# INJECTED CITICOLINE IMPROVES IMPAIRMENT AND DISABILITY DURING ACUTE PHASE TREATMENT IN ISCHEMIC STROKE PATIENTS

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## ABSTRAK

*Strategi pengobatan stroke iskemik adalah mengurangi ukuran kerusakan dan penyelamatan sel-sel syaraf dari kematian pada masa awal kejadian iskemik. Recombinant-Tissue Plasminogen Activator (r-TPA) adalah satu-satunya terapi yang direkomendasikan, tetapi penggunaannya sangat terbatas. Sitikolin adalah neuroprotectant yang memiliki efek terapi pada beberapa tahapan kaskade iskemik. Namun, penggunaannya sampai sekarang masih menjadi perdebatan. Tujuan penelitian ini adalah untuk menganalisis penggunaan suplementasi sitikolin injeksi pada pasien stroke iskemik akut terkait perbedaan perubahan tingkat gangguan (impairment), tingkat keterbatasan (disability) dan tingkat halangan (handicap) antara kelompok yang mendapatkan terapi suplementasi sitikolin injeksi 2x500 mg iv bolus dengan kelompok tanpa suplementasi selama rawatan fase akut. Penelitian ini merupakan penelitian prospektif eksperimental dengan desain cohort study pada pasien stroke iskemik akut yang memenuhi kriteria inklusi dan eksklusi dengan atau tanpa suplementasi sitikolin injeksi 2x500 mg iv bolus selama bulan Januari – April 2015 di RS Stroke Nasional Bukittinggi. Penilaian tingkat gangguan dilakukan dengan NIHSS, tingkat keterbatasan dengan Barthel Indeks dan tingkat halangan dengan modified Rankin Scale. Penilaian dilakukan sebanyak 2 kali, yaitu pada awal sebelum perlakuan dan setelah perlakuan. Metode statistik yang digunakan pada penelitian ini adalah uji Wilcoxon sign rank, Paired T-test, dan Mann-Whitney test. Penelitian ini dilakukan pada 50 subyek yang dibagi 2 kelompok, kelompok kontrol tanpa suplementasi dan kelompok perlakuan dengan suplementasi sitikolin injeksi 2x500 mg iv bolus. Data demografi dan karakteristik dasar tidak berbeda antar kelompok. Terdapat perbedaan perubahan tingkat gangguan. Kelompok kontrol menunjukkan rerata penurunan NIHSS 0,96±1,74 dan kelompok perlakuan menunjukkan penurunan NIHSS 2,84±1,46 ($p < 0,05$). Terdapat perbedaan perubahan tingkat keterbatasan. peningkatan rerata Barthel Indeks kelompok kontrol 9,60±11,17 dan kelompok perlakuan 20,40±13,99 ($p < 0,05$). Namun perubahan tingkat halangan tidak ada perbedaan. Pemberian suplementasi sitikolin injeksi pada pasien stroke iskemik selama perawatan fasa akut menunjukkan perbedaan perbaikan pada perubahan tingkat gangguan (impairment) dan tingkat keterbatasan (disability), tetapi tidak menunjukkan perbedaan pada perubahan tingkat halangan (handycaps).* ***(FMI 2015;51:245-251)***

