International Journal of Medical and Pharmaceutical Research
Website: https://ijmpr.in/ | Print ISSN: 2958-3675 | Online ISSN: 2958-3683
NLM ID: 9918523075206676
Volume: 4 Issue:5 (Sept-Oct 2023); Page No: 39-51

Original Article

Evaluation of Therapeutic Efficacy of Citicoline in Acute Ischemic Stroke Patients: A Meta Analysis

Dr. Dev Patel[1], Dr. Shrenil Kavathia[2], Dr. Devang Rana[3]*

[1] Intern, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India
[2] MBBS Graduate, B.J. Medical College, Ahmedabad, Gujarat, India
[3] Assistant Professor, Department of Pharmacology, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India

ABSTRACT

Introduction: Stroke is the third leading condition with the highest mortality and death and is a major cause of disability. The estimated number of deaths due to stroke is about 5.71 million people as per the WHO data, and is estimated to peak at 7.8 million in 2030. Citicoline is believed to exert neuroprotection and neurorestoration intracellularly by supporting cellular phospholipid synthesis. Citicoline is used in Acute Ischemic Stroke patients, however, there is not enough statistical evidence available for the benefits of the same. Hence, this calls for a meta-analysis of RCTs on a larger scale to generate highest level of scientific evidence regarding the controversial negative studies of Citicoline when tested against placebo.

Objectives: To review and analyze statistical evidence from existing randomized controlled trials, the therapeutic efficacy of Citicoline in acute ischemic stroke (AIS) patients.

Materials & Methods: A total of 17 studies, involving 5127 patients were included. The studies were double-blind, randomized, and placebo-controlled clinical trials studying the effect of Citicoline on patients with Acute Ischemic Stroke. The included patients suffered from an Acute Ischemic Stroke with a minimum therapeutic window of 6 hours. The treatments tested were either Citicoline, with doses ranging from 250 to 4000 mg daily, or placebo. The duration of the treatment ranged from 10 days to 9 weeks. The principal summary measures were the Odd's Ratio(OR) and Relative Risk (RR). For the measurement of treatment effect Rev Man 5.4.1 version software by Cochrane Database will be utilized to calculate Odd's ratio and Relative Risk(RR).

Results: The RR(for 5127 participants) was 1.301(random effect model) and 1.163(fixed effect model)[95% confidence interval (CI) 1.081 to 1.2521 (fixed effect model), $p<0.001$] and the overall OR(for 5127 participants) was 1.769(random effect model) and 1.281(fixed effect model)[95% confidence interval (CI) 1.137 to 1.443 (fixed effect model), $p<0.001$], indicating a slight advantage of Citicoline over placebo treatment. Citicoline was also found to be associated with a less number of adverse events and deaths compared to placebo.

Conclusion: Citicoline is proven to be slightly more efficacious than placebo, with lesser adverse events and deaths. However the margin of benefit is narrow. Future trials comparing the same, on higher number of patients is necessary to draw a final conclusion on it.

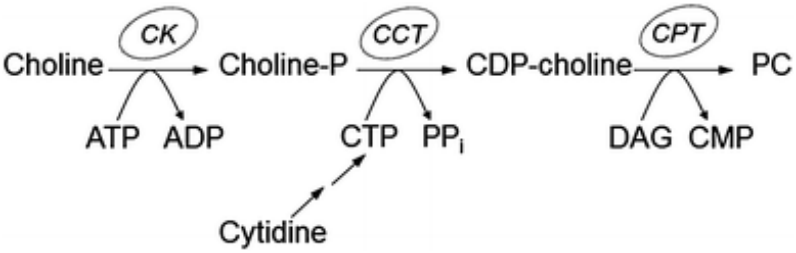
Key Words: *Citicoline, Placebo, Stroke, Randomized Controlled Trials, Meta Analysis*

***Corresponding Author**
Dr. Devang Rana*
Assistant Professor, Department of Pharmacology, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India

INTRODUCTION

Ischemic stroke is characterized by the sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function. Acute ischemic stroke is caused by thrombotic or embolic occlusion of a cerebral artery. Stroke is the third leading condition with the highest mortality and death. Stroke is one of the major causes of death and disability in India. The estimated adjusted prevalence rate of stroke is 84–262/100,000 in the rural and 334–424/100,000 in the urban areas [1]. The estimated number of deaths due to stroke was about 5.71 million people as per the WHO data, and this number will be increased to 7.8 million in 2030 [2, 3].

Lipids are known to play an important role in brain injury especially in ischemic stroke patients [3]. Citicoline is identical to the natural precursor of phospholipid phosphatidylcholine. Some theories claim its conversion to cytidine and choline which then enter the brain separately and are used to resynthesize CDP-choline inside the brain cells which then exerts neuroprotection and neurorestorative properties intracellularly by supporting cellular phospholipid synthesis [4].



Citicoline also has pleiotropic effects in stroke mainly, it inhibits release of free fatty acids, inhibits release of glutamate, decreases apoptotic pathways, decreases free radical formation, favoring synthesis of nucleic acids, proteins, ACh, enhancing synaptic outgrowth, increasing neuroplasticity and probable decrease in stroke size with improved behavioural performance, learning and memory tasks [5, 6 & 7].

However, there is not enough statistical evidence available and research done explaining the changes in the effects of Citicoline especially its role in post-stroke cognitive changes.

Hence, this calls for a meta-analysis where direct comparison of studies of RCTs is carried out on a larger scale to generate highest level of scientific evidence regarding the controversial negative studies of Citicoline when tested against placebo.

STUDY OBJECTIVE

To review and analyze statistical evidence from existing randomized controlled trials, the therapeutic efficacy of Citicoline in acute ischemic stroke (AIS) patients.

MATERIALS AND METHODS :

STEP 1: STUDY APPROVAL PROCESS:

Study began after receiving the ICMR approval and that of the Institutional Ethics Committee (IEC).

