11° CONGRESSO NAZIONALE AGE

Roma – 18/21 marzo 2015

ASP
azienda
sanitaria
provinciale
catanzaro

Lo studio IDEALE

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Geriatra ASP Catanzaro

Roma - Hotel Aran Mantegna, 21 Marzo 2015

Key points

- Ruolo della citicolina: perché uno studio
- Presentazione dello Studio Ideale
- Conclusioni significative

Vascular Mild Cognitive Impairment: background

- Aumento di prevalenza di ultra65enni con lieve *impairment* cognitivo su base vascolare
- Ridotta perfusione cerebrale, stress ossidativo e neurodegenerazione
- Le vasculopatie cerebrali possono accellerare l'atrofia e portare ad anomalie della sostanza bianca, infarti asintomatici, infiammazione e ridotto metabolismo glucidico, ridotta perfusione cerebrale e della densità vascolare
- Potenziale compromissione delle attività quotidiane
- Frequenti richieste di intervento del SSN

Ruolo della citicolina

- CDP-colina (citidina-5'-difosfo-colina), composto endogeno normalmente prodotto dall'organismo
- Quando è introdotto come farmaco, può essere chiamato citicolina
- La Citicolina:
  - inibisce l'apoptosi associata ad ischemia cerebrale
  - inibisce differenti modelli di neurodegenerazione
  - potenzia la neuroplasticità
  - precursore naturale della sintesi fosfolipidica, principalmente fosfatidilcolina o piuttosto agisce come fonte di colina sulla via metabolica di sintesi dell'acetilcolina
  - da studi di farmacocinetica si evidenzia che è ben assorbita ed altamente biodisponibile dopo somministrazione orale.

Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly.

Fioravanti M., Yanagi M.

Cochrane Database Syst Rev. 2005 Apr 18;(2):CD000269

..CDP-choline (cytidine 5'-diphosphocholine) is a precursor essential for the synthesis of phosphatidylcholine, one of the cell membrane components that is degraded during cerebral ischaemia to free fatty acids and free radicals.

Animal studies suggest that CDP-choline may protect cell membranes by accelerating resynthesis of phospholipids.

CDP-choline may also attenuate the progression of ischaemic cell damage by suppressing the release of free fatty acids.

La CDP-colina:

- activates the biosynthesis of structural phospholipids in the neuronal membranes
- increases cerebral metabolism
- increases noradrenaline and dopamine levels in the CNS

- neuroprotective effects in situations of hypoxia and ischemia
- improved learning and memory performance in animal models of brain aging
- restores the activity of mitochondrial ATPase and of membrane Na+/K+ ATPase
- inhibits the activation of phospholipase A2 and accelerates the reabsorption of cerebral edema in various experimental models

Secades and Frontera, 1995

Impieghi clinici

- **Malattia cerebrovascolare**
- **Trauma cranico di varia entità**
- **Disturbi cognitivi a differente eziologia**
- **Glaucoma**
- **Ambliopia**
- **Malattia di Parkinson**

Lo Studio IDEALE

- Italiano, multicentrico, in aperto
- Scopo: valutare efficacia e sicurezza della citicolina orale in anziani con lieve *impairment* cognitivo su base vascolare (VaMCI)
- 387 pz provenienti da sei regioni italiane (Calabria, Campania, Lazio, Liguria, Piemonte e Veneto)

Criteri di inclusione

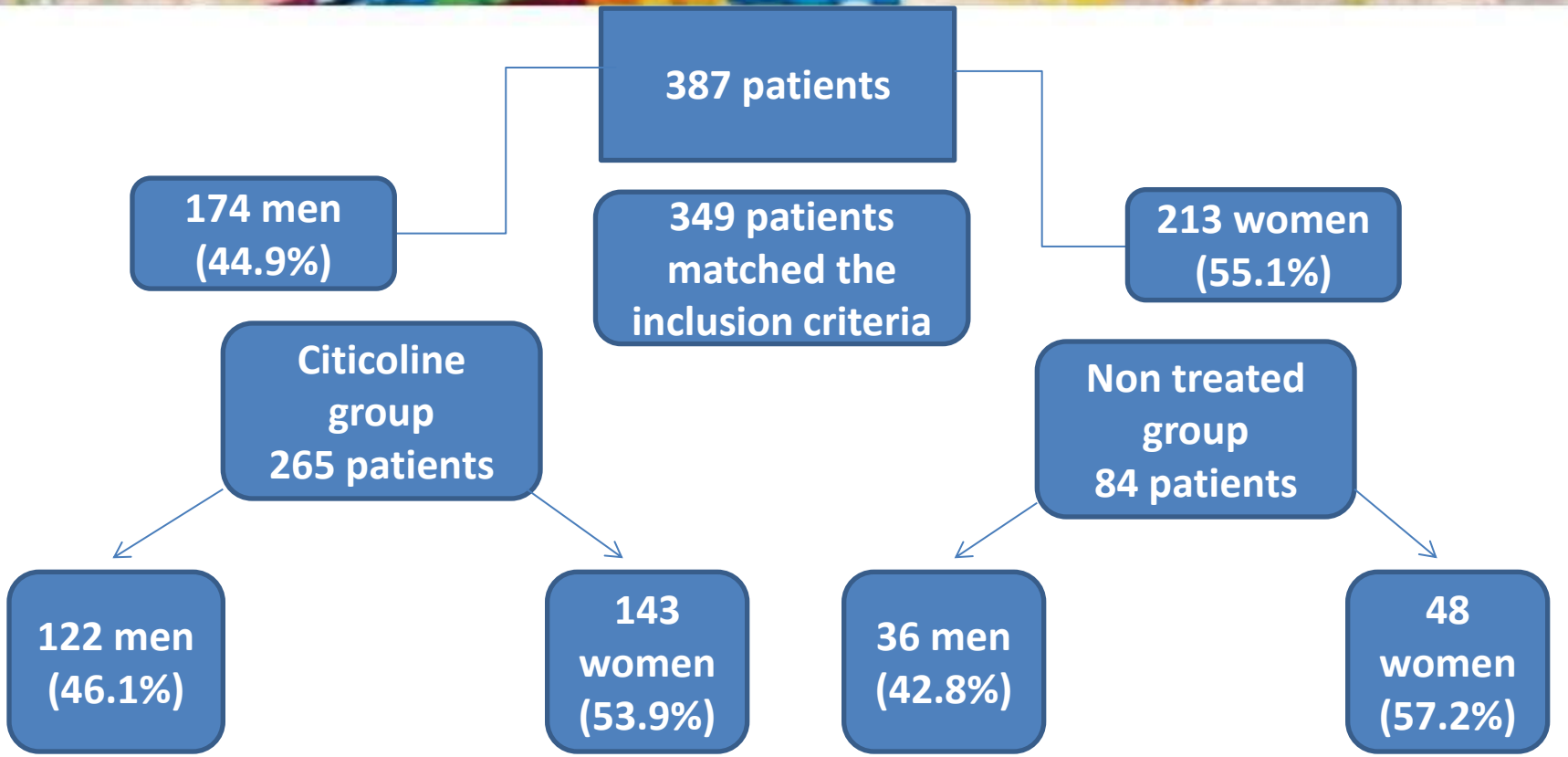
- Età ≥ 65 anni
- MMSE ≥ 21 o
- Disturbi soggettivi di memoria e nessuna evidenza di deficit al MMSE
- Lesioni vascolari alla neuroradiologia
- Persone con probabile AD escluse