***Kata kunci:*** *sitikolin, sitikolin injeksi, neuroproteksi, terapi fasa akut, stroke iskemik akut*

## ABSTRACT

*Treatment strategy of ischemic stroke is to reduce the extent of the damage and rescue neurons from death in the early days of ischemic events. Recombinant Tissue-Plasminogen Activator (r-TPA) is the only recommended therapy, but their use is very limited. Citicoline is a neuroprotectant with a therapeutic effect on several stages of the ischemic cascade. However, its use is still being debated. The purpose of this study was to analyze the use of supplementation citicoline injection in patients with acute ischemic stroke in relations to differences in changes in the level of interference (impairment), rate limitation (disability) and the level of obstruction (handicap) between the group receiving supplementation of citicoline injection 2x500 mg iv and the group without supplementation during acute phase treatment. This study was a prospective cohort study using experimental design in patients with acute ischemic stroke who met the inclusion and exclusion criteria with or without supplementation citicoline between January - April 2015 in the National Stroke Hospital, Bukittinggi. Rate of interference was assessed with NIHSS, level of limitations with Barthel Index, and level of obstruction with modified Rankin Scale. Assessment was done 2 times, before and after the treatment. Statistical methods used in this study were Wilcoxon signed rank test, paired T-test and Mann-Whitney test. This study was conducted on 50 subjects divided into 2 groups, a control group without supplementation and group treated with injected citicoline of 2x500 mg iv. Demographic and baseline characteristics did not differ between groups. There were differences in level of interference changes. Mean decrease in control group was 0.96 ± 1.74 NIHSS, while that in treatment group was 2.84 ± 1.46 NIHSS ($p <0.05$). There we re differences in changes in the level of limitations. Mean increase of Barthel Index in control group 9.60 ± 11.17 and in treatment group 20.40 ± 13.99 ($p <0.05$). However, changes in the level obstacle showed no difference. In conclusion, citicoline injecti on supplementation in patients with ischemic stroke during acute phase treatment showed improvement differences in changes in the level of distraction (impairment) and the rate limitations (disability), but showed no difference in changes in the level of obstruction (handycaps).* ***(FMI 2015;51:245-251)***

***Keywords:*** *citicoline, injected citicoline, neuroprotection, acute phase therapy, acute ischemic stroke*

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## INTRODUCTION

Stroke is a multifactorial disease with many causes, along with major clinical manifestations, and a major cause of disability and death in developing countries. Every year there are 13 million new stroke patients, about 4.4 million of them died within 12 months (WHO 2006). Stroke attacks individuals in reproductive age and elderly who could potentially cause new problems in health development (Adams et al 2006). In Indonesia, stroke is the leading cause of death along with heart disease and cancer (Ministry of Health 2007). Data in the National Stroke Hospital, Bukittinggi, showed that from January to August 2014, there were 2,581 cases of stroke with 75.86% (54.95% male, 45.05% female) were ischemic strokes. Stroke occurred in the age range of 44-64 years (43.74%).

The effects of a stroke depends on the affected part of the brain, how serious the stroke, age, health condition and personality of the patient. A stroke may lead to emotional instability and impaired memory (Heart and Stroke Foundation 2005). Stroke pathophysiology is also very complex and involves excitotoxicity mechanisms, inflammation pathways, oxidative damage, ion imbalance, apoptosis, angiogenesis, neuroprotection, and neurorestoration.

Treatment strategy for ischemic stroke is focused more on reducing the extent of ischemic damage and to safe nerve cells from death in early days after the incident. Until now, intravenous recombinant-Tissue Plasminogen Activator (r-TPA) is the only one approved by the United State Food and Drug Administration (US FDA) for the treatment of acute ischemic stroke. However, its use is limited because of the narrow therapeutic window and should be provided with strict requirements (Sahota & Savitz 2011).

Citicoline is one neuroprotectant reported to have therapeutic effects on several ischemic cascade in acute ischemic stroke and efficiency in a variety of animal models. As neuroprotectant, citicoline is useful to improve both structural integrity and function of nerve membranes that can assist in membrane repair. Citicoline has also been studied as a therapy in stroke patients, although the test results are still under debate (Conant & Schauss 2004). Until today citicoline use as neuroprotectant remains a debate. For acute phase ischemic stroke treatment, the National Formulary (FORNAS) in 2014 did not include neuroprotectant (citicoline) as one approved therapy. This results in less maximum efforts to safe the pen-umbra during the acute phase of the attack for the participants of the National Health Insurance (JKN) with ischemic stroke. Therefore, it is necessary to study the use of citicoline supplementation injection in patients with acute ischemic stroke who were observed during acute care period in the hospital.

## MATERIALS AND METHODS

This was a prospective experimental study using cohort study design on subjects diagnosed with of acute ischemic stroke in A and C Wards, Department of Neurology, National Stroke Hospital, Bukittinggi. Subjects met the inclusion criteria: male/female, aged 44-65 years, diagnosed with ischemic stoke, onset <96 hours and signed informed consent. Patients were excluded from the study if they had epilepsy early in the disease or with an indication of an epileptic seizure before, such as patients with simultaneous organic brain disease (craniocerebral trauma, tumor), with acute myocardial infarction, impaired liver function or kidney failure, oncological diseases, pregnancy, or using anticoagulants directly or indirectly. Impairment rate assessment was performed using NIHSS, disability rate using Barthel Index, and handicap rate using modified Rankin Scale. The assessments were done twice, as data baseline and at the end of the acute phase of ischemic stroke.