STEP 2: SEARCH METHODS FOR IDENTIFICATION OF STUDIES :

Randomised Control Trials of Citicoline administration in AIS patients will be undertaken. Published Studies will be identified from:

- Cochrane Central Register of Clinical trials
- MeSH (Medical Subject Headings) including ‘Citicoline’ and ‘acute ischemic stroke’
- Medline(accessed via Ovid)
- Embase (accessed via Ovid)
- Scopus database
- Google Scholar
- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform(ICTRP)
- CTRI.nic.in
- Searching other resources: in addition, we will hand search relevant journals, review the reference lists of retrieved studies to search for additional reports of relevant studies.
- Studies till January, 2023 will be undertaken for meta-analysis.

STEP 3: CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW:

- Randomised controlled trials (RCTs) which lasting for at least 4 weeks by using: "An adequate method of allocation concealment (e.g. sealed opaque envelopes)" or a ‘quasi’ method of randomization(e.g. allocation by date of birth)
- RCTs following PRISMA guidelines.
- We will include published and studies without language restriction.
- All the single-blind, double-blind or un-blinded studies will be included.
- Observational studies, Animal Studies and uncontrolled RCTs will be excluded.

STEP 4: ENROLLMENT OF RCTS BASED ON INCLUSION AND EXCLUSION CRITERIA:

INCLUSION CRITERIA:

The studies to be included in the search will have to meet the following criteria:

1) Randomised controlled trials which follow the PRISMA guidelines,
2) Trials carried out on Adult (age >18) humans will be included,
3) No sex restrictions,
4) Randomised, placebo-controlled, double blind clinical trials with oral/intravenous/nasogastricCiticoline,
5) Trials that compared the effects of Citicolineand placebo,

6) Patients with moderate to severe AIS.

EXCLUSION CRITERIA :

The studies that will be excluded from the analysis:

1) Those which did not meet the inclusion criteria,
2) Non-prospective or non-randomised clinical trials,
3) Studies with incomplete information,
4) Observational studies.

STEP 5: TYPES OF INTERVENTIONS:

Interventional studies that examined the effects of Citicoline and placebo in improving stroke conditions in patients of AIS will be included.

STEP 6: TYPES OF OUTCOME MEASURES:

A] PRIMARY OUTCOMES:

Improvements in Post-Stroke cognitive scale. [Cognitive tests - National Institutes of Health Stroke Scale (NIHSS), modified Rankin Score (mRS), Glasgow outcome scale (GOS) and Barthel Index (BI) score.]

B] SECONDARY OUTCOMES :

1) Occurrence of adverse events
2) Death

STEP 7: DATA COLLECTION AND EXTRACTION ;

- Investigator will independently review the titles and abstracts of the studies from the online databases to identify all potential eligible studies.
- All potentially relevant records will be retrieved as complete manuscripts and assessed for compliance with the inclusion criteria.
- Multiple publication bias will be addressed by including the most recent/relevant study from multiple studies using data
- Data will be collected and extracted by one author, double checked by second reviewer and discrepancies will be resolved through discussion.
- Data will be extracted per patient rather than per event.
- Data will be collected and extracted by using Cochrane Data collection & extraction form for intervention reviews.

STEP 8: NULLIFICATION OF BIAS

Authors assured to include studies in which allocation of Citicoline and placebo groups were adequately randomized and there was no conflict of interest as well as match to inclusion and exclusion criteria.

STEP 9: MEASUREMENT OF TREATMENT EFFECTS:

For the measurement of treatment effect **RevMan 5.4.1version software by Cochrane Database** will be utilized to calculate Odd's ratio. A Random and Fixed effect model will be applied to calculate the standardized mean difference of change between groups. p-value less than 0.05 will be considered as statistically significant value. The I2 will be used to measure the heterogeneity between studies and a value > 30.0 will be considered to reflect heterogeneity.

STEP 10: SUMMARY MEASURES:

The principal summary measure were the **Odd's Ratio(OR) And Relative Risk(RR)** (at 95% Confidence Interval). Funnel Plot and Forest Plot were plotted.

STEP 11: DATA SYNTHESIS AND RESULTS:

- Analysis of efficacy of Citicoline in AIS patients will be done by using different methods like forest plot, funnel plot etc. wherever necessary.
- Flow diagram of the process in which all the studies will be undergone before inclusion in meta-analysis is described in Figure 1

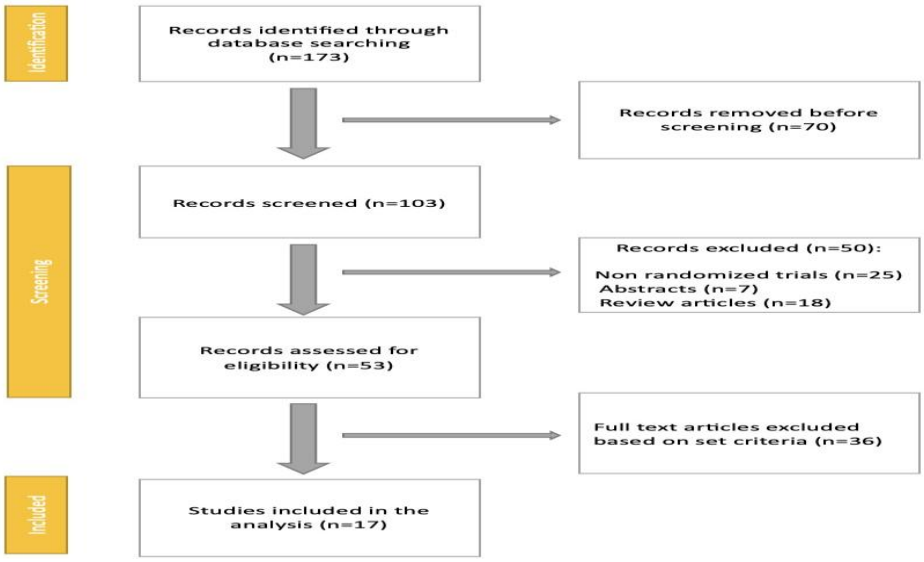


Figure 1: Flow diagram depicting the preferred reporting items for meta-analysis

As shown in Figure 1, a total of 53 published papers were identified and 36 of those were rejected for various reasons.

