Perception Mapping of Indian Physicians on Role of Citicoline In Management of Stroke

CONTENTS

Sr.no	Title	Page no
1	Background and Objective of the Survey	2
2	Methodology of the Survey	4
3	Literature Review	5
4	Survey Form	21
5	Survey Findings	24
6	Summary	34

Background and Objective of the Survey

Background:

Stroke remains a critical health issue in India, representing a major cause of morbidity and mortality. The management of stroke involves acute intervention and long-term rehabilitation strategies. Citicoline, a neuroprotective agent, has shown promise in enhancing neurodegenerations and cognitive recovery post-stroke. It is involved in the synthesis of phosphatidylcholine, essential for brain health. However, despite its potential benefits, its use in clinical practice varies widely among physicians, influenced by a variety of factors that may include personal clinical experience, exposure during medical training, peer influence, and the influence of pharmaceutical marketing.

Moreover, there are significant disparities in healthcare infrastructure and stroke care facilities across different regions of India, which can affect the treatment modalities offered. Economic factors also play a crucial role as the cost of Citicoline and the economic status of patients can impact its prescription rates. Understanding these dynamics is essential for improving stroke outcomes and optimizing treatment protocols across diverse healthcare settings.

Perception mapping of on role of Citicoline:

Citicoline, known for its neuroprotective properties, plays a crucial role in the synthesis of phosphatidylcholine, vital for brain health and functioning. This mapping study aims to uncover the breadth of opinions and attitudes towards Citicoline—from widely endorsed to skeptically received within the medical community.

The ultimate goal of perception mapping in this context is to identify patterns and variations in the acceptance and use of Citicoline, facilitating a better understanding of its perceived value and limitations. This insight can drive more informed decisions in clinical practices, guide patient education, and influence future research and development strategies for Citicoline and similar therapeutics.

Objective:

1. **Assess Awareness and Knowledge:** Determine the level of awareness and knowledge among Indian physicians about Citicoline, including its mechanism of action, benefits in stroke recovery, and recommended dosages.

2. Understand Prescribing Behaviors: Explore how often and in what contexts Citicoline is prescribed by physicians for both acute and rehabilitative stroke care. This includes analyzing the influence of clinical guidelines and evidence on prescribing practices.

3. Identify Influencing Factors: Investigate a broad range of factors that influence the prescription of Citicoline. These include:

- **Educational Background:** The impact of medical education and ongoing professional development on physician familiarity with and confidence in using Citicoline.
- **Economic Factors:** How the cost of Citicoline and the economic status of patients affect its prescription, including considerations of insurance coverage and out-of-pocket expenses.
- **Pharmaceutical Marketing:** The role of marketing efforts by pharmaceutical companies, including educational seminars, workshops, and distribution of literature.
- **Cultural and Regional Differences:** Regional variations in the acceptance of Citicoline, which may reflect local medical practices, availability of medication, and regional health care policies.

4. Evaluate Impact on Patient Outcomes: Examine physicians' perceptions of the impact of Citicoline on patient outcomes, based on their clinical experiences and observations.

5. Policy and Educational Recommendations: Based on the findings, propose recommendations for policy adjustments, educational campaigns, and marketing strategies to enhance the appropriate use of Citicoline in stroke management across India.

This extended study aims not only to map the current perceptions and usage patterns of Citicoline among Indian physicians but also to identify actionable insights that could lead to improved clinical outcomes and more standardized stroke treatment protocols nationally.

Methodology of the Survey

A survey was conducted to understand the current Opinion on **"Perception mapping of Indian physicians on role of Citicoline in management of Stroke"** and to understand the market better and offer better services to improve the patient outcome. A total of 100 doctors from India participated in the survey.

Step 1:

A literature search was done on the topic. Below topics were covered in literature search:

- Citicoline In Acute Ischemic Stroke: A Randomized Controlled Trial
- The Role of Citicoline in Neuroprotection and Neuro Repair in Acute Stroke

Abstract:

- Neuroprotective Effect of Citicoline

Step 2:

A survey questionnaire was prepared based on the literature search. The survey form was shared through digital medium with 100 doctors across India.

Step 3:

Their responses were analysed and the findings are provided in this survey analysis booklet.

Literature Review

Citicoline In Acute Ischemic Stroke: A Randomized Controlled Trial

Introduction

Stroke remains a predominant cause of death and disability globally, necessitating immediate medical attention to mitigate its effects. Prompt treatment is critical, as the duration between onset and intervention is directly correlated with the outcomes; hence the maxim "time is brain" aptly applies. Current therapeutic strategies for acute ischemic stroke include rapid recanalization of the blocked artery through thrombolysis using agents such as Alteplase or Tenecteplase within the initial 4.5 hours post-stroke. Simultaneously, the protection of brain tissue from ischemic injury, although still under investigation, holds potential for reducing cerebral damage.