Data obtained were in the form of patient demographic data, and data assessment results were in NIHSS, Barthel Index and Modified Rankin Scale. Obtained data were tested statistically using SPSS. Test for normality used Shapiro-Wilk test. To identify the difference of changes in NIHSS score, Barthel Index and Modified Rankin Scale before and after therapy, comparative hypothesis test was done with Wilcoxon signed rank test, while for the difference of change in NIHSS, Barthel Index and Modified Rankin Scale between groups, comparative hypothesis tests of Mann-Whitney was done.

## RESULTS

For three month-observation at Wards A and C, National Stroke Hospital, Bukittinggi, 51 subjects were found. One died, so 50 subjects were divided into two

groups. Twenty-five subjects were grouped in control group without citicoline supplementation and 25 other subjects were in the group treated with citicoline supplementation therapy 2x500 mg iv. Sample characteristics comprised gender and previous medical history (Table 1).

Baseline data characteristics between control and treatment group showed no significant differences in the parameters of age, observation onset, NIHSS, Barthel Index, and Rankin Scale baselines (Table 2).

Table 1. Samples' characteristics of gender and previous disease history

| Subjects' characteristics | Control group | | Treatment group | | Samples | |
|---|---|---|---|---|---|---|
| | Total (patients) | % | Total (patients) | % | Total (patients) | % |
| Sex | | | | | | |
| Male | 16 | 64.00 | 14 | 56.00 | 30 | 60.00 |
| Female | 9 | 36.00 | 11 | 44.00 | 20 | 40.00 |
| Previous diseases*) | | | | | | |
| Hypertensive disease | 22 | 88.00 | 17 | 68.00 | 39 | 78.00 |
| Diabetes mellitus | 5 | 20.00 | 3 | 12.00 | 8 | 16.00 |
| Heart disease | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Stroke | 0 | 0.00 | 2 | 8.00 | 2 | 4.00 |

Table 2. Characteristics of age, onset observation, baseline NIHSS, baseline Barthel Index, and baseline modified Raankin scale in control and treatment groups

| Variables | n | Median (maximum-minimum) | Mean ± SD | P |
|---|---|---|---|---|
| Age | | | | |
| Control group | 25 | 56 ( 45 – 65 ) | 55.36 ± 5.23* | 0.466 |
| Treatment group | 25 | 58 ( 45 – 65 ) | 56.32 ± 6.49 | |
| Observation onset | | | | |
| Control group | 25 | 1 ( 1 – 2 ) | 1.20 ± 0.41 | 0.127 |
| Treatment group | 25 | 1 ( 1 – 2 ) | 1.40 ± 0.50 | |
| Baseline NIHSS | | | | |
| Control group | 25 | 9 ( 2 – 17 ) | 9.32 ± 3.67* | 0.385 |
| Treatment group | 25 | 8 ( 4 – 20 ) | 8.56 ± 3.62 | |
| Baseline Barthel Index | | | | |
| Control group | 25 | 40( 10 – 80 ) | 39.80 ± 15.58 | 0.617 |
| Treatment group | 25 | 40 ( 5 – 70 ) | 39.60 ± 15.74* | |
| Baseline modified Rankin Scale | | | | |
| Control group | 25 | 4 ( 1 – 4 ) | 3.44 ± 0.821 | 0.768 |
| Treatment group | 25 | 4 ( 2 – 5 ) | 3.60 ± 0.866 | |

Table 3. NIHSS in control and treatment groups

| NIHSS scores | Mean | Median | SD | Minimum | Maximum | (p) |
|---|---|---|---|---|---|---|
| Control group | | | | | | |
| Baseline NIHSS | 9.32 | 9 | 3.67 | 2 | 17 | 0.011 |
| NIHSS at observation end | 8.36 | 8 | 3.82 | 2 | 15 | |
| Treatment group | | | | | | |
| Baseline NIHSS | 8.56 | 8 | 3.62 | 4 | 20 | 0.001 |
| NIHSS at observation end | 5.72 | 5 | 4.02 | 0 | 16 | |
| NIHSS change during observ. | | | | | | |
| Control group | 0.6 | 1 | 1.74 | -2 | 3 | 0.001 |
| Treatment group | 2.84 | 4 | 1.46 | 0 | 4 | |