STUDY CHARACTERISTICS :

The 17 studies selected were double-blind, randomized, and placebo-controlled clinical trials studying the effect of Citicoline on the recovery of patients with acute ischemic stroke. The oldest study was published in 1980 and the most recent study was published in 2022; thus, there is a gap of 42 years between the first and the last study.

The included studies involved 5127patients. All the patients were 18 years or older, suffering from an acute ischemic stroke and with a minimum therapeutic window of 6 hours. The treatments tested were either Citicoline, with doses ranging from 250 to 4000 mg daily, or placebo. The duration of the treatment ranged from 10 days to 9 weeks. Citicoline was administered intravenously in 4 studies, orally in another 5 studies, and both intravenously and orally in 5 studies. No information about the route of administration was available for 2 studies. The route of administration was either oral or nasogastric for 1 study.

The studies involved have different primary outcome targets, but all have neurological improvements at leastas secondary outcome, allowing cognitive scale improvement to be evaluated in the efficacy of the intervention. The timing of outcome measures varies between 10 days and 12 months.

The studies were selected after reviewing the citation, the abstracts, and the full papers when available. Compiling all the results, around 50 studies on acute stroke were selected to be fully reviewed for inclusion in the analysis. Among the 50 studies selected, only 17 fulfilled the criteria to be included in this meta-analysis.

Out of the 17 studies used for observational purposes, 2 studies were excluded from analytical calculation either because of data errors or insufficient data availability.

Doses, follow-up periods, therapeutic windows and other details of the 17 studies are mentioned in the Table 1. Total patients have been written after excluding the ones who did not finish the study due to any reasons, or their follow-up data was not available.

Table 1: Characteristics of studiesa

Study	Year	No. of patients	Age (y)	Baseline Severity (Placebo)	Baseline Severity (Citicoline)	Therapeutic Window	Dose (mg)	Route	Follow up
W.M.Clark [8]	1999	394	70.5	12.7	13.3	24h	500/d/6w	p.o.	12w
T.Sobrino [9]	2011	48	70.8	9(6,18)	8(2,16)	24h	2000/d/6w	p.o./n.g.	3m
Boudouresques and Michel [10]	1980	45	63.6	Mild-Mod	Mild-Mod	48h	750/d/10d	i.v.	10d
J.A.S. [11]	2013	347	67.2	14(10-16)	13(10-17)	6w	1000/d/12m	-	6/12m
Goas et al [12]	1980	64	62.8	Mild-	Mild-Mod	48h	250-	i.v.	90d

				Mod			750/d/20d		
W.M.Clark [13]	2001	898	67.5	14.5	13	24h	2000/d/6w	p.o.	6w
J.A.S. [14]	2016	163	67.5	14(10-16.5)	13(10-16)	6w	1000/d	p.o.	-
Manish Mittal [15]	2012	49	>18y	16±9.23	15.58±11.36	24h	500/d/6w	p.o./i.v.	3m
Corso et al [16]	1982	33	71.5	Mild-Mod	Mild-Mod	7-10d	1000/d/30d	i.v.	30d
Tazaki et al [17]	1988	272	29-90	Mild-Mod	Mild-Mod	14d	1000/d//14d	i.v.	14d
W.M.Clark [18]	1997	259	67.8	13	11.6(500mg) 13.2(1000) 13.6(2000)	24h	500-2000/d/6w	p.o.	12w
J.J.S. [19]	2006	38	70.75	13.7	10.6	6h	2000/d/2w	p.o./i.v.	12w
Alviarez and Gonzalez [20]	2007	59	69.8	-	-	8h	2000/d/6w	i.v.(3d), then p.o.	6w
Dávalos et al (ICTUS) [21]	2012	2298	72.8	15	15	24h	2000/d/6w	i.v.(3d), then p.o.	12w
Warach et al [22]	2000	100	70.3	-	-	24h	500/d/6w	p.o.	12w
C. León-Jiménez [23]	2010	173	-	14.33	14.30	48h	2000/d/2-4w, then 1000/d/5-7w, total 9w	-	30,90d
Agrawal [24]	2022	98	61	Mild-Mod-Sev	Mild-Mod-Sev	6w	2000/d/3d then 2000/d/39d	i.v.(3d), then p.o.	12w

Baseline severity is considered only in the format of NIHSS and the studies where baseline cognition measurement was provided in a different scale are followed by '-' sign. Certain other columns where information was not provided by the studies are filled with '-'.
i.v.= intravenous
p.o.=oral
n.g.=nasogastric

SYNTHESIS OF RESULTS:
The odds ratio, relative risk and confidence intervals are presented in the upcoming section.