Criteri di inclusione

- TC o RMN encefalo, dosaggio di vitamina B12, folati, funzione tiroidea.
- Dipendenza funzionale investigata dalle scale di autonomia ADL e IADL
- GDS per tono dell'umore, NPI per disturbi comportamentali
- CIRS (Cumulative Illness Rating Scale), per la valutazione del numero e della severità delle patologie

Neuroradiologia

- Infarti lacunari
- Infarti vecchi
- Microinfarti multipli
- Ipodensità periventricolari della sostanza bianca (CT)
- Iperintensità della sostanza bianca periventricolare (RM), puntate o confluenti
- Lesioni focali



Mean age 79.9 ± 7.8 years old (range 65-94)

Mean age 78.9 ± 7.01 years old (range 67-90)

Timetable

1. T0: Clinical frame and assessment scales
2. T1 (*three months after T0*): Clinical frame and assessment scales
3. T2 (*six months after T1*): Clinical frame and assessment scales

Outcome

1. Improvement in MMSE, ADL and IADL in the study group compared to the controls
2. Side effects assessment
3. The study group was treated by fasting oral citicoline 500 mg twice a day all over the time.

Citicoline group

Età media 79.9±7.8 anni (range 65-94)
122 uomini (46.1%), 143 donne (53.9%)
Istruzione 6.1±3.8 anni

- Education 6.1±3.8 years
- Smokers (5.6%)
- ADL 4.0±1.8
- IADL 5.6 ±1.2
- GDS 5.6±2.2
- CIRS 3.2±1.3
- NPI 8.4±4.5
- Comorbidities
  - Hypertension (75%)
  - Osteoarthritis (72%)
  - Heart disease (43%)
  - Diabetes (35%)
  - COPD (15%)
  - Depression (20%)
  - Stroke (15%)
- Drugs
  - *Cardiovascular drugs (84%)
  - **NSAIDs (48%)
  - Antidiabetics (35%)
  - Antidepressants (20%)
  - Others (20%)

Non treated group

Età media 78.9 ± 7.01 anni (range 65-94)
36 uomini (42.8%), 48 donne (57.2%)
Istruzione 5.9 ±2.6 anni

- 36 men (42.8%), 48 women (57.2%)
- Education 5.9 ±2.6 years
- Smokers (7.1%)
- ADL 4.1±1.6
- IADL 5.7±2.3
- GDS 5.8±1.4
- CIRS 3.4±1.8
- NPI 9.2±2.1
- Comorbidities
  - Hypertension (77%)
  - Osteoarthritis (70%)
  - Heart disease (38%)
  - Diabetes (37%)
  - COPD (18%)
  - Depression (23%)
  - Stroke (11%)
- Drugs
  - *Cardiovascular drugs (81%)
  - **NSAIDs (52%)
  - Antidiabetics (37%)
  - Antidepressants (23%)
  - Others (24%)

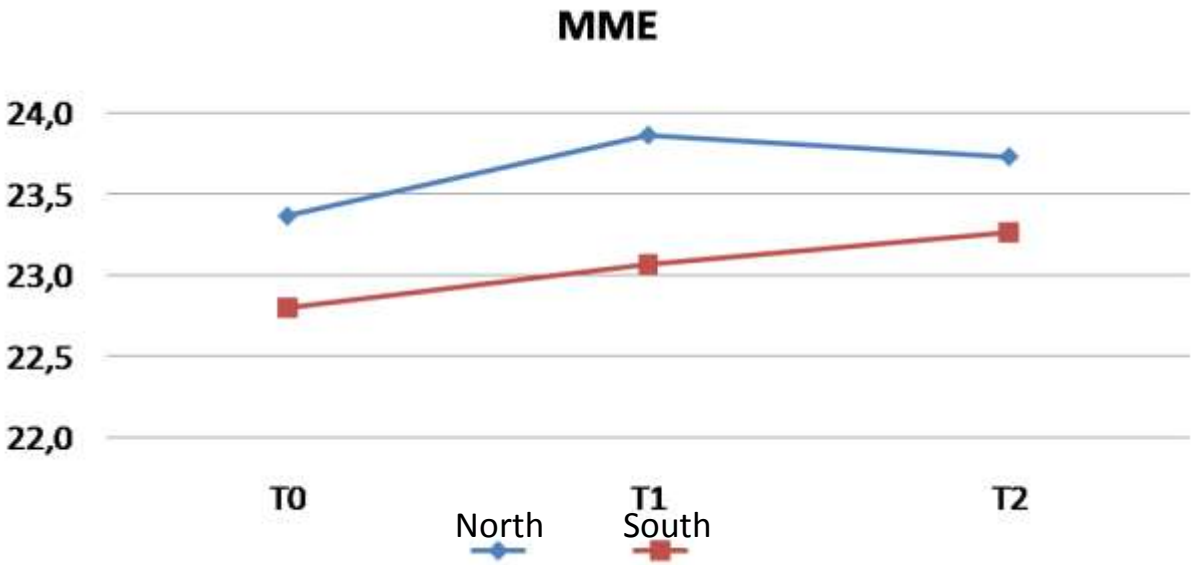
*antiihypertensive drugs, antiaggregants, diuretics, nitrates, β-blockers, digoxin; **Non-Steroidal AntiInflammatory Drugs

