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Original Research Article

Role of citicoline in improvement of cognition, memory and post stroke disability in stroke patients

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ABSTRACT

Background: Citicoline has emerged as a potential neuroprotectant in experimental models in stroke patients. Citicoline has shown some beneficial effects in human ischaemic stroke and with an excellent safety profile while in haemorrhagic stroke data is limited. Authors conducted this study to test role of citicoline in stroke patients in terms of cognition, memory and post stroke disability.
Methods: In this prospective study, patients had to be previously independent, aged >18 years of age, presented within 24 hours of onset of symptoms of stroke diagnosed by neuroimaging (CT or MRI). Patients received either a placebo or 500 mg/12 h citicoline for 12 weeks (orally or intravenously). The primary aim was to evaluate improvement in cognition, memory and post stroke disability after 12 weeks. The efficacy endpoint was the percentage of subjects with MMSE and DRS at 12 weeks.
Results: Total 75 stroke patients were enrolled, 40 in control group and 35 in citicoline group were allotted randomly. Patients in citicoline group were given intravenous citicoline 500 mg/12 hour during hospital stay and orally 500 mg/12 hour after discharge for up to 12 weeks. Control Group was given Placebo. cognition, memory and post stroke disability show positive improvement in citicoline group.
Conclusions: Citicoline shows beneficial effects in stroke in terms of cognition, memory and post stroke disability.

Keywords: Citicoline, Neuroprotection, Post-stroke disability

INTRODUCTION

Stroke or cerebrovascular accident is a common cause of death, and the leading cause of long term disability in the world. In ischemic stroke, recognition of the penumbra in which ischaemic changes may be reversed partly or completely by treatment especially if started within a short period of time after vessel occlusion. This therapeutic time frame is divided into two components- the reperfusion window period and the neuroprotection window period. If blood flow is resumed during the reperfusion window period, it limits the extent of neuronal damage and forms the basis of rationale for thrombolysis. Advances in neuroimaging in recent years had revolutionised the concept of a rigid 3-hour window.[1]

Both DWI and PI have improved acute stroke diagnosis and may impact on patient selection for thrombolysis and neuroprotective therapy. The neuroprotection window is currently the subject of immense laboratory and clinical research.

Intracerebral haemorrhage (ICH) has a worse prognosis than cerebral infarction.[2] In general, the treatment of ICH is controversial and the role of surgery still remains unclear.[2,3] There is some evidence that brain ischaemia plays a role in the secondary brain injury seen in some experimental models of the ICH neurological deterioration occurs in 23% of ICH cases, and its presence results in a worse prognosis.[4,5]

Neuroprotective therapy is directed at these biochemical events that occur consequent to arterial occlusion. Numerous preclinical studies in animal models of global and focal ischaemia had shown efficacy by targeting each of the steps along this ischaemic cascade.[6] Citicoline is a neuroprotectant drug with positive effects in experimental models and in the treatment of the acute phase of cerebral ischaemia, showing, in some cases, a significant reduction in the volume of cerebral infarction.[7-10] Citicoline also has a positive effect on brain oedema and in ICH models.[7,11,12] In these models, citicoline reduced the volume of the ischaemic lesion associated with the haematoma.

METHODS

Research design

The present study was prospective study single centred conducted in the KPS institute of medicine, GSVM Medical College Kanpur (Tertiary centre) during January 2010 to September 2011. Patients were randomly assigned to control or citicoline group. This study received approval from ethics committee of this institute.

Study instrument

Improvement in the clinical profile, disability and cognitive improvement was assessed by using Mini Mental Status examination (MMSE) and Glasgow Coma Scale (GCS) at the time of admission and during follow up.

Disability was graded by using Disability Rating Scale (DRS). The Disability Rating Scale (DRS) was developed and tested with older juvenile and adult individuals with moderate and severe traumatic brain injury (TBI) in an inpatient rehabilitation setting. One advantage of the DRS is its ability to track an individual from coma to community. DRS score ranges from 0-29.

A person without disability scores 0 and score 29 indicates extreme vegetative state. Measurement across a wide span of recovery is possible because various items in this scale address all three World Health Organization categories: impairment, disability and handicap.[13] The first three items of the DRS ("Eye Opening," "Communication Ability" and "Motor Response") are a slight modification of the Glasgow Coma Scale and reflect impairment ratings.[14] Cognitive ability for Feeding, Toileting and Grooming reflect level of disability. The "Level of Functioning" item is the modification of a measure used by Scranton and reflects handicap, as does the last item, Employability.[15]

Subject characteristics

Subjects were more than 18 years of age and had to be admitted within 24 hours after the onset of symptoms of stroke diagnosed by neuroimaging (CT or MRI).