RESULTS

Table 2[A] Relative Risk of Citicoline versus placebo

Study	Intervention	Controls	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
W.M.CLARK [8]	116/267	50/127	1.104	0.855 to 1.425			7.64	10.33
J.A.S [11].	99/172	85/175	1.185	0.971 to 1.446			12.56	11.64
W.M.CLARK [13];	185/452	156/446	1.170	0.989 to 1.384			17.64	12.35
Manish Mittal [15]	24/24	25/25	-					
W.M.CLARK [18]	47/194	10/65	1.575	0.845 to 2.933			1.29	4.27
J.J.S. [19]	5/19	1/19	5.000	0.643 to 38.868			0.12	0.54
Alviarez and Gonzalez [20]	13/29	10/30	1.345	0.704 to 2.569			1.19	4.03
Dávalos et al (ICTUS) [21]	329/1148	343/1150	0.961	0.846 to			30.80	13.19

				1.091				
Warach et al 92 (USA3) [22]	20/52	19/48	0.972	0.595 to 1.586			2.07	5.83
C. León-Jiménez [23]	75/86	53/87	1.432	1.188 to 1.725			14.30	11.93
Boudouresques and Michel [10]	11/23	2/22	5.261	1.312 to 21.093			0.26	1.12
Goas et al [12]	16/31	8/33	2.129	1.065 to 4.257			1.04	3.65
Corso et al [16]	13/17	5/16	2.447	1.129 to 5.302			0.83	3.08
Tazaki et al [17]	68/133	35/139	2.031	1.458 to 2.828			4.54	8.63
Agrawal [24]	32/49	31/49	1.032	0.768 to 1.387			5.72	9.42
Total (fixed effects)	1053/2696	833/2431	1.163	1.081 to 1.251	4.068	<0.001	100.00	100.00
Total (random effects)	1053/2696	833/2431	1.301	1.116 to 1.516	3.371	0.001	100.00	100.00

Table 2[B] Test for heterogeneity

Q	39.6909
DF	13
Significance level	P = 0.0002
I^2 (inconsistency)	67.25%
95% CI for I^2	42.69 to 81.28

Table 2[C] Publication bias

Egger's test	
Intercept	1.9173
95% CI	0.4941 to 3.3405
Significance level	P = 0.0125
Begg's test	
Kendall's Tau	0.3626
Significance level	P = 0.0708

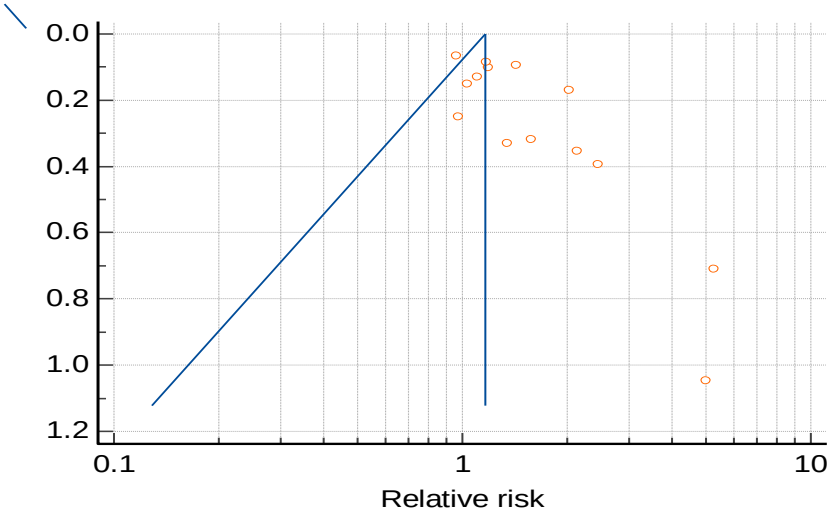


Figure 2: Funnel Plot comparing relative risk of Citicoline and Placebo

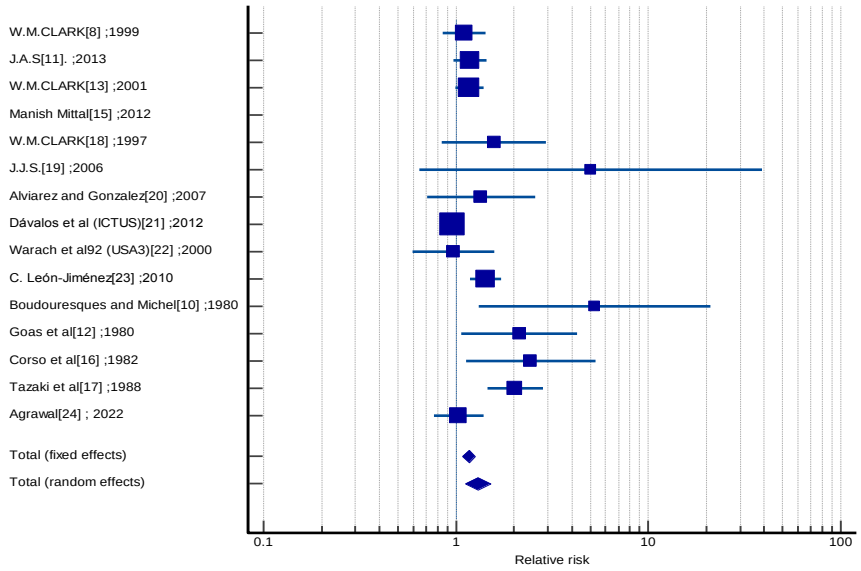


Figure 3: Forest plot comparing relative risk of Citicoline and placebo

For this outcome, relative risk greater than 1 indicates clinical advantage of Citicoline. Data available from 5127 patients (15 trials) was evaluated and a forest plot was plotted. The patients who withdrew from the treatment were not included in the calculation.

2696 out of 5127 participants were randomized to Citicoline (52.6%) and 2431 out of 5127 participants were randomized to placebo (47.4%)

The relative risk (for 5127 participants) was 1.301(random) and 1.163(fixed) [95% confidence interval (CI) 1.081 to 1.2521 (fixed), p<0.001], indicating a slight advantage of Citicoline over placebo treatment as per Table 2.

In addition, Figure 2 and 3 show the Funnel and Forest plots depicting relative risk of Citicoline versus placebo respectively.