	Patients	%*
Campania	79	29,9
Calabria	66	24,9
Lazio	22	8,3
Liguria	30	11,3
Piemonte	48	18,1
Veneto	20	7,5
Total	265	100

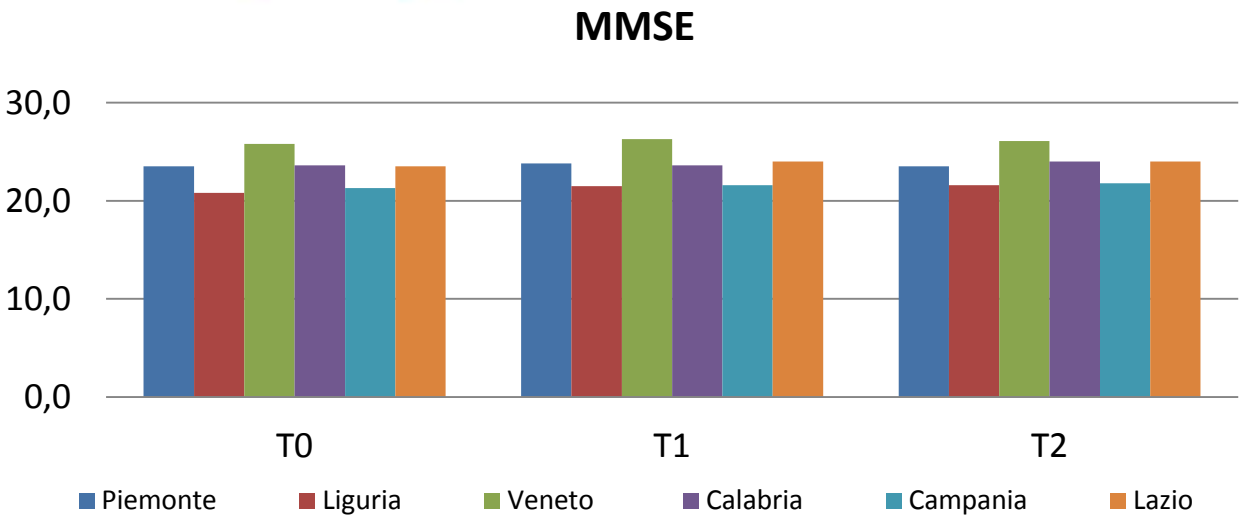
**percent determined on the overall patients (cirticoline group)involved in the study*

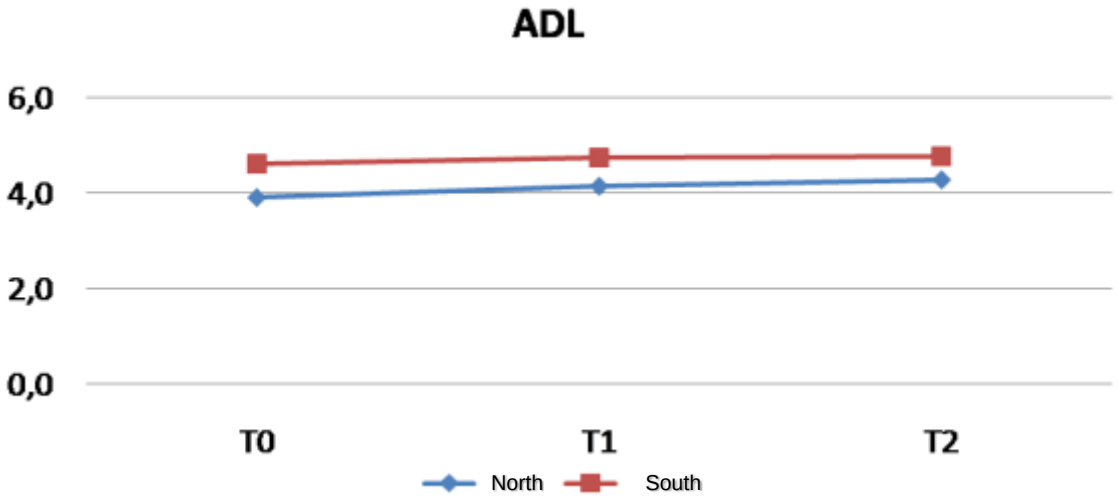
	Patients	%*
South Italy	167	63,1
North Italy	98	36,9
Total	265	100