Baseline severity was defined as patients with a score larger than 3 points on the Glasgow Coma Scale and larger than 7 on the National Institutes of Health Stroke Scale (NIHSS), Written informed consent was taken. Exclusion criteria were as follows-patients presenting with GCS score of <3, CT or conventional MRI evidence of brain tumour, cerebral oedema with a clinically significant mass midline shift with compression of ventricle, and brainstem, History of ventricular dysrhythmia, acute myocardial infarction within 72 hours prior to enrolment, unstable angina, decompensated congestive heart failure, Drug addiction like cocaine, amphetamine and expectancy of life less than 3 months due to comorbidity.

Study treatment

For randomisation a table of random digits was used. Both, the placebo and the active drug ampoules were completely indistinguishable to the patients. The treatment schedule was 500 mg intravenous citicoline or a placebo every 12 h during hospitalisation and orally 500 mg every 12 hourly at the time of discharge and onwards. The total time of treatment was 12 weeks.

Outcome measures

The primary endpoint was effectiveness. The effectiveness of the treatment was assessed in terms of improvement in cognition, memory and reduction in the post stroke disability. The efficacy endpoint was assessed using Disability Rating Scale (DRS) at 3 months. NIHSS scores were measured at baseline and week 12.

Statistical analysis

The monitoring of the study, the data management, and the statistical analysis was done using SPSS software. Statistical analysis was conducted according to the intention to treat principle. The intention-to-treat population was defined as patients randomised with at least one efficacy evaluation after receiving at least one medication dose, and fulfilling inclusion and exclusion criteria of this study. All comparisons with these variables were conducted using the chi square test. The descriptive and clinical variables were analysed at baseline to maintain homogeneity between groups. For the analysis of ordinal variables, we used non-parametric statistical tests. Values of $p < 0.05$ were considered significant.

RESULTS

This study was conducted on 75 patients of cerebrovascular accident including ischemic, haemorrhagic and subarachnoid haemorrhage, with proven CT/MRI of head compatible with finding of stroke. but 11 patients (5 from citicoline group and 6 from control group) did not turned for follow up so we can't assess what happened to them whether improved or died.

Table 1: Demographic profile, baseline characteristics and risk factors.

Parameters	Placebo (n=40)	Citicoline (n=35)
Age (in years)		
<40 years	6 (15%)	4 (11.5%)
40-60 years	10 (25%)	9 (25.7%)
>60 years	24 (60%)	22 (62.8%)
Sex		
Male	25 (62.5%)	24 (68.5%)
Female	15 (37.5%)	11 (31.5%)
Risk factors		
Hypertension	20 (50%)	22 (62.8%)
Diabetes	10 (25%)	8 (22.9%)
Smoking	10 (25%)	9 (25.7%)
Dyslipidemia	8 (20%)	7 (20%)
Alcoholism	7 (17.5%)	6 (17.1%)
Cardiac disease	8 (20%)	5 (14.3%)
Past history of TIA/Stroke	9 (22.5%)	9 (25.7%)
Types of stroke		
Ischemic	27 (67.5%)	23 (65.7%)
Haemorrhagic	9 (22.5%)	10 (28.6%)
Subarachnoid	4 (10%)	2 (5.7%)

Mean age of onset of stroke was 62.5 years in this study, 61.3% of patients in our study were more than 60 years of age (Table 1). Incidence of stroke were higher as age of patient increases. In this study stroke was more prevalent in male (65.3%) as compared to female (34.7%) (Table 1). In present study 65.7 % patients have ischemic stroke while 28.6% patients have haemorrhagic stroke which is higher than previously reported it may due poor compliance to antihypertensive drug or small study sample while 48.5% patients presented with headache or coma. 37.1% presented with vomiting especially in those patients who had intracerebral haemorrhage, SAH or large infarct and oedema (Table 1). 85.3% patients present with right sided hemiparesis while 37.4% have left sided hemiparesis. Left sided lesion was more common in patients of cognitive impairment due to stroke. Decreased level of consciousness was present in 65.9% of our cases (in which 37.4% were drowsy and 25.7% were comatose). Decreased level of consciousness created the problem in scoring of MMSE. A slightly higher percentage of decreased level of consciousness might be due to delay in seeking treatment.

In the present study 43.1% patients present with aphasia (in which 25% in control group and 18.1% in study group. Aphasia created the problem in scoring MMSE and DRS of patients despite being conscious.

The average Mini Mental Score (MMSE) of control group improved from 15±6.0 on admission to 17.6 ±6.55 at 12 weeks ($t=2.0$ and $p<0.05$).while in citicoline group MMSE shows statistically significant improvement {12.34±7.2 on admission and 18.7±6.6 at 12 weeks ($t=5.6$, $p<0.001$)}.MMSE was 5-19 range in 64% in control group (64% have cognitive impairment) 8.8% patient have normal cognition at 12 weeks. While in citicoline group 83% patients have MMSE in 5-19 range,13.3% patients have normal cognition at 12 weeks (Table 2).