Table 3[A] Odds Ratio of Citicoline versus placebo

Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%)	
							Fixed	Random
W.M.CLARK [8]	116/267	50/127	1.183	0.769 to 1.819			7.86	10.34
J.A.S [11]	99/172	85/175	1.436	0.940 to 2.193			8.12	10.41
W.M.CLARK [13]	185/452	156/446	1.288	0.983 to 1.688			19.94	11.80
Manish Mittal [15]	24/24	25/25	-					
W.M.CLARK [18]	47/194	10/65	1.759	0.831 to 3.721			2.59	7.30
J.J.S. [19]	5/19	1/19	6.429	0.672 to 61.471			0.29	1.61
Alviarez and Gonzalez [20]	13/29	10/30	1.625	0.566 to 4.664			1.31	5.11
Dávalos et al (ICTUS) [21]	329/1148	343/1150	0.945	0.790 to 1.131			45.05	12.44
Warach et a l92 (USA3) [22]	20/52	19/48	0.954	0.427 to 2.132			2.25	6.85
C. León-Jiménez [23]	75/86	53/87	4.374	2.034 to 9.404			2.49	7.17
Boudouresques and Michel [10]	11/23	2/22	9.167	1.729 to 48.598			0.52	2.67
Goas et al [12]	16/31	8/33	3.333	1.151 to			1.29	5.06

				9.651				
Corso et al [16]	13/17	5/16	7.150	1.532 to 33.372			0.61	3.03
Tazaki et al [17]	68/133	35/139	3.109	1.863 to 5.188			5.55	9.53
Agrawal [24]	32/49	31/49	1.093	0.478 to 2.498			2.13	6.67
Total (fixed effects)	1053/2696	833/2431	1.281	1.137 to 1.443	4.083	<0.001	100.00	100.00
Total (random effects)	1053/2696	833/2431	1.769	1.302 to 2.402	3.652	<0.001	100.00	100.00

Table 3[B] Test for heterogeneity

Q	49.5404
DF	13
Significance level	P < 0.0001
I^2 (inconsistency)	73.76%
95% CI for I^2	55.45 to 84.54

Table 3[C] Publication bias

Egger's test	
Intercept	2.2941
95% CI	0.9985 to 3.5896
Significance level	P = 0.0023
Begg's test	
Kendall's Tau	0.3187
Significance level	P = 0.1124

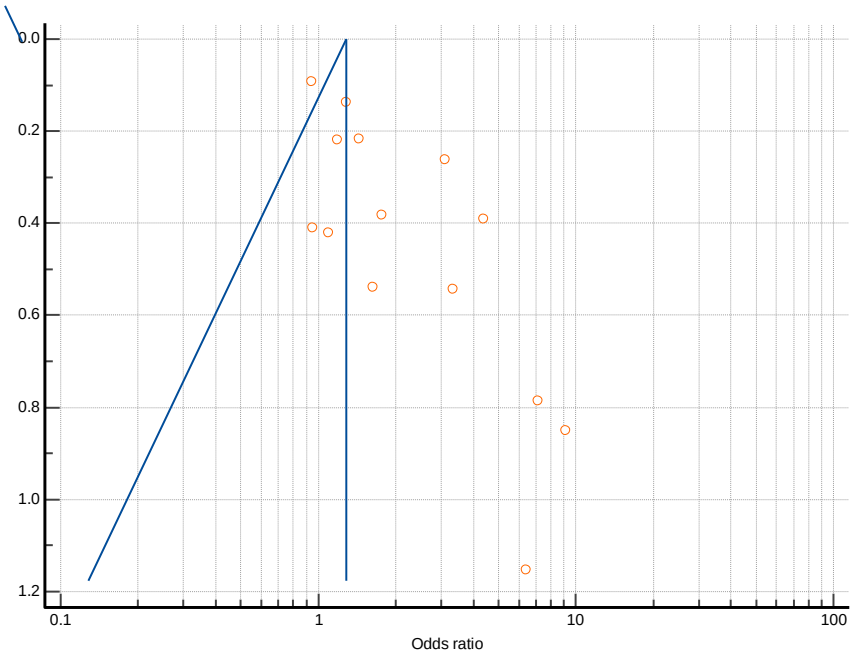


Figure 4: Funnel Plot comparing odds ratio of Citicoline and Placebo

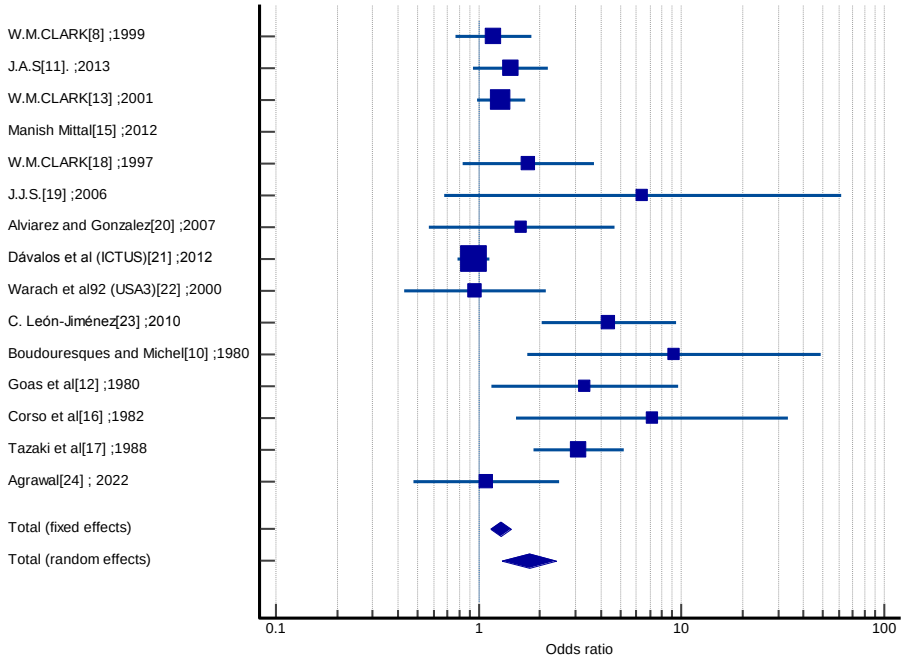


Figure 5: Forest Plot comparing odds ratio of Citicoline and Placebo

For this outcome, Odd's ratio greater than 1 indicates clinical advantage of Citicoline. Data available from 5127 patients (15 trials) was evaluated and a forest plot was plotted. The patients who withdrew from the treatment were not included in the calculation.