**percent determined on the overall patients (citicoline group) involved in the study*

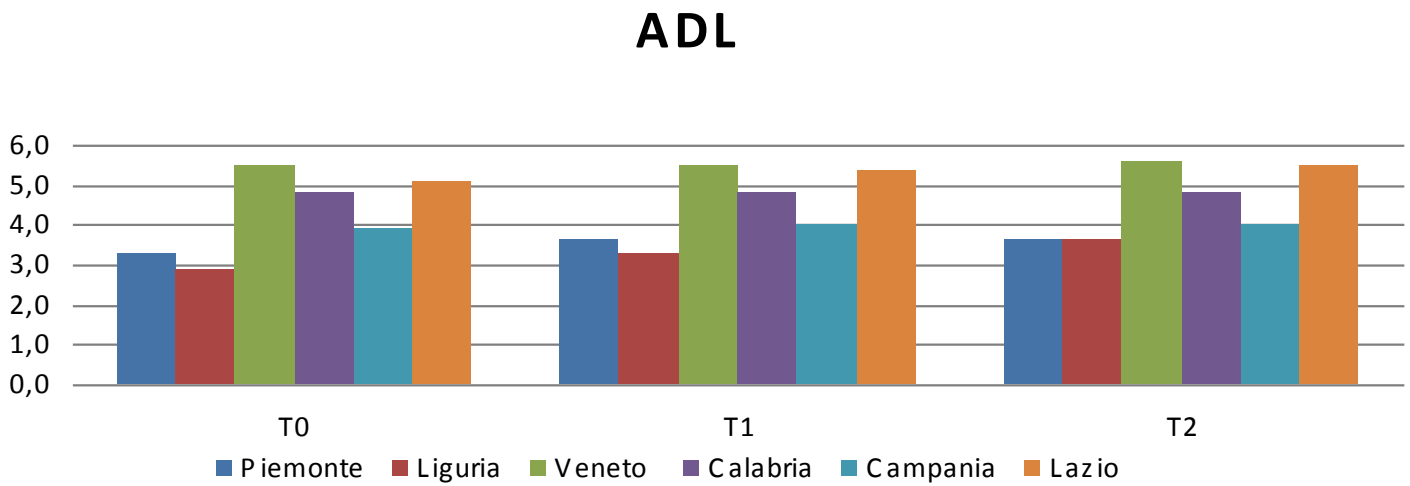


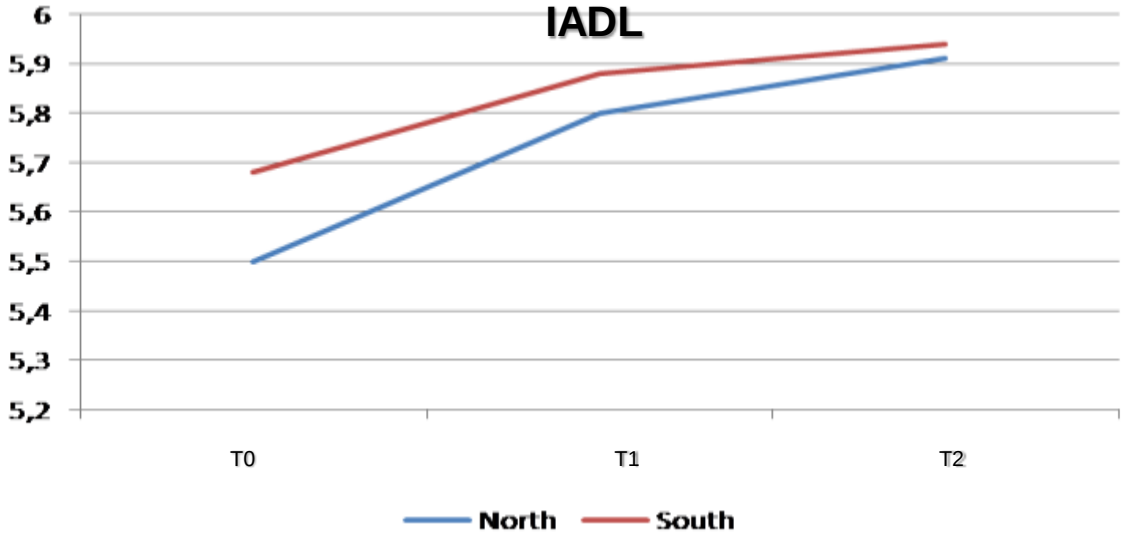
North	23,4	23,9	23,7
South	22,8	23,1	23,3



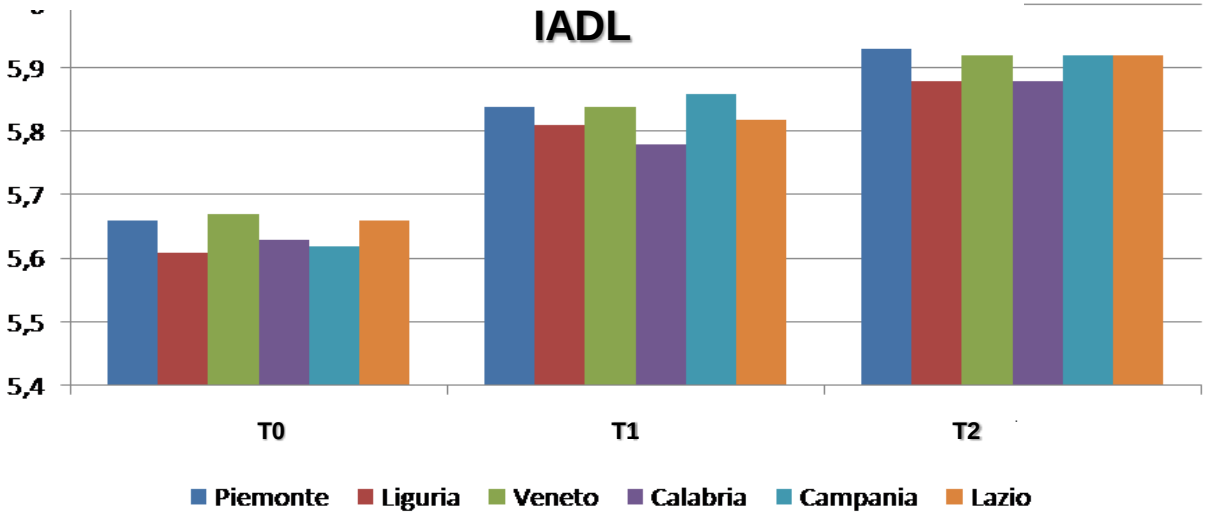


North	3,9	4,1	4,3
South	4,6	4,7	4,8





North	5,5	5,8	5,9
South	5,6	5,8	5,9

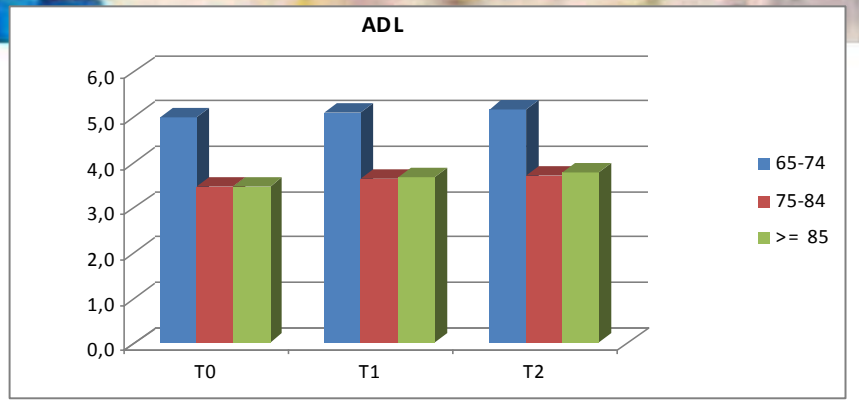


Mean cognitive and functional parameters over time and significance

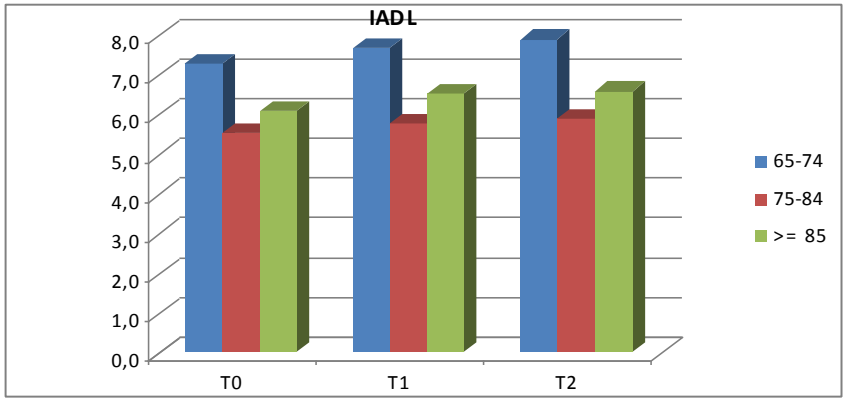
	T0	T1 (3 months)	T2 (6 months)
ADL	4,0 ± 1,8	4,1 ± 1,7	4,2 ± 1,7
IADL	5,6 ± 3,2	5,8 ± 3,2	5,9 ± 3,1
MMSE	22,4 ± 4,0	22,7 ± 4,0	22,9 ± 4,0