Recent advances in pharmacology have introduced neuroprotective agents that may amplify the brain's repair mechanisms and enhance neuroplasticity, ultimately diminishing the impact of acute ischemic events and promoting recovery. Citicoline, a neuroprotective drug, plays a pivotal role in this context. It is a synthetic form of cytidine 5´-diphosphate choline which is vital for synthesizing phosphatidylcholine and sphingomyelin—key components for cell membrane construction. During ischemic events, Citicoline helps prevent the breakdown of these membranes, reducing the accumulation of harmful substances such as free radicals and fatty acids.

Citicoline's effectiveness has been evaluated in various clinical trials involving over 1100 patients across multiple neurological conditions, including acute stroke, where it demonstrated a safety profile comparable to that of a placebo. While its direct impact on primary outcomes has shown limited efficacy, certain post-hoc analyses of studies suggest potential benefits. Moreover, a meta-analysis indicated a significant reduction in long-term mortality and disability rates when Citicoline was administered for six weeks in cases of moderate to severe ischemic stroke, yielding promising results in terms of functional and neurological recovery.

Despite these findings, recent trials like the ICTUS study have not conclusively proven Citicoline’s superiority over standard care. Furthermore, the application of Citicoline in acute ischemic stroke patients undergoing endovascular thrombectomy or in the immediate period following intravenous thrombolysis has yet to be thoroughly investigated. Our study aims to assess whether Citicoline administration immediately post-recanalization could enhance clinical and radiological outcomes three months after treatment compared to standard care alone.

Methods

Study Design and Participants

The Citicoline in Acute Ischemic Stroke (CAISR) trial was a single-center, randomized, placebo-controlled, parallel-group study with blinded endpoint assessment, conducted at a tertiary hospital in India. The study spanned from May 2017 to September 2020, targeting patients with acute ischemic stroke undergoing recanalization therapy recruited from emergency and neurology inpatient services. Ethical approval was granted by the All India Institute of Medical Sciences Institute Ethics Committee, and the trial adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Consent was obtained from all participants or their authorized representatives, and the trial was registered at the Clinical Trial Registry of India (CTRI/2018/011900).

Inclusion Criteria

- Participants aged 18 years or older.
- Clinical and radiographic evidence of acute ischemic stroke, verified by the stroke team.
- Eligibility for intravenous thrombolysis or endovascular thrombectomy as determined by a stroke neurologist and interventional neuroradiologist, with the participant receiving one or both therapies.
- Signed informed consent obtained.

Exclusion Criteria

- Intracranial hemorrhage.
- Known allergies to citicoline or contrast materials.
- Brain tumors evident on CT or MRI scans.
- Pre-existing conditions that could interfere with the interpretation of neurological assessments.
- Pre-existing dementia with a disability score of 3 or higher on the modified Rankin Scale (mRS).
- Ongoing treatment with citicoline.

Randomization and Allocation

Participants were randomly assigned in a 1:1 ratio to receive either citicoline or a placebo, immediately following recanalization therapy. This randomization utilized a stratified variable block method through a computer-generated table, taking into account whether patients underwent thrombolysis alone or combined with endovascular thrombectomy. Outcome assessors were blinded to treatment allocation.

Intervention

Patients in the citicoline arm received an intravenous dose of 1gm of citicoline dissolved in 100ml of normal saline immediately after recanalization therapy. This was followed by a continued dosage of 1gm twice daily for three days. This protocol was designed to assess the

efficacy of citicoline in enhancing recovery post-stroke when administered in the acute phase following recanalization.

Outcome Assessment and Workflow

The CAISR trial evaluated the efficacy of Citicoline in stroke recovery through a randomized, placebo-controlled study at a tertiary hospital in India. Stroke volume changes were assessed via MRI at six weeks, while neurological and functional outcomes were measured at three months using NIHSS, mRS, and Barthel Index. The study ensured the blinding of assessors to maintain data integrity.

Workflow

Eligible acute ischemic stroke patients underwent standard imaging and recanalization therapies before being randomized to receive Citicoline or placebo. Follow-up assessments were blinded and conducted at three months.

Sample Size and Statistical Analysis

The study required 116 patients to detect a significant treatment effect, assuming a differential response rate between placebo and Citicoline groups based on prior research. Statistical analysis was performed using chi-squared tests, t-tests, and non-parametric tests as appropriate, with significant results considered at a p-value of <0.05. All analyses were conducted using Stata version 13, and patients who did not complete the study were assigned the worst scores on outcome measures.

Results

In the Citicoline in Acute Ischemic Stroke (CAISR) trial, 99 patients were enrolled to evaluate the effectiveness of Citicoline versus a placebo in acute ischemic stroke management. The study reported no significant differences in recovery outcomes between the two groups.