2696 out of 5127 participants were randomized to Citicoline (52.6%) and 2431 out of 5127 participants were randomized to placebo (47.4%).

The overall pooled odd's ratio (for 5127 participants) was 1.769(random) and 1.281(fixed) [95% confidence interval (CI) 1.137 to 1.443 (fixed), P<0.001], indicating a slight advantage of Citicoline over placebo treatment as per Table 3.

In addition, Figure 4 and 5 show the Funnel and Forest plots depicting relative risk of Citicoline versus placebo respectively.

SECONDARY OUTCOME ANALYSIS

Data for the secondary outcome assessment was available only for 9 studies which are included here. There was a clear positive outcome with Citicoline leading to lesser number of deaths and serious adverse events. Analysis by J.J.S. [19] shows equal adverse events between the Citicoline and placebo groups. However the study included only 19 patients in each group and thereby only 38 in total. The number is not significant enough to draw a conclusion.

Study by J.A.S. [11] shows about 0.3% more deaths or serious adverse events in the Citicoline group compared to the placebo group. The total number of patients included in this study were 163 and thereby slightly significant to be considered.

However, data from the rest of the studies show significant difference in the Citicoline and placebo groups, clearing showcasing Citicoline to be the safer alternative. Another point to be considered here is that the deaths occurred during the respective studies cannot be surely labeled to be primarily because of intervention or non intervention reasons.

Table 4 shows Citicoline is the safer option analyzing the data available as of now.

Table 4: Comparing adverse events and deaths between Citicoline and placebo groups

Study	No. of patients died/ experienced serious adverse events -placebo (% of total placebo patients)	No. of patients died/ experiencedserious adverse events -Citicoline (% of total Citicoline patients)
W.M.Clark [8]	23 (18%)	45 (17%)
J.A.S. [11]	21 (12%)	17 (9.9%)
W.M.Clark [13]	321(72%)	294(65%)
J.A.S. [14]	6 (7.8%)	7 (8.1%)

Tazaki et al [17]	11 (7.9%)	6 (4.5%)
Dávalos et al (ICTUS) [21]	242 (21%)	221 (19%)
C. León-Jiménez [23]	62 (71%)	35 (40.7%)
J.J.S. [19]	2 (10.5%)	2 (10.5%)
Agrawal [24]	7(14%)	5(10.2%)

DISCUSSION

Our primary objective was to review and analyze the difference in efficacy of Citicoline vs placebo. The studies included in the analysis are double-blind and placebo controlled.

Our primary outcome - Improvements in post-stroke cognitive scale - National Institutes of Health Stroke Scale (NIHSS), modified Rankin Score (mRS), Glasgow outcome scale (GOS) and Barthel Index (BI) score - is a measurement of effectiveness in accordance with improvement in neurological outcomes of stroke patients. It measures the efficacy and safety of the drug Citicoline and if it is any better when compared to placebo.

The overall pooled odd's ratio (for 5127 participants) was 1.769(random) and 1.281(fixed) [95% confidence interval (CI) 1.137 to 1.443 (fixed), P<0.001], indicating a slight advantage of Citicoline over placebo treatment.

The relative risk (for 5127 participants) was 1.301(random) and 1.163(fixed) [95% confidence interval (CI) 1.081 to 1.2521 (fixed), p<0.001], indicating a slight advantage of Citicoline over placebo treatment.

Till now, numerous number of studies have been performed and the caliber of Citicoline treating AIS patients has been questioned ever since. There are studies which have found a major advantage in using Citicoline when compared to placebo and there are studies which have found a neutral relation between the two.

Some of those studies are reliable while some of those are not much considering the small number of patients involved in them.

Similar trial was conducted in 2012 (ICTUS Trial) [21], on 2298 patients. It failed to prove any benefits of Citicoline over placebo. Global recovery was similar in both groups (odds ratio 1.03, 95% CI 0.86–1.25; p=0.364). In the analysis of the per-protocol population, no benefit from Citicoline over placebo was reported, neither in the primary-efficacy endpoint nor in the secondary endpoints or even adverse events. The NIHSS as well the mortality rates were comparable in both the groups.

Following the results of ICTUS, the efficacy of Citicoline was questioned. However, there are some points which should be considered before making a firm belief on ICTUS trial. This trial of 2012 included patients from a major time period (about 10 years). That said, the standard care methods would have changed. Furthermore, the trial did not interfere with any secondary drug involvements in stroke improvements. The administration of rtPA was not considered and hence was a point of difference in the patients. The sensitivity of ICTUS trial might have reduced because of inclusion of both rtPA treated and untreated patients. There are chances that Citicoline effect is not so significant if the patient has already received rtPA and many in this trial did.

Additionally, patients with the most severe strokes and large acute ischemic lesions on CT or MRI were not excluded from the trial. Citicoline treatment effect might have been diluted by the inclusion of patients with established large irreversible infarction.

These factors might have affected the study and resulted in a conclusion where Citicoline was announced safe but not efficacious for use in moderate to severe AIS [21].

On the other hand, a study performed in 1980 concluded Citicoline as beneficial with a significant cognitive improvement difference between Citicoline and placebo [OR=9.167] However, the study was performed on a small number of patients and a larger study is essential to confirm the same [10].

Manish Mittal compared the efficacy of 2 drugs - Edaravone and Citicoline - and placebo. Analysis of 49 patients was done but no significant benefit of Citicoline was noted. However, Edaravone was proven to be beneficial in AIS patients compared to both Citicoline and placebo [15].