Table 4. Barthel Index in control and treatment groups

| Barthel Index (BI) scores | Mean | Median | SD | Minimum | Maximum | (p) |
|---|---|---|---|---|---|---|
| Control group | | | | | | |
| Baseline Barthel Index | 39.80 | 40 | 15.58 | 10 | 80 | 0.001 |
| Barthel Index end | 49.40 | 50 | 17.04 | 10 | 80 | |
| Treatment group | | | | | | |
| Baseline Barthel Index | 39.60 | 40 | 15.74 | 5 | 70 | 0.001 |
| Barthel Index end | 60.00 | 55 | 22.59 | 10 | 100 | |
| Barthel Index change during observation | | | | | | |
| Control group | 9.60 | 5 | 11.17 | 0 | 45 | 0.005 |
| Treatment group | 20.40 | 20 | 13.99 | -10 | 45 | |

Level of impairment assessed with NIHSS, improved rate of impairment was found characterized by a decrease in mean NIHSS in both groups. In control group the mean baseline NIHSS was 9.32 ± 3.67 and NIHSS at the end of observation was 8.36 ± 3.82 (P <0.05) with 95% CI -1.680 - (-0.240-). In treatment group, 22 subjects showed decreased NIHSS scores, constant in three, and none showed increased score with mean baseline NIHSS of 8.56 ± 3.62 and mean NIHSS at the end of 5.72 ± 4.02 (p<0.05 ). In comparison, mean decrease of NIHSS score in control group was 0.96 ± 1.74 while that in treatment group was 2.84 ± 1.46 (P <0.05) as shown in Table 3.

In regard with level of disability as measured with Barthel Index, there was improvement characterized by the increase of mean Barthel Index in both groups. In control group there were 17 subjects showed increased Barthel Index score and eight subjects remained with mean baseline Barthel Index of 39.80 ± 15.58 and mean Barthel Index at the end of observation was 49.40 ± 17.04 (p<0.05).

In treatment group, mean baseline Barthel Index was 39.60 ± 15.75 and mean at the end was 60.00 ± 22.59 (p <0.05). In comparison, mean increase of Barthel Index score in control group was 11.17 ± 9.60 and the mean decrease of Barthel Index score in treatment group was 20.40 ± 13.99 (P <0.05) as shown in Table 4.

Wilcoxon signed ranks test results for modified Rankin scale at baseline and at the end of treatment in control group showed significance of 0.102 (p> 0.05), whereas the analysis of modified Rankin Scale at baseline and at the end of observation in treatment group revealed significance of 0.014 (p <0 , 05), showing significant difference. In the analysis at the end of observations on modified Rankin Scale in control and treatment group, the significancy was found to be 0.730 (p> 0.05).

## DISCUSSION

Ischemic penumbra is defined as a tissue formed by infarction. The tissue could potentially be saved and are currently being a target of stroke reperfusion and requirement protection therapy. Penumbra tissue evolves towards irreversible tissue damage at different levels in individual patients with stroke resulting therapeutic different windows depending on the duration of the risk of each tissue infarction (Castellanos et al 2006).

The state of the local energy deficit such as that in ischemia will lead to neurons and glial depolarization which then triggers Ca2+ channels activation as well as extracellular glutamate excitatory amino acids excretion (Purba 2011). Glutamate excess binds to 3 glutamate receptors, the N-methyl-D-aspartate (NM DA), which will lead to the entry of Na+ and Ca2 +, α-amino-3-hydroxy-5-methyl-4-Isoxazoles propionic acid (AMPA) which causes disruption of homeostasis, along with the influx of H2O, which causes toxic edema and cell lysis; and metabotropic receptors that block phospholipase C and inositol triphosphate induction along with mobilization of Ca2+ stored in the cell. Another condition is Ca2+ influx through ion channels due to excitatory neurotransmitters binding with NMDA receptor. This situation is exacerbated by ischemic events, in which CA2+ will come out from mitochondria and endoplasmic reticulum thus substantially intracellular calcium accumulation is taking place, causing irreversible damage to neurons (Dirnagl et al 1999, Lo et al 2003).