Key Findings:

Demographics and Baseline Characteristics: The median ages were 61 years in the Citicoline group and 54.5 years in the placebo group, with a majority of participants being male. Most strokes were left-sided and located in the middle cerebral artery (MCA) territory. Both groups presented similar blood pressure and ASPECTS scores at admission.

Treatment Timing and Approach: Patients in the Citicoline group arrived at the emergency department sooner than those in the placebo group (135 minutes vs. 162.5 minutes). A slightly higher percentage of placebo group patients received endovascular treatment.

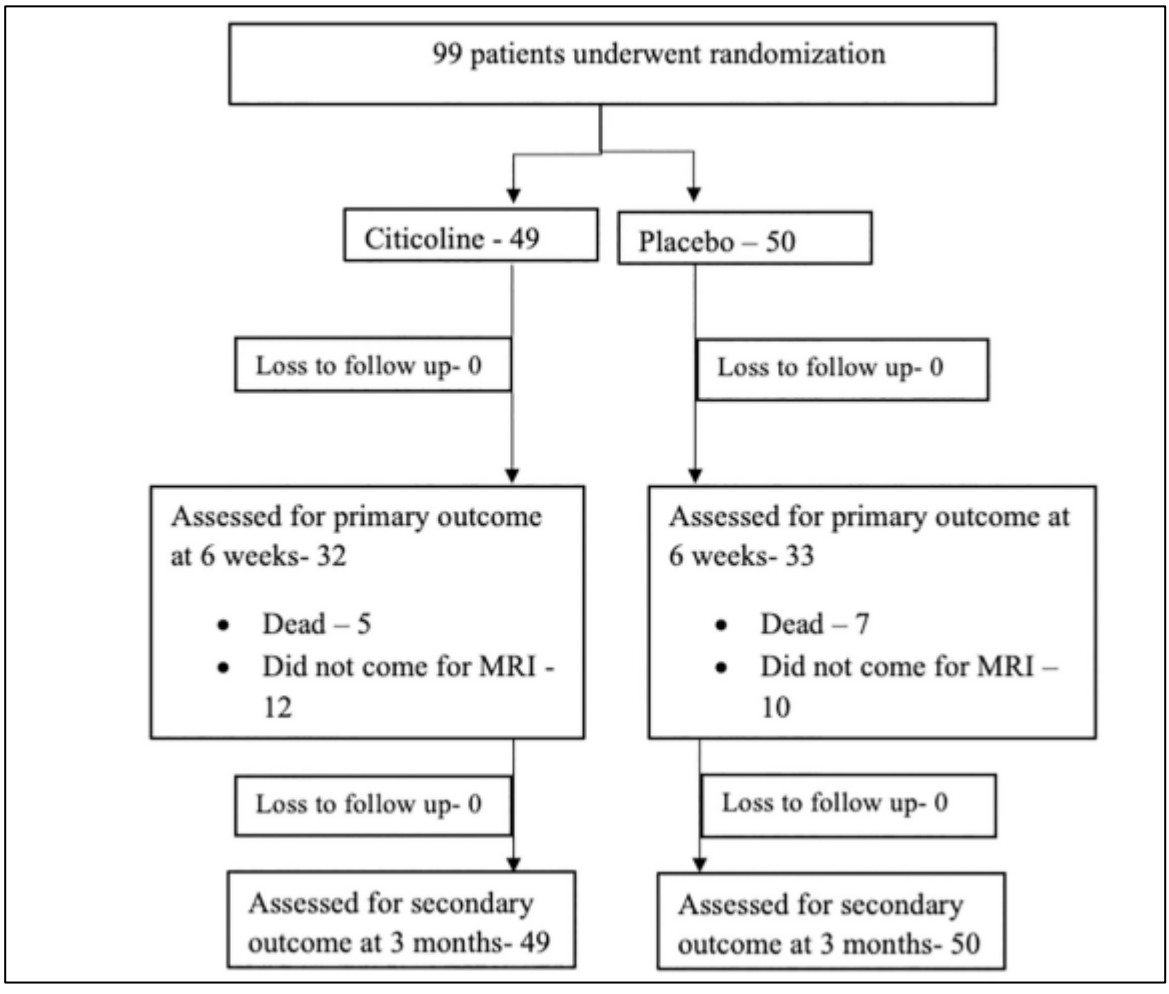

Fig 1. Consort flow diagram.

Stroke Characteristics and Risk Factors: Small vessel disease was the most common subtype of stroke identified, with hypertension being the prevalent risk factor in both groups.

Clinical Outcomes: No significant differences were observed in median National Institutes of Health Stroke Scale (NIHSS) scores at three months or in the median modified Rankin Scale (mRS) scores at initial presentation and follow-up. Stroke volumes measured at six weeks were also similar between groups.

Impact of COVID-19: The trial faced challenges due to the COVID-19 pandemic, which affected patient follow-up and MRI assessments, leading to an early termination of the trial.