Average disability rating score (DRS) of control group was 13.8±7.3 on admission and 10.9±7.2 at 12 weeks ($t=2.30$ and $p<0.05$). 8.8% of control group having DRS near normal at admission which improved to 20.6% at 12 weeks. In citicoline group DRS on admission was 11.4±6.8 and 7.8±7.2 ($t=2.69$, $p<0.05$) at 12 weeks which shows positive impact in disability improvement (Table 3). Authors also compared Glasgow coma scale (GCS) of control group with the GCS of study group at admission ($x^2=2.48$, $p>0.05$). It shows favourable GCS of citicoline group as compared to control group but not statistically significant. But Glasgow Coma Scale is not a good to assess the effect of citicoline.

Table 2: Results of memory and cognition at admission and 12 weeks.

MMSE	Placebo		Citicoline	
	At admission	12 weeks	At admission	12 weeks
0-4	2 (5.8%)	3 (8.8%)	4 (13.3%)	1 (3.3%)
5-9	3 (8.8%)	5 (14.7%)	6 (20%)	3 (10%)
10-14	9 (26.5%)	7 (20.5%)	8 (26.7%)	5 (16.7%)
15-19	13 (38.2%)	10 (29.4%)	6 (20%)	8 (26.7%)
20-24	5 (14.7%)	6 (17.6%)	5 (16.7%)	9 (30%)
25-30	2 (5.8%)	3 (8.8%)	1 (3.3%)	4 (13.3%)

Table 3: Results of post-stroke disability at admission and 12 weeks.

DRS	Placebo		Citicoline	
	At admission	12 weeks	At admission	12 weeks
0-1	1 (2.9%)	3 (8.8%)	1 (3.3%)	4 (13.3%)
2-3	2 (5.8%)	4 (11.8%)	2 (6.6%)	5 (16.7%)
4-6	4 (11.8%)	6 (17.6%)	6 (20%)	9 (30%)
7-11	6 (17.6%)	8 (23.5%)	7 (23.3%)	4 (13.3%)
12-16	8 (23.5%)	5 (14.7%)	8 (26.6%)	4 (13.3%)
17-21	5 (14.7%)	3 (8.8%)	3 (10%)	2 (6.6%)
22-24	5 (14.7%)	2 (5.8%)	2 (6.6%)	1 (3.3%)
25-29	3 (8.8%)	3 (8.8%)	1 (3.3%)	1 (3.3%)

DISCUSSION

Neuroprotection is an emerging concept in stroke patients. Optimal treatment for ICH is controversial, use of citicoline to 'protect' the brain against the ischaemic insult observed in these cases.[3] Mean age of onset of stroke in India ranges from 63-65 years for men and 57-68 years for women.[16] Age specific stroke was higher for all age group in men.[17]

In an Indian study found male to-female ratio 1.7 in stroke patient, which was similar to our study (1.8:1).[18] It should be considered that the pathophysiology of cerebral injury after ICH shares several mechanisms with ischaemic injury.[19-23] So, there may be an option to the use of neuroprotectant (like citicoline in this study).

Up to now, the efficacy and safety of neuroprotectant drugs has only been tested in patients with ICH in subgroup analyses from the CLASS study and from the GAIN studies.[24-26] In the CLASS study it was demonstrated that clomethiazole was safe, but there was no evidence of efficacy due to the small sample size.

In addition, the GAIN studies did not show positive results for acute ischaemic stroke patients.[27,28] In our case, we studied the effects of citicoline on the outcome of patients with stroke.

Citicoline is a drug with some evidence of effectiveness in the treatment of acute ischaemic stroke.[12,18,19] Citicoline is a very safe drug in acute ischaemic stroke patients.[29] The International Citicoline Trial on Acute Stroke, ICTUS was designed to confirm the encouraging results of the data pooling analyses and to replicate those trends.[29]

ICTUS was an international, multicentre, prospective, double-blind, randomized, placebo-controlled trial with participation of neurology services from 37 centres. Mortality was comparable between the two groups. Global recovery at 90 days was similar in patients who received citicoline and in those who received placebo. Citicoline is safe but does not provide efficacy evidence for the treatment of moderate-to-severe acute ischemic stroke. Citicoline at high doses is as effective as i.v. thrombolysis in experimental stroke.[30]

The results of current study, despite limitations concerning the sample size and statistical significance, are similar to those seen in other ischaemic stroke studies. Present study data shows a positive trend in favour of citicoline in comparison with placebo as regards to the cognition, memory and post stroke disability.

Limitations of study was single centre study having small study population. The stroke pathogenesis involve various pathway of neuronal injury so single drug may not be effective neuroprotection at all pathways. Decreased level of consciousness and aphasia in otherwise conscious patients was problematic in scoring of MMSE.

CONCLUSION

Citicoline established as a neuroprotectant in various studies. In present study citicoline has a positive effect in stroke patients in terms of cognition and post stroke disability. Larger clinical studies to be needed to generalise this study results in the population.

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