of efficacy and adherence to treatment. Furthermore, the presence of a high early drop-out rate suggests that future studies using similar approaches should include a run-in period.

At present, therefore, VCI remains a condition lacking specific treatment, and this implies that further efforts are needed. Whether better adherence to the complete

Table 1 Comparison of baseline characteristics in total sample, patients who completed the study, or dropped out

	Score range	Total sample n = 62	Study completed n = 48	Drop-out n = 14	P
Age, years	–	75.8 ± 7	75.7 ± 6.8	76.4 ± 9.2	0.725*
Education, years	–	8.3 ± 4.6	**7.7 ± 3.9**	**10.4 ± 5.9**	**0.047***
Sex (% males)	–	48%	48%	50%	0.891#
Hypertension	–	74%	71%	86%	0.263#
Hypercholesterolemia	–	81%	85%	64%	0.078#
Diabetes	–	21%	21%	21%	0.962#
Smoking habits	–	43%	40%	57%	0.244#
History of stroke	–	42%	40%	50%	0.487#
Alcohol consumption	–	61%	58%	71%	0.376#
Physical activity	–	50%	54%	36%	0.224#
MoCA score	0–30	18.7 ± 4.3	19 ± 4	17.5 ± 5.2	0.264*
ADL (preserved items)	0–6	5.6 ± 0.9	5.7 ± 0.8	5.5 ± 1.2	0.501*
IADL (impaired items)	0–8	3.2 ± 2.8	3.0 ± 2.7	3.7 ± 3.1	0.382*
DAD score	0–100	84.7 ± 21	85.4 ± 20.0	82.4 ± 24.9	0.637*
Combined treatment (%)	–	–	50%	50%	1.000#

Bold values denote statistical significance at the $p < 0.05$ level

ADL Activities of Daily Living, *DAD* Disability Assessment in Dementia, *IADL* Instrumental Activities of Daily Living, *MoCA* Montreal Cognitive Assessment

*Independent sample *t* tests

#Chi square tests

protocol, perhaps reached with a less demanding regimen, would have generated a different outcome is an open question.

Within the VCI spectrum, in the present study, SVD was defined by evidence of moderate to severe white matter lesions to guarantee adequate homogeneity of the study sample, despite possibly reducing generalizability and sample size, in line with previous experiences gathered by the authors both in the LADIS European collaboration and in the V-MCI Tuscany study [44, 45].

Our study has limitations. The first one is the small sample size. However, we could not identify any trend in the results, and therefore, it seems unlikely that the same protocol could lead to different results in a larger sample. Based on this pilot experience, it can be hardly hypothesized that a large, multicentric trial could lead to different results, unless better adherence is achieved, for example, by reducing the number of daily treatment doses from three to two. Another limitation is the lack of a placebo arm. Since nimodipine is not a licensed treatment for VCI, the inclusion of a placebo arm could have been appropriate. The comparison treatment nimodipine–placebo has already been tested and proven to be of limited efficacy, and thus, we wanted to explore the role of a two-drug treatment [25]. Within this study design, a two-by-two factorial analysis would have allowed comparisons of the drug combination against either drug alone or double

placebo, thus increasing our potential to explore the synergistic effect. Despite the added value of a more complex study design, feasibility issues and the foreseen sample size forced us to limit our pilot study to two arms. A third possible limitation is the lack of an intention-to-treat (ITT) analysis, which could have minimized the effect of non-compliant patients and dropouts. However, in this small pilot trial, the cognitive assessment at the time of drop-out was not foreseen, and thus an ITT analysis was not applicable. Another limitation is the fact that we used drugs that had been already tested singularly in patients with VCI; the novelty of this trial approach was the assessment of the possible use of a combination of these drugs. A final possible limitation is the choice of the cholinergic drug for this trial; in the future, it could be interesting to explore whether different results could be achieved with an acetyl-cholinesterase inhibitor added to the calcium antagonist.

5 Conclusions

In the CONIVaD pilot study, the combined treatment with choline alphoscerate and nimodipine in patients with SVD and mild-to-moderate cognitive impairment resulted in low patient adherence to treatment, particularly for nimodipine, and no significant efficacy. Safety

Table 2 Comparisons of baseline characteristics of patients in the two treatment arms