Outcome Measures:
The study defined a favorable outcome as an NIHSS or mRS score of 0-2 or a Barthel index score of ≥95 at three months. The rates of achieving these scores were similar between the two groups.
Mortality was comparable between the groups, with twelve total deaths reported (five in the Citicoline group and seven in the placebo group).

Table 1. Outcome measures (primary and secondary)

Outcome measures (Median)	Citicoline (n = 49)	Placebo (n = 50)	P-value	OR with 95% CI
PRIMARY OUTCOME				
Change in stroke volume from baseline to 6 weeks (cm^3)	4.22	2.63	0.483	
SECONDARY OUTCOME				
mRS 0–2 at 90 days	32 (65.3%)	31 (62%)	0.732	0.92 (0.40–2.05)
NIHSS 0–2 at 90 days	20 (40.8%)	20 (40%)	0.934	0.96 (0.39–2.40)
Barthel index > = 95 at 90 days	8 (16.3%)	10 (20%)	0.564	0.87 (0.22–2.98)
Mortality rate at 90 days	10.2 (5/49)	14 (7/50)	0.468	

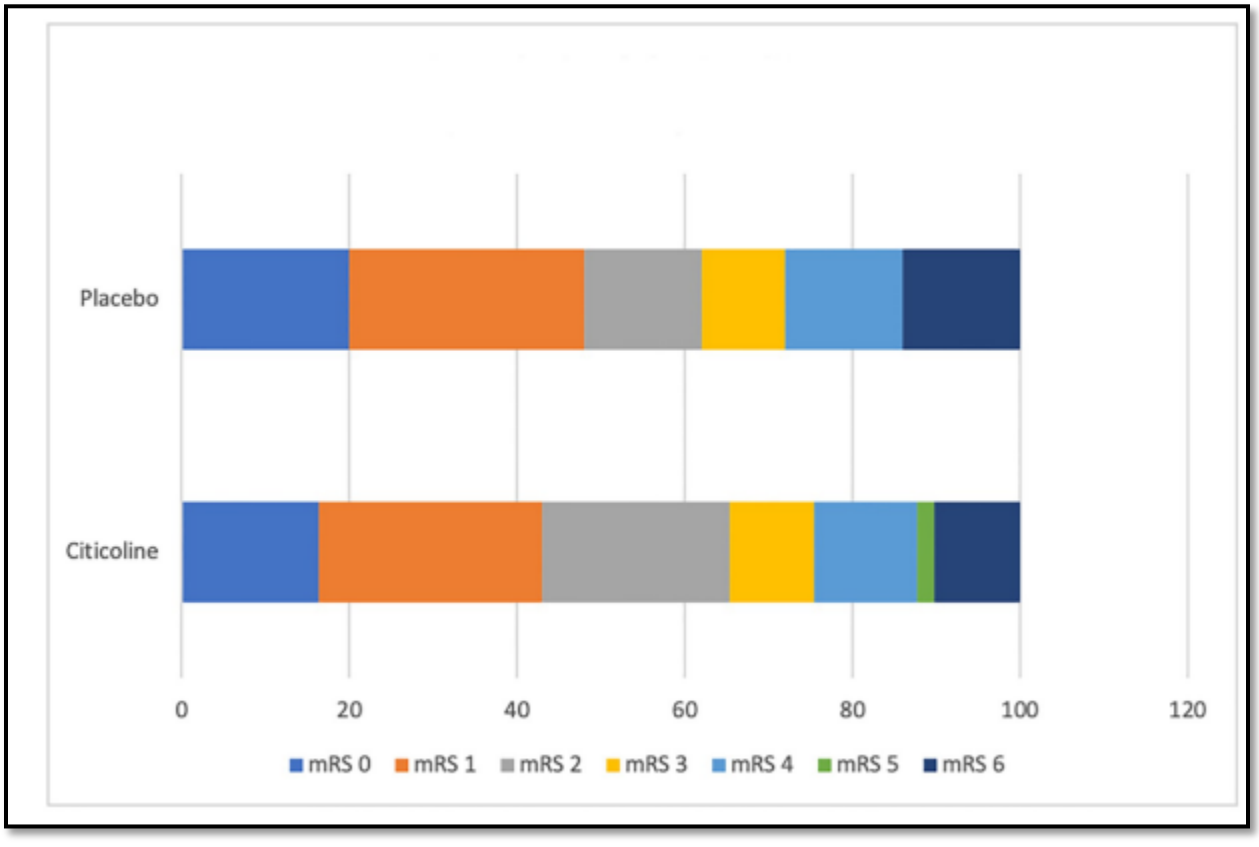

Fig 2. Shift analysis of the modified rankin scale (p value-0.700).