	ADL		IADL		MMSE	
	T_0-T_1	T_0-T_2	T_0-T_1	T_0-T_2	T_0-T_1	T_0-T_2
t	0,6801	1,1056	0,6770	0,9976	0,8431	1,1409
p	0,4968	0,2694	0,4987	0,3190	0,3996	0,2545

Years	T0	T1	T2
65-74	5,0	5,1	5,1
75-84	3,4	3,6	3,7
>= 85	3,5	3,6	3,8

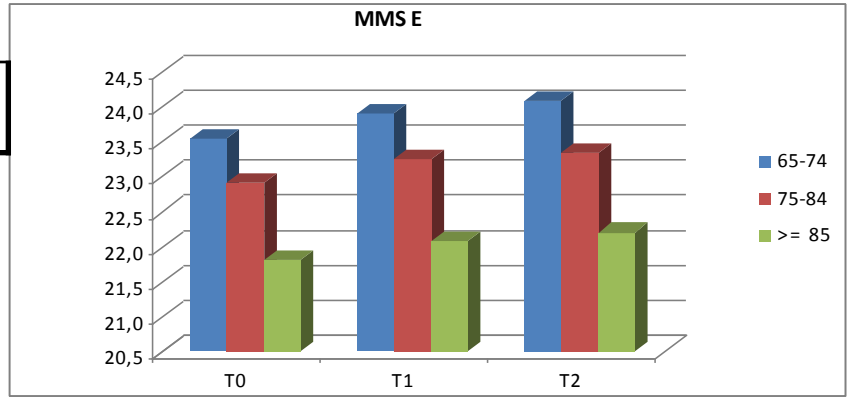


Years	T0	T1	T2
65-74	7,3	7,7	7,9
75-84	5,5	5,8	5,9
>= 85	6,1	6,6	6,6



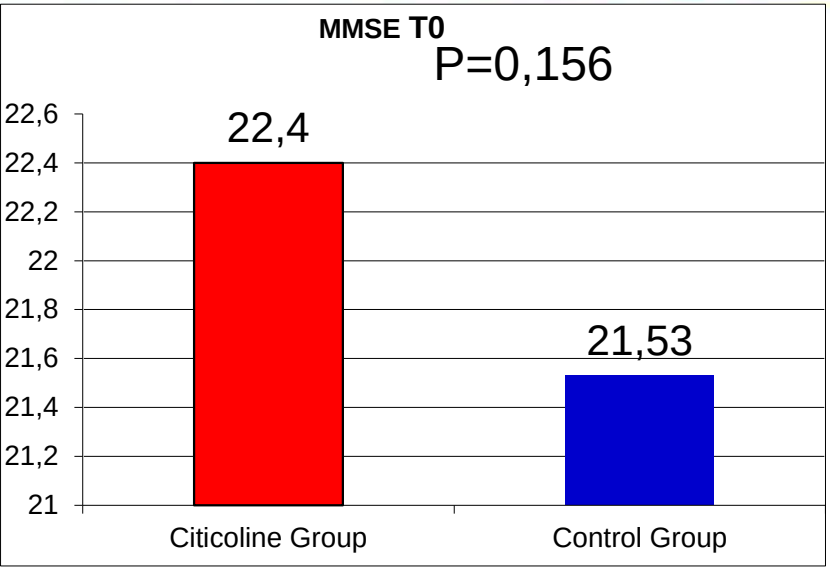
Years	T0	T1	T2
65-74	23,5	23,9	24,1
75-84	22,9	23,3	23,3
>= 85	21,8	22,1	22,2