	Score range	Arm 1 n = 24	Arm 2 n = 24	p
Age, years	–	76.3 ± 5.5	75 ± 7.2	0.475*
Education, years	–	**9.3 ± 4.2**	**6 ± 2.9**	**0.003***
Sex (% males)	–	42%	62%	0.149#
Hypertension	–	58%	83%	0.057#
Hypercholesterolemia	–	87%	83%	0.683#
Diabetes	–	21%	21%	1.000#
Smoking habits	–	42%	37%	0.768#
History of stroke	–	37%	42%	0.768#
Alcohol consumption	–	58%	58%	1.000#
Physical activity	–	50%	58%	0.562#
MoCA score	0–30	19.9 ± 3.2	18.1 ± 4.6	0.121*
RAVL score (immediate)	0–75	32.7 ± 7.2	35.8 ± 9.4	0.214*
RAVL score (recall)	0–15	6.3 ± 2.5	6.9 ± 3	0.415*
Symbol Digit Modalities Test score	0–110	35.5 ± 8.3	37.3 ± 8.5	0.504*
Color Word Stroop Test	Time (s)	41.3 ± 47.1	36.5 ± 26.5	0.670*
Trail Making Test part A	Time (s)	67.9 ± 61.1	58.6 ± 44.9	0.571*
Trail Making Test part B	Time (s)	121 ± 54.5	113.9 ± 70.8	0.835*
ADL (preserved items)	0–6	5.7 ± 0.9	5.7 ± 0.7	0.864*
IADL (impaired items)	0–8	3.2 ± 2.9	2.8 ± 2.5	0.598*
DAD score	0–100	84.3 ± 18.4	86.5 ± 21.8	0.707*
CES-D score	0–60	14.7 ± 10.7	13.3 ± 10.4	0.654*
SA-SIP30 score	0–100	32.3 ± 22.8	27.2 ± 20.7	0.416*

Bold values denote statistical significance at the $p < 0.05$ level

ADL Activities of Daily Living, *CES-D* Center for Epidemiologic Studies Depression Scale, *DAD* Disability Assessment in Dementia, *IADL* Instrumental Activities of Daily Living, *MoCA* Montreal Cognitive Assessment, *RAVL* Rey Auditory-Verbal Learning Test, *SA-SIP30* Stroke Adapted-Sickness Impact Profile 30

*Independent sample *t* tests

#Chi square tests

Fig. 2 Adherence to the treatment (expressed as the ratio between the taken dose and the theoretical total dose) in patients who completed the study (n = 48)
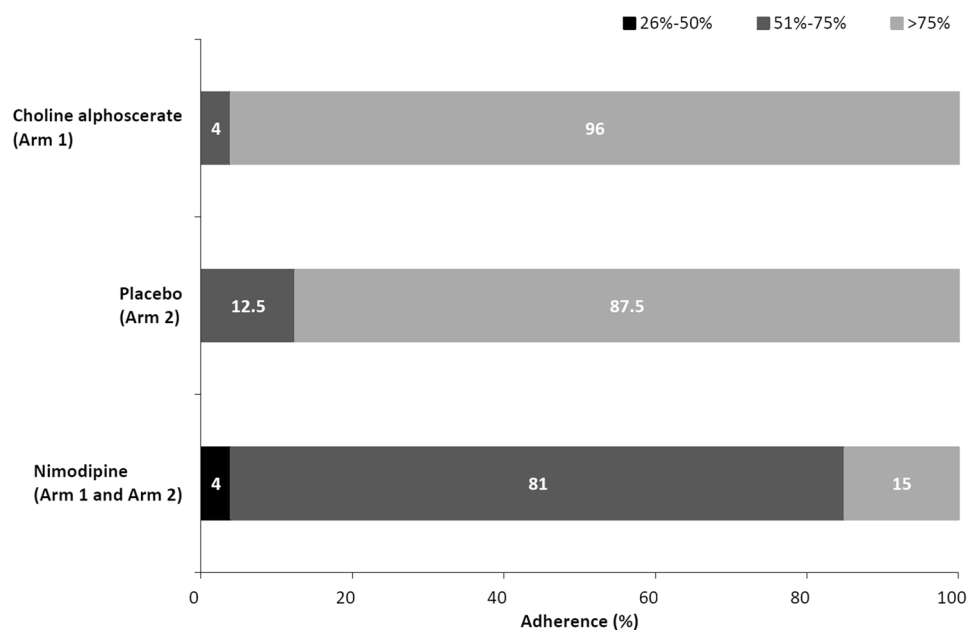
Table 3 Comparisons between arms of treatment for the primary cognitive outcome (MoCA) and for the secondary cognitive and functional outcomes