Discussion

The "Time is brain" concept underscores the urgency in treating ischemic strokes, as the rate of neuronal death escalates with each passing minute. This urgency has driven research towards not only enhancing reperfusion techniques but also in deploying neuroprotectants like Citicoline to safeguard the ischemic penumbra from further damage. While Citicoline is widely used in stroke management, its efficacy remains under scrutiny.

Previous Studies and Current Findings:
Several studies have explored the efficacy of Citicoline. Notably, a phase II trial indicated potential benefits at varying doses, yet a subsequent phase III trial failed to demonstrate a

significant impact on stroke outcomes. This phase III trial, however, hinted at possible benefits in severe stroke cases through post-hoc analysis, suggesting that Citicoline might reduce infarct volumes. Despite these insights, another phase III trial focusing on patients with moderate-to-large strokes didn't meet its novel endpoints, though outcomes might have appeared favorable under traditional measures.

The CAISR trial aimed to determine Citicoline's efficacy immediately post-recanalization, focusing on both radiological and clinical outcomes compared to standard treatment. Unfortunately, it concluded without significant findings in primary or secondary endpoints, aligning with previous large-scale studies like the ICTUS trial which also showed no substantial benefits from Citicoline.

Comparative Insights:
Comparatively, the CAISR trial enrolled younger and less severely affected stroke patients than the ICTUS trial. It also used Tenecteplase as the thrombolytic agent, differing from other trials predominantly using Alteplase. Despite these variations, both trials reported similar mortality rates and functional outcomes, indicating no significant advantage of Citicoline in improving post-stroke recovery.

Challenges and Considerations:
The failure to achieve meaningful outcomes raises several considerations. The potential "ceiling effect" of existing treatments like thrombolysis and mechanical thrombectomy may limit the observable benefits of additional neuroprotectants. Furthermore, challenges such as insufficient sample sizes, impacted by the COVID-19 pandemic, likely reduced the study's power, complicating the detection of significant differences.

In summary, while Citicoline shows some promise in specific analytical contexts or under certain conditions, the comprehensive evidence from large-scale randomized controlled trials like CAISR and ICTUS does not support its widespread efficacy in improving clinical outcomes in acute ischemic stroke beyond current standard treatments.
Future research could benefit from addressing these gaps, particularly focusing on the optimal timing of administration and exploring its effects in conjunction with evolving stroke treatment protocols.

Conclusion

The CAISR trial was pioneering in several respects, evaluating the efficacy of Citicoline when administered immediately after recanalization therapy—a critical period for protecting the penumbral tissue most vulnerable to ischemic damage. Notably, it was the first study of its kind to include patients with posterior circulation strokes and those undergoing mechanical thrombectomy. It was also unique in using Tenecteplase for thrombolysis within its cohort of neuroprotectant trials.

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The Role of Citicoline in Neuroprotection and Neuro Repair in Acute Stroke

Introduction

Stroke is a leading cause of disability and the primary cause of death globally. While its prevalence is decreasing in Western countries, it is rising in Asia.[1] In Pakistan, risk factors such as Diabetes Mellitus and Hypertension are notably increasing; projections suggest Pakistan will rank fourth globally for diabetes prevalence by 2020.[1] Additionally, about one in three individuals over 45 suffers from hypertension, many undiagnosed, contributing to the high stroke rates in the region.

The primary focus for managing acute stroke involves enhancing post-stroke recovery through improved emergency responses and immediate medical interventions. Recent strategies include the use of 'neuroprotective agents' that help correct brain metabolic disturbances caused by strokes.[2] Citicoline, a drug used in this context, is noted for its dual benefits of neurovascular protection and potential brain repair capabilities.[3] Administered exogenously, Citicoline has demonstrated efficacy in reducing cell membrane degradation, thereby lowering free fatty acid concentrations.[4]

It is also associated with the faster resolution of cerebral edema.[5,6] The pharmacological properties and mechanisms of action of Citicoline suggest its suitability for treating cerebral vascular diseases, varying severity of head injuries, and diverse cognitive disorders.[7,8] This study aims to assess the effectiveness of Citicoline administered intravenously at doses ranging from 250 to 1000 mg/day for the first 72 hours followed by oral administration for 25 days in patients with acute stroke.

Methodology

This research was carried out in the Medicine department of CMH Jhelum, Pakistan, between December 2017 and May 2018, following approval by the Institutional Review Board. The sample size was determined using the WHO calculator, and participants were recruited through non-probability consecutive sampling.

Inclusion Criteria:

Patients aged over 18, presenting within 24 hours of stroke symptoms, exhibiting a focal neurological deficit lasting more than 60 minutes, and with CT or MRI brain scans corresponding to a clinical diagnosis of acute stroke were included. Only those who were functionally independent prior to the stroke onset were eligible.