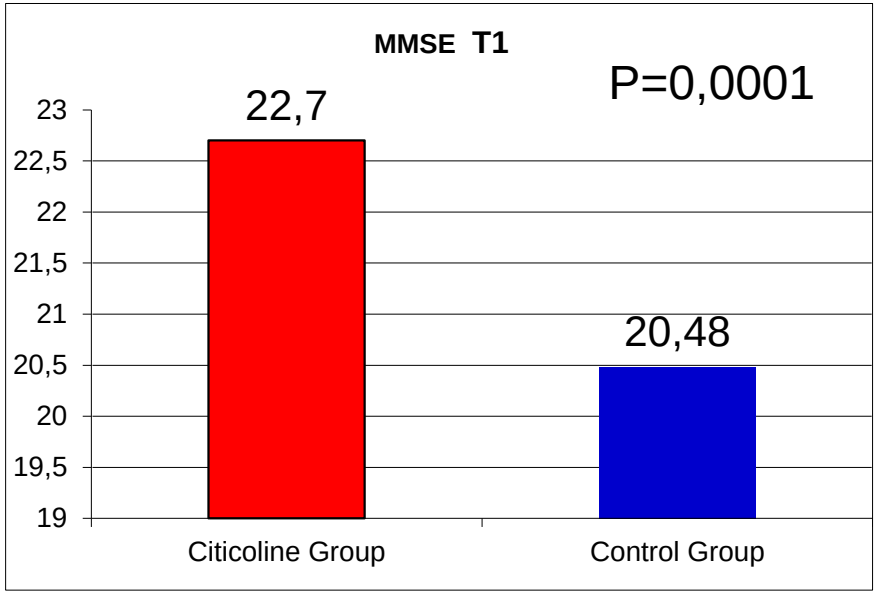
p: 0,1642

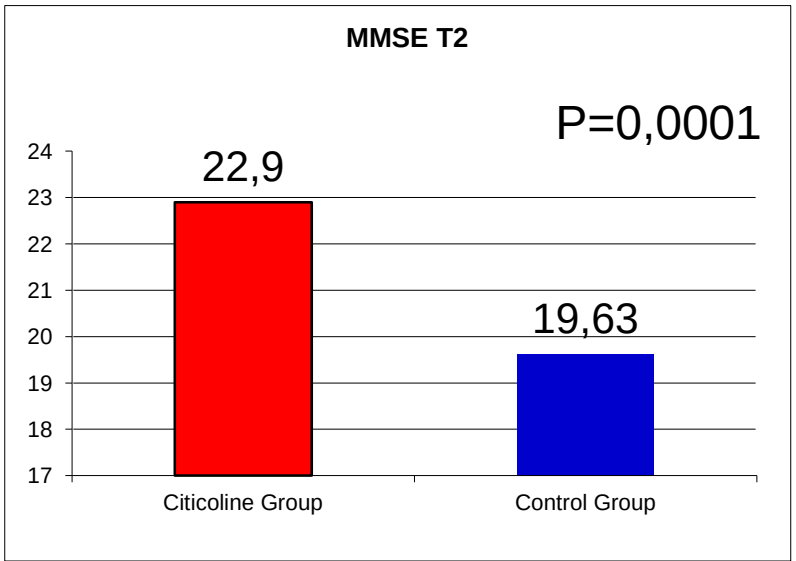


MMSEc*	CITICOLINE GROUP n= 265	CONTROLS n= 84	t	P
T0	22,4±4	21,53±6,99	1,422	0,156
T1	22,7±4	20,48±6,61	3,728	0,0001
T2	22,9±4	19,63±6,35	5,437	0,0001

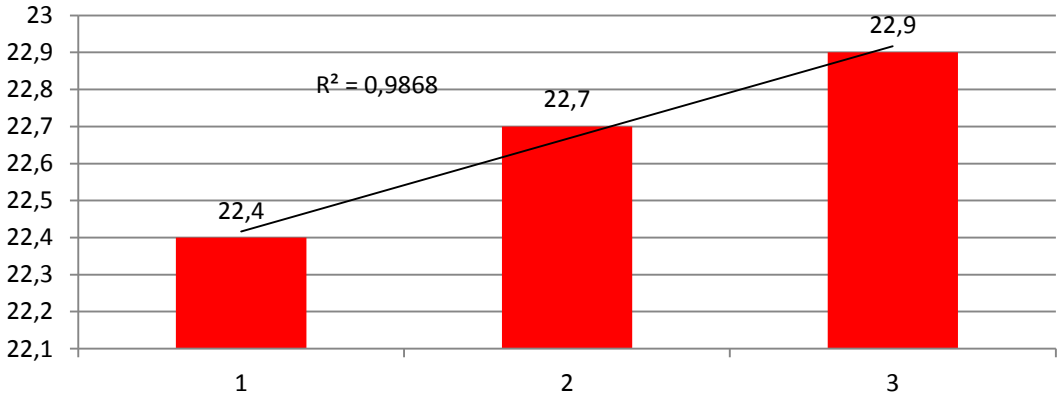
*MMSEc = MMSE corrected according to age and education


MMSE T0
P=0,156
22,4
21,53
22,6
22,4
22,2
22
21,8
21,6
21,4
21,2
21
Citicoline Group
Control Group


MMSE T1
P=0,0001
22,7
20,48
23
22,5
22
21,5
21
20,5
20
19,5
19
Citicoline Group
Control Group

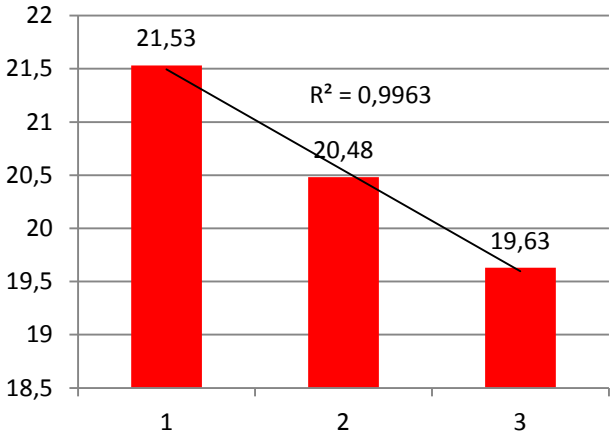

MMSE T2
P=0,0001
22,9
19,63
24
23
22
21
20
19
18
17
Citicoline Group
Control Group