In this study, a control group who received antithrombolytic therapy with acetosal 1x80 mg and/or clopidogrel 1x1 and other therapies suitable for clinical complications without citicoline injection supplementation showed significant improved levels of impairment, such as that in treatment group receiving antithrombolytic therapy with 1x80 mg acetosal and/or 1x1

clopidogrel and other therapies suitable for clinical complications with citicoline injection supplementation of 2x500 mg iv.

The use of early aspirin to reduce long-term mortality and disability due to ischemic stroke is supported by several clinical trial studies. One of them was the International Stroke Trial (IST) where 300 mg/day aspirin significantly reduces recurrent stroke within the first 2 weeks with no effect on premature death, thus significantly decreased the mortality and disability rate for 6 months. The Chinese Acute Stroke Trial (CAST) showed the use of aspirin 160 mg/day reduced the risk of recurrence and death in the first 28 days, but the long-term mortality and disability rate is not different compared with controls. In the last meta-analysis, the overall benefits of antiplatelet therapy in patients with atherothrombosis disorder was estimated to be around 22%. Aspirin shows the best studied results from the available antiplatelets and considered as first-line single agent (DiPiro et al 2008)

Several studies have demonstrated the benefits of citicoline injection in patients with ischemic stroke. Warach et al (2000) examined the effect of the neuroprotective and neurodegenerative citicoline on the growth of the cerebral ischemic lesion in a double-blind controlled and placebo study in patients with acute ischemic stroke with onset of symptoms 24 hours or less, with NIHSS score 5 or higher, and the size of the lesion was 1-120 cc in gray matter as measured on DWI. Results showed that citicoline improved clinical outcomes in patients with ischemic stroke, which is evidenced by a reduction in the size of lesions caused by ischemic stroke (Warach et al 2000).

Another study on the effectiveness citicoline use in patients with acute phase ischemic stroke was reported Martynov et al (2013) by observing the dynamics of neurological symptoms were assessed using Scandinavian Stroke Scale (SSS), Barthel Index and Modified Rankin Scale and functional in 89 severe ischemic stroke patients in acute phase. A 1000 mg citicoline was given by intravenous infusion during the first 7 days followed with oral administration in a dose of 1000 mg two weeks later. From this study, the results of citicolineat use on day 7 showed significant improvement in SSS scores in treatment group and at the time of discharge from the hospital (day 21-24 of the disease). There was better and and significant recovery ($p<0.05$) in the treatment group. Citicoline efficacy was significantly ($p <0.05$) higher in patients aged less than 70 years and if citicoline was given in the first hours of the stroke (Martynov et al 2013).

In The Lancet, Davalos et al (2012) reported the results of the International Citicoline Trial on Acute Stroke (ICTUS) of the 2298 patients with onset <24 hours with severity level of moderate to severe, from November 2006 to October 2011 at 37 centers in Spain , 11 in Portugal and 11 in Germany. A number of 1 148 of them received citicoline 2000 mg per day and 1150 others received placebo. The results showed no significant difference between treatment and control groups.

Some possible explanations for these balanced results are that the standard of treatment for stroke patients in ICTUS study was very good so it was difficult to demonstrate additional benefits of the citicoline. Analysis in ICTUS study was done to establish the possibility of beneficial effects of citicoline compared with placebo in patients not treated with rt-PA ($P <0.041\ 5$). In an unusual way, 47% of the patients were treated with rt-PA, while the average percentage use of rt-PA in stroke patients in western countries is in the range of 6%-22%, in the world under 10%. rt-PA may reestablish blood flow in the penumbra, so, citicoline can be diluted and difficult to improve performance over the effect of rt-PA, which is caused by the effect of thrombolysis. Additionally, the severity of most stroke patients in the study was also high so that no susceptible penumbra areas were saved by citicoline. As a result, in the subgroup without rt-PA, citicoline efficacy showed a positive trend. This was coherent with the fact that the thrombolytic treatment seems to have disturbing potential beneficial effects of citicoline (Overgaard 2014).