Table-I: Baseline characteristics of the Patients (n=30)

Baseline Characteristics	Control Group n=14		Cases Group n=16	
Age (years) Mean±SD	67.78±11.31		59.31±11.03	
Gender (Male:Female)%	42:58		62:48%	
Baseline National Institute of Health Stroke scale (NIHSS)	Ischemic stroke(n)	Hemorrhagic stroke (n)	Ischemic stroke(n)	Hemorrhagic stroke(n)
1-4 (minor stroke)	2	0	1	0
5-15 (moderate stroke)	7	0	4	0
16-20(moderate to severe stroke)	3	1	7	1
21-24 (severe stroke)	0	1	1	2
Risk factors (%)				
Hypertension	6		4	
Diabetes	1		2	
Ischemic heart disease/ atrial fibrillation	3		5	
Previous stroke	2		3	
No identifiable risk factor	3		1	

Exclusion Criteria:

Excluded were patients with severe systemic or neurological conditions that could confound the results, those with a recent history of myocardial infarction, ventricular arrhythmias, unstable heart conditions, or eligibility for thrombolytic therapy (rTPA)

Table-II: Comparison of National Institute of Health Stroke scale score (n=30)

Groups	Number	National Institute of Health Stroke scale NIHSS Score (Mean±SD)	*p*-value
At Start of Study			
Cases	16	13.13±7.13	0.299
Controls	14	14.93±5.01	
At 28th Day of Study			
Cases	13	6.62±6.66	0.299
Controlss	13	9.48±6.94	

All participants or their legal representatives were fully briefed on the trial's nature and objectives, and written informed consent was obtained. Stroke diagnosis was confirmed within 48 hours via CT or MRI to exclude other conditions. Participants were randomly assigned to either receive Citicoline or be placed in the control group, adhering to an Intention-To-Treat (ITT) protocol where all enrolled patients were evaluated for study purposes^[9,10].

Participants were admitted for treatment and could be discharged after a minimum of 72 hours. Treatment involved an IV infusion of Citicoline 1000mg twice daily for three days, followed by an oral dose of 500mg twice daily for 25 days. Standard medications such as antihypertensives, antidiabetics, osmotic diuretics, lipid-lowering agents, and, where necessary, antiplatelet agents like aspirin or clopidogrel were administered to both groups. Thrombolytic therapy was not employed in this study.

Neurological assessments were conducted using the Canadian Neurological Stroke Scale (CNSS) at baseline, 72 hours into treatment, at hospital discharge, and during the third and fourth weeks. For consistency and ease of analysis, CNSS scores were converted to the National Institutes of Health Stroke Scale (NIHSS) using the formula NIHSS = 23 - 2xCNSS^[11]. The NIHSS, typically used for assessing ischemic stroke severity, was also employed here to evaluate hemorrhagic strokes to simplify statistical analysis and improve accuracy^[12,13].

Statistical analyses were performed using SPSS version 20. The Student t-test was used to compare the efficacy of Citicoline in treated patients from admission to the 28th day of treatment. Differences were deemed statistically significant at a p-value of ≤ 0.05.

Results

The study involved 30 patients, of which 25 (83.3%) were diagnosed with an ischemic stroke, and 5 (16.7%) with a hemorrhagic stroke, as confirmed by brain CT scans or MRI within 48 hours of symptom onset. Distribution between the groups was as follows: the Citicoline-treated group included 13 patients (43.3%) with ischemic strokes and 3 (10%) with hemorrhagic strokes. In contrast, the control group comprised 12 patients (40%) with ischemic strokes and 2 (6.7%) with hemorrhagic strokes.

Efficacy of Treatment

The primary efficacy analysis measured improvement in the National Institutes of Health Stroke Scale (NIHSS) scores at 72 hours post-admission and on the 28th day after stroke onset. At the baseline, the Citicoline group exhibited a more significant improvement in NIHSS scores than the control group (68% vs. 53%). There was a noted 30% reduction in NIHSS scores among Citicoline-treated patients compared to those in the control group. Despite these observations, the differences were not statistically significant when analyzed using the Student's t-test at the end of the 28-day treatment period (p-value > 0.05).

Recovery and Mortality Rates

Complete recovery, defined as an NIHSS score of less than 1, was observed in 7 patients (23.3%). Of these, 16.7% were in the Citicoline-treated group compared to 6.6% in the control group. The total mortality rate across the study population was 13.3%, with an equal distribution of 6.7% in the control group and 6.6% in the Citicoline group. The fatalities were more prevalent among patients with moderate to severe and severe strokes, with 3.3% of ischemic stroke patients and 10% of those with hemorrhagic strokes succumbing. None of the deaths were directly attributed to Citicoline, and no serious adverse events associated with Citicoline treatment were reported.

This analysis highlights the potential of Citicoline in enhancing neurological recovery post-stroke, although the results did not reach statistical significance in terms of NIHSS score improvement over the treatment period. Further studies with larger sample sizes may be necessary to conclusively determine the efficacy of Citicoline in stroke recovery.