MMSE CITICOLINE GROUP



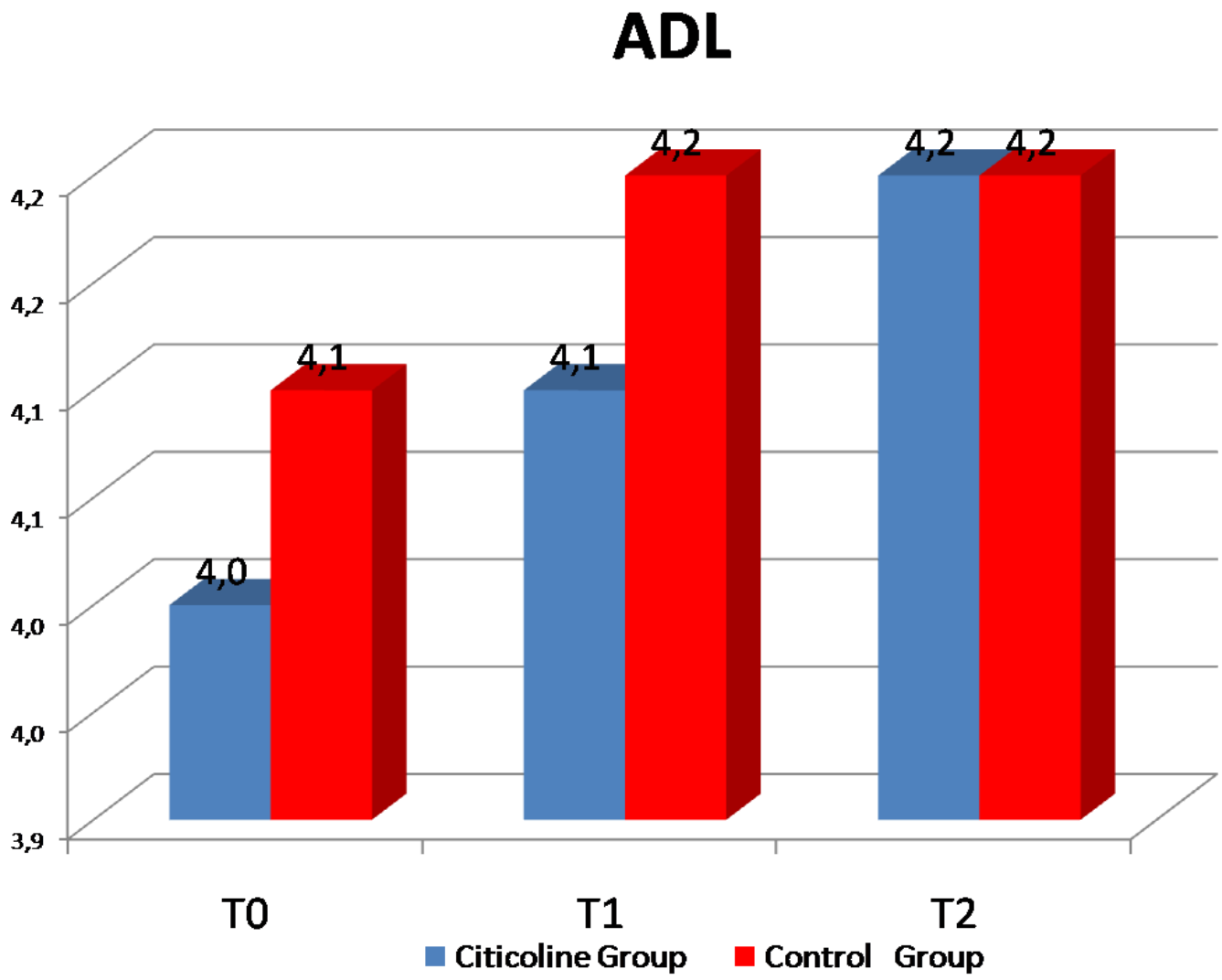
P=0,35

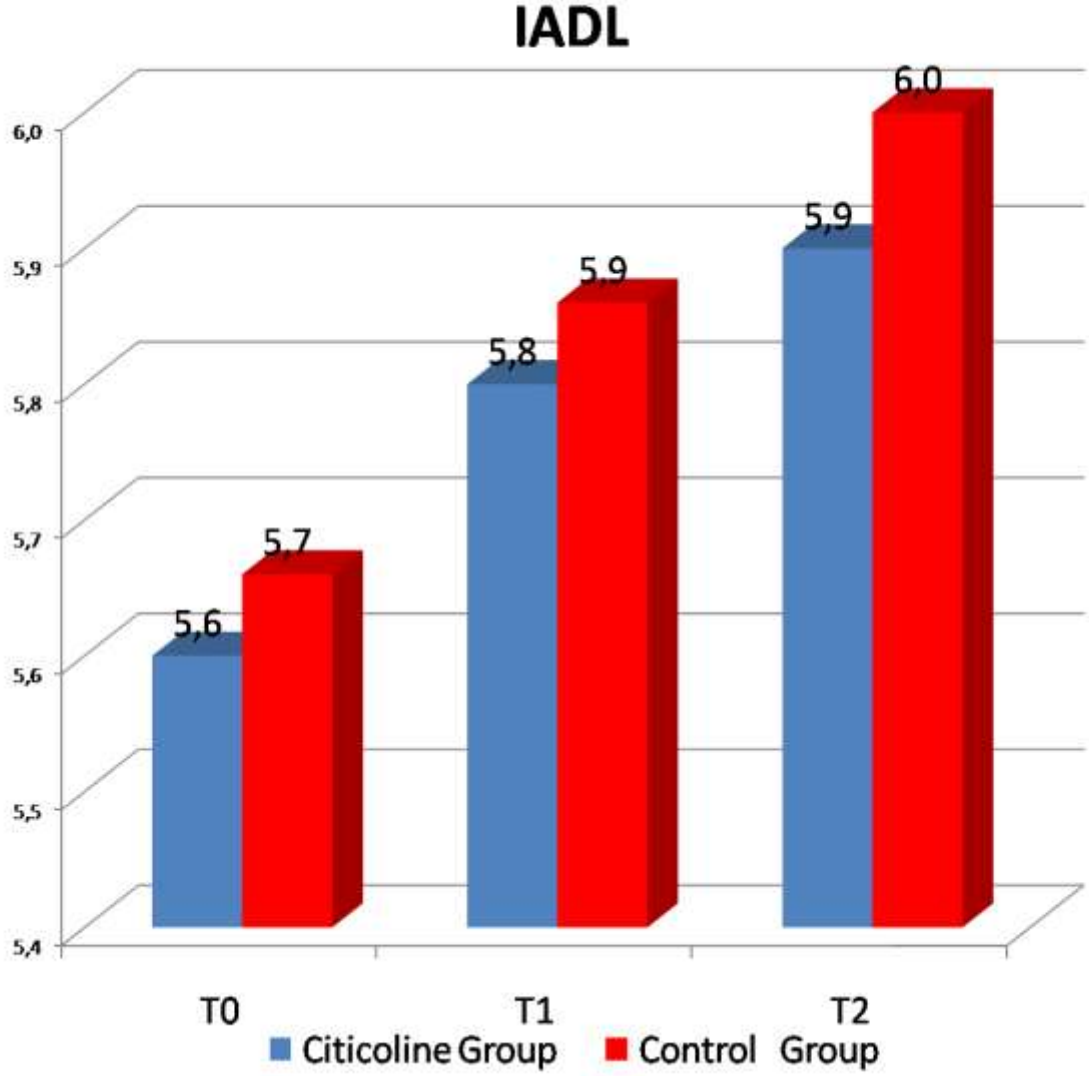
MMSE CONTROLS



P=0,94

	MMSE Citicoline group		MMSE controls	
	T0-T1	T0-T2	T0-T1	T0-T2
T	0,863	1,439	1	1,792
P	0,388	0,151	0,319	0,075


ADL
4,2
4,2
4,1
4,1
4,0
4,0
3,9
4,0
4,1
4,1
4,2
4,2
4,2
T0
T1
T2
Citicoline Group
Control Group


IADL
6,0
5,9
5,8
5,7
5,6
5,5
5,4
5,6
5,7
5,8
5,9
5,9
6,0
T0
T1
T2
Citicoline Group
Control Group

Stroke. 2011 Jan;42(1 Suppl):S33-5. Epub 2010 Dec 16.