A recent study done in 2022 aimed to find out whether administration of Citicoline immediately after recanalization therapy for acute stroke improves both radiological (decrease in infarct volumes at six weeks) and clinical outcomes (mRS and NIHSS of 0–2 and Barthel index > = 95 at three months) compared to standard treatment alone. However, it

was found not to meet any of these primary or secondary endpoints. The study could not demonstrate benefit of Citicoline in the study population where it was used immediately after recanalization therapy.

The study however could not achieve the planned sample size and the included sample size might not be enough to detect a meaningful difference in functional outcomes [24].

A recent review of literature [25] assessed the efficacy of Citicoline versus placebo or standard treatment and concluded that there is little to no difference in their neurological improvement, adverse effects or mortality rates.

Citicoline was however found to be associated with a lesser number of adverse events and deaths (Table 4).

Scrutiny through the reviews and the results obtained through this study point towards the choice of Citicoline over placebo. But the results are not drastic enough to act on. Citicoline can be proven to be safe and efficacious upto a small margin. Larger trials are necessary to draw a final conclusion on this. This is in view with the studies conducted previously and thus have broadly similar conclusion.

Moreover, this study and the other studies and results are derived by comparing Citicoline with placebo only. Other drugs helpful in stroke - Piracetam, Alteplase, Edaravone - should be studied side by side with Citicoline. Efficacy trials of other nootropic drugs and cholinergic drugs which aid in improving cognitive functions, should also be undertaken. Such studies will open a wider spectrum in understanding the efficacy of Citicoline and if it is equally or more beneficial than the other drugs.

POSITIVE POINTS OF THE STUDY

The analysis includes studies from a vast period of time - 42 years - and includes data from in total 5127 patients. The study focused on neurological improvements as well as adverse effects based on various parameters and cognitive scales and helps derive yet another conclusion in the Citicoline saga.

LIMITATIONS OF THE STUDY

As per the ICMR guidelines the study has been carried out in a short time frame. Provided a longer duration the study would have been more elaborate and meticulous. A longer time period would have given more time to access various other databases and unpublished as well as ongoing studies. Furthermore, owing to some reasons, a few databases were not accessible.

There was paucity in the data obtained from the randomized controlled trials. As the outcomes analyzed across the various studies varied, maintaining a uniform pattern proved to be difficult. The data available spans over the worldwide population. There are hardlyany studies conducted across the Indian subcontinent. Hence there is a lack of evidence comparing the efficacy and safety of Citicoline to placebo in the Indian population.

Also, because of lack of a single standard cognitive scale, the results and conclusions in all the studies are given in different scales. Numerical improvements in NIHSS, mRS, GOS, BI are considered but there is no single cognitive scale which is uniform throughout all the studies. That limits the specific improvement analysis in terms of any scale, to be done.

FUTURE IMPLICATIONS

The study opens ideas and gives another conclusion to the already existing hundreds about treating Acute Ischemic Stroke. Better and larger clinical trials are necessary to give a final conclusion. Moreover, this study and the studies included are a comparision of Citicoline and placebo. More elaborate studies on other drugs like Piracetam, Edaravone, Alteplase, various other nootropic drugs, cholinergic drugs as well the efficacy comparision between them can be done. Such comparative studies including a variety of drugs can give a better conclusion about the efficacy of Citicoline and if it should be continued in clinical practices.

CONCLUSION

1) This was a meta-analysis with the comparative evaluation of efficacy and safety of Citicoline and placebo in Acute Ischemic Stroke patients. The study was executed with the intention to analyze the difference in the effectiveness between the two.

2) Our primary objective was improvement in cognitive scales post stroke. In our study there was a marginal difference achieved between Citicoline and placebo in terms of cognitive improvement. The choice of Citicoline should be made over placebo as it has marginal improvements atleast. It is better to give something to the patient instead of placebo.

3) Citicoline remains one of the least studied drug medication out of all stroke medications. It has a very good potential to be nootropic of choice in the stroke patients, increasing a significant amount of cognition.

4) Citicoline was also found to be associated with a lesser number of adverse events and deaths compared to placebo.

Hence this study provides evidence that Citicoline is slightly more efficacious than placebo and can be used depending on the suitability.

SUMMARY

The aim of this study was to review and analyze statistically the evidence from existing randomized controlled trials. This analysis was carried out with the objective to assess the effectiveness of the drug at improving post stroke cognitive functions. 17 trials were assessed for the primary objective of improvement in cognitive scales. Meta analysis was performed and odd's ratio and relative risk - funnel and forest plot - were obtained for all the objectives.

The overall pooled odd's ratio (for 5127 participants) was 1.769(random) and 1.281(fixed) [95% confidence interval (CI) 1.137 to 1.443 (fixed), P<0.001], indicating a slight advantage of Citicoline over placebo treatment as per Table 3.

The relative risk (for 5127 participants) was 1.301(random) and 1.163(fixed) [95% confidence interval (CI) 1.081 to 1.2521 (fixed), p<0.001], indicating a slight advantage of Citicoline over placebo treatment as per Table 2.

Citicoline is proven to be slightly more efficacious than placebo, with lesser adverse events and deaths. However the margin of benefit is not very huge. Future trials comparing the same, on higher number of patients is necessary to draw a final conclusion on it.

ACKNOWLEDGEMENT:

This research was supported by the Indian Council of Medical Research (ICMR). We thank the Dean of our college and the Superintendent who allowed us to conduct the research in the hospital premises. We would also like to show our gratitude to the Department of Neurology for the endless support and guidance at every step of the project. We would like to extend our gratitude to the Department of Pharmacology who provided insight and expertise that greatly assisted the research.