Discussion

The current investigation focused on the effectiveness of Citicoline, a potential neuroprotective agent, in enhancing neurological outcomes in acute stroke patients, as assessed by the NIH Stroke Scale (NIHSS). Despite the neuroprotective promise of Citicoline, the results of this study, conducted with a limited sample size, did not support its efficacy, aligning instead with recent findings that equate Citicoline's impact to that of a placebo.

Review of Relevant Literature

Recent research, including a trial mentioned by Clark et al., supports the outcomes of the ICTUS trial, which also reported no significant difference between Citicoline and placebo in improving neurological, functional, and cognitive outcomes^[15]. A systematic review by Pinzon et al., analyzing four randomized clinical trials, found that three of these trials reported no statistically significant differences between Citicoline and control groups in treating ischemic stroke, although one trial did suggest Citicoline's effectiveness in preventing post-stroke cognitive impairment^[16].

Furthermore, a meta-analysis by Davalose et al. indicated that Citicoline could improve neurological outcomes when administered at a dose of 500mg^[17]. However, a study by Marques et al. highlighted that while brain ischemia might trigger neurogenesis post-traumatic brain injury (TBI), the endogenous neurogenesis stimulated by Citicoline is insufficient to fully repair brain damage after a stroke^[18]. In contrast, an earlier systematic review by Secades et al. was among the first to report positive results with Citicoline, showcasing its potential as a neuroprotective agent^[19].

Implications for Future Research

These mixed results emphasize the need for more extensive research to determine the efficacy of Citicoline conclusively. Notably, none of the cited studies were conducted in Pakistan, highlighting a significant gap in the local context. Given the preliminary and inconclusive findings from this study, there is a strong case for conducting a large-scale clinical trial in Pakistan. Such research could provide much-needed data on Citicoline's effectiveness in a local setting and potentially offer new avenues for treating acute stroke.

In summary, while Citicoline has shown some promise in improving neurological and functional outcomes, these effects have not yet reached statistical significance in most studies. The current research landscape suggests a need for further, more comprehensive trials to explore Citicoline's potential fully. This is particularly pertinent for regions like Pakistan, where local data on Citicoline's efficacy is lacking, and such a trial could be a beacon of hope for clinicians seeking effective treatments for acute stroke.

Conclusion

This study found that Citicoline treatment does not significantly impact recovery outcomes in stroke patients, both ischemic and hemorrhagic, as measured by NIHSS scores from the onset to the 28th day of treatment. Further research with a broader scope may be required to fully assess its efficacy.

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Neuroprotective Effect of Citicoline

Citicoline (cytidine-5′-diphosphocholine), a critical intermediary in the biosynthesis of phosphatidylcholine (PtdCho), has garnered considerable interest as a potential neuroprotectant in recent years. This study focuses on examining the effects of citicoline on cell survival in primary retinal cultures and its efficacy in combating conditions that model retinal neurodegeneration. Derived from rat embryos, these primary retinal cultures were treated with escalating doses of citicoline up to 1000 µM. The assessment included analyzing apoptosis, caspase activation, and characterizing cell types through immunocytochemistry. Further tests involved exposing the cultures to neurodegenerative conditions simulated by high glutamate or high glucose (HG) mediums, with and without the addition of citicoline. The aim was to evaluate neuronal degeneration, particularly apoptosis and synapse loss.

The findings indicate that citicoline is safe for the retinal neuroglial population up to the highest tested concentration. Notably, at 100 µM, citicoline significantly mitigated the damaging effects of both glutamate and HG, reducing apoptotic activity and loss of synapses. These results reinforce citicoline's capacity for neuroprotection and suggest that primary retinal cultures under degenerative conditions can serve as effective platforms for exploring citicoline's mechanisms.

Beyond its direct cellular effects, citicoline has demonstrated benefits in various central nervous system (CNS) injury models and pathological brain conditions. Its effectiveness was notably seen in several phase III clinical trials for stroke, although other trials have shown mixed results. The therapeutic properties of citicoline are believed to stem from its role in enhancing PtdCho synthesis in damaged brain regions. However, experimental support for this is limited. Our research in models of transient cerebral ischemia suggests that citicoline may support the rebuilding of PtdCho and sphingomyelin, while possibly inhibiting destructive biochemical processes like phospholipase activation.

Citicoline's neuroprotective effects potentially include preserving crucial cellular components such as cardiolipin and sphingomyelin, maintaining arachidonic acid levels in PtdCho and phosphatidylethanolamine, boosting glutathione synthesis and related enzyme activities, reducing lipid peroxidation, and restoring Na+/K+-ATPase function. The underlying mechanism for these effects appears to involve mitigating the activation of phospholipase A2. Moreover, citicoline contributes to neurotransmitter synthesis by providing choline for acetylcholine production and stimulating dopamine release.