Neuroprotection and recovery: recent data at the bench on citicoline.

Hurtado O, Lizasoain I, Moro MÁ.

Source

Unidad de Investigación Neurovascular, Departamento de Farmacología, Facultad de Medicina, Universidad Complutense, Avda Complutense s/n, 28040 Madrid, Spain. neurona@med.ucm.es

Abstract

BACKGROUND AND PURPOSE: In this work, we review recent data on the actions of citicoline, citicoline is a drug with demonstrated neuroprotective properties in both animals and humans. Summary of Review- For neuroprotection, mechanisms involved are the improvement of cellular functions aimed to control excitotoxicity and to maintain cellular adenosine 5'-triphosphate levels by preserving membrane function and integrity at different levels. Importantly, these actions are theoretically achieved without interfering with possible underlying mechanisms for neurorepair. Furthermore, citicoline stimulates neuronal plasticity and improves sensorimotor recovery in the chronic phase of experimental stroke. CONCLUSIONS: Although the mechanisms of some of these actions remain to be elucidated, **so far citicoline appears as a drug with the ability to promote "safe" neuroprotection capable of enhancing endogenous protective pathways at the same time as preparing the scenario for plasticity.**

Stroke. 2011 Jan;42(1 Suppl):S40-3. Epub 2010 Dec 16.

Citicoline in vascular cognitive impairment and vascular dementia after stroke.

Alvarez-Sabín J, Román GC.

Source

Neurovascular Unit, Department of Neurology, Universitat Autónoma de Barcelona, Hospital Vall d'Hebron, Barcelona, Spain.

Abstract

Cognitive decline after stroke is more common than stroke recurrence. Stroke doubles the risk of dementia and is a major contributor to vascular cognitive impairment and vascular dementia. Neuropathological studies in most cases of dementia in the elderly reveal a large load of vascular ischemic brain lesions mixed with a lesser contribution of neurodegenerative lesions of Alzheimer disease. Nonetheless, few pharmacological studies have addressed vascular cognitive impairment and vascular dementia after stroke. Citicoline has demonstrated neuroprotective effects in acute stroke and has been shown to improve cognition in patients with chronic cerebrovascular disease and in some patients with Alzheimer disease. A recent trial lasting 6 months in patients with first-ever ischemic stroke showed that citicoline prevented cognitive decline after stroke with significant improvement of temporal orientation, attention, and executive function. Experimentally, citicoline exhibits neuroprotective effects and enhances neural repair. **Citicoline appears to be a safe and promising alternative to improve stroke recovery and could be indicated in patients with vascular cognitive impairment, vascular dementia, and Alzheimer disease with significant cerebrovascular disease.**

Neurol Sci. 2010 Dec 15;299(1-2):188-92. Epub 2010 Sep 27.

Citicoline, use in cognitive decline: vascular and degenerative.

- Citicoline improves both the immediate and the delayed recall of words and objects
- It ameliorated short and long-term memory, capacity of attention and perceptual-motor capacity, as well as behavioural and emotional control
- Improvement of verbal memory functioning in older individuals with relatively inefficient memory

cognitive impairment. Despite this, its mechanism of action still remains unclear, but several experimental models in acute cerebral ischaemia suggest that it could have a brain repair action. Due to the lack of significant adverse effects and its high tolerability, there has been a growing interest for this molecule in recent years. In this article, a review of the most significant published clinical trials in cognitive decline has been made. A few Citicoline trials have studied its effects at medium and long-term on vascular cognitive impairment and Alzheimer's disease. **Results show that Citicoline seems to have beneficial impact on several cognitive domains**, but the methodological heterogeneity of the these studies makes it difficult to draw conclusions about these effects. New trials with a greater number of patients, uniform diagnostic criteria for inclusion and standardized neuropsychological assessment are needed to evidence with much more consistency Citicoline efficacy upon cognitive disorders. The use of new neuroimaging procedures in current trials could be of great interest.

Clinical Interventions in Aging

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ORIGINAL RESEARCH

Effectiveness and safety of citicoline in mild vascular cognitive impairment: the IDEALE study

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Clinical Interventions in Aging 2013:8 131–137

Clinical Interventions in Aging

Dovepress

ORIGINAL RESEARCH

Retrospective and observational study to assess the efficacy of citicoline in elderly patients suffering from stupor related to complex geriatric syndrome

This article was published in the following Dove Press journal:
Clinical Interventions in Aging
11 May 2012

Salvatore Putignano
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Abstract: A significant percentage of elderly subjects (50%–80%) suffering from sub-acute ischemic cerebrovascular disease, with or without moderate or severe cognitive memory decline and with or without associated behavioral and psychological symptoms, shows a complex syndrome. This syndrome is related to the progressive impairment of health conditions and/or stressing events (ie, hospitalization), characterized by confusion and/or stupor, which are cons…n suffer fr…al instabili…c events and thus have an increased risk of disability and mortality. There are several studies in literature which demonstrate the efficacy of citicoline, thanks to its neuroprotective function, for the recovery and in postischemic cerebral rehabilitation. It has been shown that, even soon after an ischemic stroke, administration of oral citicoline (500–4000 mg/day) improves the general conditions evaluated with the Rankin scale and the National Institute of Health Stroke Scale 12. In particular, it has been shown that the CDP-choline improves the cognitive and mental performance in Alzheimer's dementia and vascular dementia. We have evaluated the administration of citicoline in geriatric patients following a protocol of intravenous study on improvement of individual performances.

Efficacy of citicoline in post-ischemic cerebrovascular disease

Take home messages

- Un miglioramento del MMSE è stato riscontrato tra T2, T1 e T0 (aumento di 0.5 punti), anche se non significativo
- Il gruppo non trattato ha presentato un declino del MMSE (-1.9 punti); una signicativa differenza è stata riscontrata tra i gruppi trattati e quelli non trattati
- I punteggi ADL ed IADL sono rimasti sostanzialmente invariati in entrambi i gruppi
- E' stata riscontrata una leggera differenza nel punteggio della GDS tra il gruppo attivo e quello di controllo (p=0.06, ns)
- Non sono stati riscontrati eventi avversi nel corso dello studio
- Questo studio ha dimostrato che la citicolina è efficace e sicura, quindi può essere raccomandata nell'impairment cognitivo lieve di origine vascolare

"Ogni uomo, se lo desidera, può diventare lo scultore del proprio cervello"

Grazie per l' attenzione