REFERENCES

1. Ghosh S, Das SK, Nath T, Ghosh KC, Bhattacharyya R, Mondal GP. (2015). The effect of Citicoline on stroke: A comparative study from the Eastern part of India. *Neurol India*. 63:697-701
2. Agarwal S, Patel BM. (2017). Is aura around Citicoline fading? A systemic review. *Indian J Pharmacol*. 49:4-9
3. Secades JJ. (2012). Probably role of Citicoline in stroke rehabilitation: review of the literature. *Rev Neurol*. 54: 173-9
4. Grieb, P. (2014). CNS Drugs. 28: 185
5. José Álvarez-Sabín and Gustavo C. (2013). Román; The Role of Citicoline in Neuroprotection and Neurorepair in Ischemic Stroke; *Brain Sci*. 3(3): 1395–1414.
6. Karsten Overgaard MD; (2014). Volume 23, Issue 7, Pages 1764-1769
7. Saver JL; (2008). Citicoline: update on a promising and widely available agent for neuroprotection and neurorepair; *Rev Neurol Dis*. 5(4):167-77.
8. Clark WM, Williams BJ, Selzer KA, et al. (1999). A randomized efficacy trial of Citicoline in patients with acute ischemic stroke. Stroke. 30:2592-2597.
9. Toma´s Sobrino, Raquel Rodrı´guez-Gonza´lez, Miguel Blanco, David Brea, Marı´aPe´rez-Mato, Manuel Rodrı´guez-Ya´n˜ez, Rogelio Leira, Jose´ Castillo; (2011). CDP-choline treatment increases circulating endothelial progenitor cells in acute ischemic stroke; *Neurol Res*. 33(6):572-7.
10. Boudouresques AB, Michel B. (1980). Therapeutic conduct in light of a cerebral vascular accident and the use of CDP-choline [in French]. Presented at: International Symposium: *Brain Suffering and Precursors of Phospholipids. Paris*. 109-121.
11. Alvarez-Sabín J, Ortega G, Jacas C, Santamarina E, Maisterra O, Ribo M, Molina C, Quintana M, Román GC; (2013). Long-term treatment with Citicoline may improve poststroke vascular cognitive impairment; Cerebrovasc Dis. 35(2):146-54.
12. Goas JY, Bastard J, Missoum A. (1980). Results after 90 days of stroke treatment with CDP choline, concerning a double blind trial [in French]. Presented at: International Symposium: Brain Suffering and Precursors of Phospholipids. Paris; 123-128.
13. Clark WM, Wechsler LR, Sabounjian LA, et al. (2001). A phase III randomized efficacy trial of 2000 mg Citicoline in acute ischemic stroke patients. *Neurology*. 57:1595-1602.
14. Jose Alvarez-Sabín, Estevo Santamarina, Olga Maisterra, Carlos Jacas, Carlos Molina and Manuel Quintana; (2016). Long-Term Treatment with Citicoline Prevents Cognitive Decline and Predicts a Better Quality of Life after a First Ischemic Stroke; *Int J Mol Sci*. 17(3): 390.

15. Manish Mittal, Deepak Goel, Krishan K Bansal, Prashant Puri; (2012). Edaravone – Citicoline Comparative Study in Acute Ischemic Stroke (ECCS- AIS); JAPI, VOL. 60.
16. Corso EA, Arena M, Ventimiglia A, et al. (1982). La CDPCcolinanellevasculopatiecerebrali: valutazionicliniche e di semeiologiastrumentale [CDP choline in cerebral vasculopathy: clinical evaluation and instrumental semeiology]. Clin Ter. 102:379-386.
17. Tazaki Y, Sakai F, Otomo E, et al. (1988). Treatment of acute cerebral infarction with a choline precursor in a multicenter double-blind controlled study. Stroke. 19:211-216.
18. Clark WM, Warach SJ, Pettigrew LC, et al. (1997). A randomized dose-response trial of Citicoline in acute ischemic stroke patients. Citicoline Stroke Study Group. Neurology. 49:671-678.
19. Julio J. Secades, José Álvarez-Sabín, Francisco Rubio, Rafael Lozano, Antoni Dávalos, José Castillo, for the Trial Investigators; Citicoline in Intracerebral Haemorrhage: A Double-Blind, Randomized, Placebo-Controlled, Multi-Centre Pilot Study; Cerebrovasc Dis (2006);21:380–385.
20. Alviarez E, Gonzalez M. (2007). Efectividad y tolerabilidad de la Citicolinaenel ICTUS Isquémicoagudo, estudioaleatorizado, dobleciegocomparado con placebo. Archivos Venezolanos de Farmacologia y Terapeutica. 26:127-130.
21. Dávalos A, Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Ferro J, Martínez-Vila E, Serena J, Segura T, Cruz VT, Masjuan J, Cobo E, Secades JJ; (2012). International Citicoline Trial on ac Ute Stroke (ICTUS) trial investigators; Citicoline in the treatment of acute ischemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial); Lancet. 380(9839):349-57.
22. Warach S, Pettigrew LC, Dashe JF, et al. (2000). Effect of Citicoline on ischemic lesions as measured by diffusion weighted magnetic resonance imaging. Ann eurol. 48:713-722.
23. C. León-Jiménez, E. Chiquete, C. Cantú, M.J. Miramontes-Saldaña, M.A. Andrade-Ramos and J. Ruiz- Sandoval; (2010). Citicoline for Acute Ischemic Stroke in Mexican hospitals: A retrospective postmarketing analysis; Methods and Findings in Experimental and Clinical Pharmacology. 32(5)
24. Agarwal A, Vishnu VY, Sharma J, Bhatia R, Garg A, Dwivedi S, Upadhyay A, Goyal V, Singh MB, Gupta A, Rajan R. (2022). Citicoline in acute ischemic stroke: A randomized controlled trial. PloS one. 17(5):e0269224.
25. Martí-Carvajal AJ, Valli C, Martí-Amarista CE, Solà I, Martí-Fàbregas J, Cosp XB. (2020). Citicoline for treating people with acute ischemic stroke. Cochrane Database of Systematic Reviews. (8).