Membrane of neurons and glial cells, including phospholipids in its structure, is one of the damaged structures on the condition of ischemic stroke. Components of the membrane structure, especially phosphatidylcholine, is degraded by phospholipase into free fatty acids and free radicals, which activate lipid peroxidation and oxidative stress that encourage phosphorylation oxidative bonding in the mitochondria (Adibhatla et al 2006). Neuron synthesis and repair of and glial cell membrane phospholipids occur using exogenous choline precursor. One of the precursors is citicoline (cytidine-5-nucleotide diphosphocholine) itself, which, under natural conditions is present in all body cells. The experimental data provide evidence that citicoline increases phosphatidylcholine synthesis of cell membranes and promote the recovery levels of other phospholipids, glutathione and glutathione reductase activity (Farooqui et al 2000).

Citicoline has a therapeutic effect on several stages of the ischemic cascade in acute ischemic stroke. First, it stabilizes cell membranes by increasing phosphateidylcholine and sphingomyelinsintesis. Citicoline

releases two main components, cytidine and choline. In oral administration, citicoline is almost entirely absorbed, and its bioavailability is approximately the same as that in intravenous administration. Once absorbed, cytidine and choline spread widely throughout the body, bypassing the blood-brain barrier and reaches the central nervous system (CNS). Citicoline enters into the phospholipid fraction of membranes and microsomes. Citicoline activates phospholipids biosynthesis in neuronal membrane structure, improves brain metabolism and works at various levels of neurotransmitters (Secades & Lorenzo 2006). Experimentally it is proved that citicoline increases the amount of noradrenaline and dopamine in the CNS.

Second, citicoline is found to inhibit the release of free fatty acids by stimulating choline phosphotransferase reaction of the brain to phosphatidylcholine synthesis and preventing free fatty acids release, particularly arachidonic acid, which is associated with ischemia. Third, to protect the membrane, citicoline inhibits the release of glutamate during ischemia. In an experimental test by Hurtado et al (2005) citicoline may reduce glutamate release in the early stages of ischemic cascade by increasing glutamate uptake by regulating glutamate transporter. Citicoline induces translocation of this transporter from the cytosol to the membrane, and this serves to reduce the concentration of extracellular glutamate. Citicoline also significantly increases the number and level of dopamine synthesis and tyrosine levels in corpus striatum. citicoline also lowers levels of serotonin and tryptophan and serotonin synthesis levels in the brain (Martinet et al 1979). Citicoline has been shown to reduce the release of damaging caspase products activation that by inhibiting the expression of proteins involved in apoptosis following middle cerebral artery occlusion/MCAO (Krupinski et al 2002).

Citicoline promotes the synthesis of nucleic acids, proteins, acetylcholine and other neurotransmitters, and reduces free radicals formation. In addition, citicoline also restores mitochondrial ATPase activity and membranal Na+/K+-ATPase, inhibits activation of phospholipase A2 and accelerate reabsorption of cerebral edema in various experimental models (Adibhatla et al 2006). Citicoline simultaneously inhibits the different steps of the ischemic cascade to protect the injured tissue against the early and delayed mechanisms responsible for ischemic brain.

Citicoline is a safe drug, does not have a serious effect on the cholinergic system, and it is perfectly tolerable. The pharmacological characteristics, combined with its mechanism of action, suggests that this drug may be suitable for the treatment of cerebral vascular disease, head trauma of varying severity and variety of cognitive disorders. In a study conducted on the treatment of patients with head trauma, citicoline speed recovery from post-traumatic coma and healing processes in the ability to walk, give better functional outcomes and reduce the hospitalization days. Citicoline also improve cognitive and memory disorders after head trauma in a lower severity. In the treatment of acute ischemic stroke patients, citicoline enhances recovery of consciousness and motor deficits, better end results and facilitates the rehabilitation of the patients. In patients with chronic cerebral ischemia, CDP-choline increases the value on cognitive evaluation scale (Adibhatla et al 2001).

## CONCLUSION

Supplementation of injected citicoline in ischemic stroke patients during acute phase treatment showed differences in the effect on changes in impairment rate and disability rate, but showed no difference in the effect on changes in handicaps rate.

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