	Score range	Arm 1 $n = 24$		Arm 2 $n = 24$		P
		Baseline	12 months	Baseline	12 months	
MoCA						
Loss ≥ 2 points		7 (29%)		7 (29%)		1.000
Adjusted score	0–30	19.9 ± 3.2	19.1 ± 3.8	18.1 ± 4.6	18.2 ± 5.1	0.232
Δs#		− 0.82 ± 2.5		0.05 ± 3.7		0.342
RAVL (immediate)						
Stable/better*		58%		79%		0.119
Adjusted score	0–75	32.7 ± 7.2	35.6 ± 9.8	35.8 ± 9.4	37.0 ± 8.5	0.352
Δs#		2.9 ± 5.5		1.3 ± 7.4		0.378
RAVL (recall)						
Stable/better*		83%		79%		0.712
Adjusted score	0–15	6.3 ± 2.5	6.6 ± 3.0	6.9 ± 3.0	7.4 ± 2.7	0.350
Δs#		0.3 ± 1.7		0.4 ± 2.2		0.830
Symbol Digit Modalities Test						
Stable/better*		83%		79%		0.712
Adjusted score	0–110	35.5 ± 8.3	35.8 ± 9.9	37.3 ± 8.5	34.9 ± 7.2	0.861
Δs#		0.3 ± 6.6		− 2.4 ± 7.3		0.223
Color Word Stroop Test						
Stable/better*		85%		82%		0.782
Adjusted score	Time (s)	41.3 ± 47.1	54.7 ± 69.0	36.3 ± 27.1	45 ± 42.9	0.579
Δs#		− 13.4 ± 36.1		− 8.7 ± 44.5		0.694
TMT part A						
Stable/better*		61%		70%		0.536
Adjusted score	Time (s)	62.1 ± 55.7	70.1 ± 51.9	58.6 ± 44.9	70.8 ± 35.5	0.751
Δs#		− 7.9 ± 39.3		− 12.1 ± 46.6		0.751
TMT part B						
Stable/better*		65%		56%		0.546
Adjusted score	Time (s)	121 ± 54.5	95.7 ± 37.1	68.9 ± 36.7	78.9 ± 66.1	0.256
Δs#		25.3 ± 38.2		− 9.9 ± 72.5		0.306
DAD						
Stable/better*		95%		80%		0.185
Percentage score	0–100	83.6 ± 18.5	83.4 ± 22.7	86.5 ± 21.8	79.91 ± 25.2	0.957
Δs#		− 0.19 ± 12.2		− 6.62 ± 17.3		0.149
CES-D						
Total score	0–60	14.7 ± 10.7	13.7 ± 7.6	13.3 ± 10.4	15.1 ± 9.0	10.000
Δs#		1 ± 9.3		− 1.7 ± 8.4		0.289
SA-SIP30						
Percentage score	0–100	32.3 ± 22.8	27.3 ± 22.9	27.2 ± 20.7	28.6 ± 18.9	0.734
Δs#		5 ± 18.4		− 1.4 ± 14.1		0.181
ADL						
Preserved items	0–6	5.6 ± 0.9	5.4 ± 1.3	5.7 ± 0.7	5.5 ± 1.2	0.780
IADL						
Impaired items	0–8	3.4 ± 2.9	3.3 ± 3.2	2.8 ± 2.5	3.0 ± 2.6	0.578

ADL Activities of Daily Living, *CES-D* Center for Epidemiologic Studies Depression Scale, *DAD* Disability Assessment in Dementia, *IADL* Instrumental Activities of Daily Living, *MoCA* Montreal Cognitive Assessment, *RAVL* Rey Auditory-Verbal Learning Test, *SA-SIP30* Stroke Adapted-Sickness Impact Profile 30, *TMT* Trail Making Test

*Percentages of patients having a stable or better evaluation (clinical significance approach); Chi-square tests

#A positive Δ score indicates improvement (Δs approach); independent sample *t* tests

△ Adis

Table 4 Adverse reactions and events

	Expected	Serious	Total sample	Arm 1		Arm 2	
				Study completed	Drop-out	Study completed	Drop-out
Adverse reactions							
Allergic reaction, rash	Yes	No	3	0	1	1	1
Headache	Yes	No	3	1	1	0	1
Tachycardia, bradycardia	Yes	No	2	1	0	1	0
Hypotension, vasodilation, syncope, edema	Yes	No	2	0	0	0	2
Nausea, constipation, diarrhea, flatulence	Yes	No	3	0	0	1	2
Hypertension, agitation	No	No	1	0	1	0	0
Total adverse reactions			14	2	3	3	6
Trial drug decreased due to adverse reaction			1	0	0	1	0
Withdrawn due to adverse reaction			4	0	1	0	3
Adverse events							
Cerebral hemorrhage	No	Yes	1	0	1	0	0
Incidental carcinoma diagnosis	No	Yes	3	0	0	3	0
Varicella zoster virus infection relapse	No	No	1	1	0	0	0
Total adverse events			5	1	1	3	0
Trial drug decreased due to adverse event			0	0	0	0	0
Withdrawn due to adverse event			1	0	1	0	0

and tolerability were adequate. Further efforts are needed to find a specific treatment in patients with VCI.

Declarations

Conflict of interest AP, FP, ID, VR, GC, MS, LT, AM, and FF report no disclosures. LP is a member of the editorial boards of *Cerebrovascular Diseases*, *Acta Neurologica Scandinavica*, *Neurological Sciences*, *Cerebral Circulation—Cognition and Behavior*, and *European Stroke Journal* and a section editor (Vascular Cognitive Impairment) of *Stroke*. ES is a member of the editorial board of *Cerebral Circulation—Cognition and Behavior*.

Ethics approval and consent to participate The study was performed in accordance with the 1964 Helsinki Declaration and its later amendments and with the ethical standards of the institutional ethics committee, and was approved by the ethics committee of the Careggi University Hospital, Florence, Italy. Informed consent was obtained from all individual participants included in the study.

Consent to publish Patients signed informed consent regarding publishing their data.

Code availability Not applicable.

Availability of data Data are available from the corresponding author on reasonable request.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by all authors. The first draft of the manuscript was written by LP and ES, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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