The current investigation also extends to citicoline's potential antiseizure and anxiolytic properties. Experiments using the pentylenetetrazole seizure model and evaluations of sedative effects through behavioral tests highlight citicoline's efficacy. Results from these tests show significant improvements in seizure latency and sedative outcomes at dosages of 100 and 150 mg/kg. These findings point to the acute anticonvulsant and sedative potential of citicoline, adding another layer to its therapeutic profile.

This comprehensive study underscores citicoline's multifaceted role as a neuroprotectant, providing valuable insights into its application in both brain and retinal health. The demonstrated effects in primary retinal cultures affirm their utility in probing citicoline's neuroprotective mechanisms, making a compelling case for further research into its broad-spectrum benefits in neurodegenerative conditions.

SURVEY FORM

1.In your clinical practice, do you observe improvement in muscle strength (in Lower limb) in patients after haemorrhagic stroke with the treatment of Citicoline?

A. In limited number of patients

B. In majority of patients

C. In almost all patients

2. In your clinical practice do you noted improvement in speech with citicoline treatment in patients with stroke?

A. In limited number of patients

B. In majority of patients

C. In almost all patients

3. Do you observed improvement in level of consciousness in patients after hemorrhagic stroke with the treatment of Citicoline?

A. No improvement

B. Substantial improvement

C. In almost all patients

4. Do you observed improvement in gait (walk test) with the treatment of Citicoline after stroke in your clinical practice?

A. None of the patients

B. Yes, in some patients

C. Yes, in most patients

D. Almost all patients

5. What percentage of patients receive Citicoline treatment in stroke management in your clinical practice?

A. <10%

B. 10-<30%

C. 30-40%

D. >40%

6. In your clinical practice, do you observed occasional digestive intolerance with the oral treatment of Citicoline?

A. In limited patients with no clinical significance

B. In some patients with no clinical significance

C. In majority patients with no clinical significance

7. In your clinical practice, do you observe occasional excitability or restlessness with the treatment of parenteral Citicoline?

A. Yes

B. No

8. Which of the following side effects of Citicoline mostly come across in your clinical practice?

A. Headache

B. Tingling sensation

C. Numbness

9. In your clinical practice, do you observed clinically significant ECG and EEG abnormalities with the treatment of Citicoline?

A. Yes

B. No

10. In your clinical practice, which of the following age group of patients predominantly experience side effects with the treatment of Citicoline, mostly digestive intolerance?

A. <50 yrs

B. 50-65 yrs

C. >65 yrs

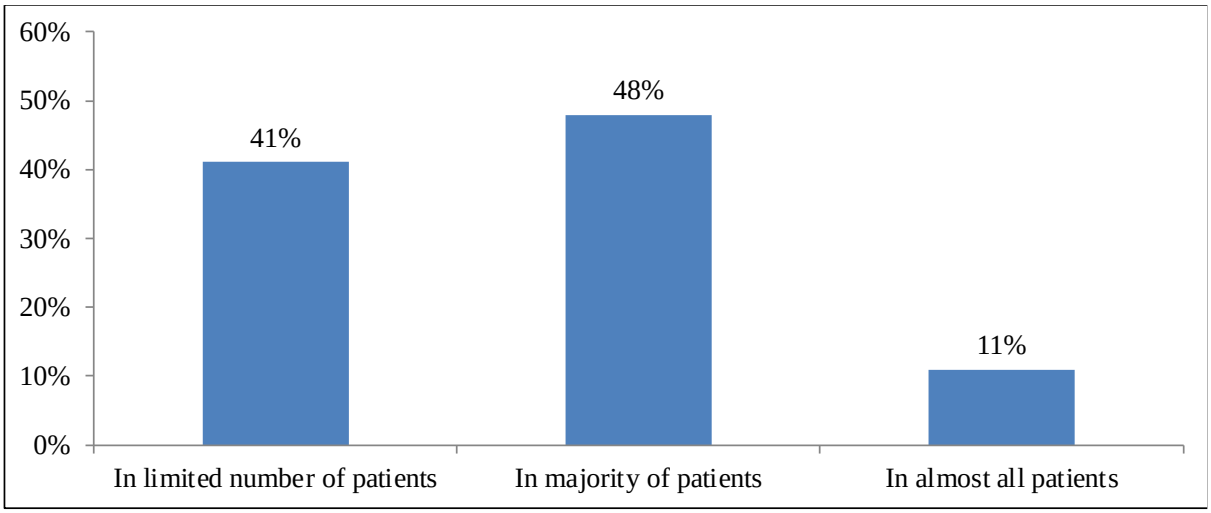
SURVEY FINDINGS

1.In your clinical practice, do you observe improvement in muscle strength (in Lower limb) in patients after hemorrhagic stroke with the treatment of Citicoline?

A. In limited number of patients

B. In majority of patients

C. In almost all patients



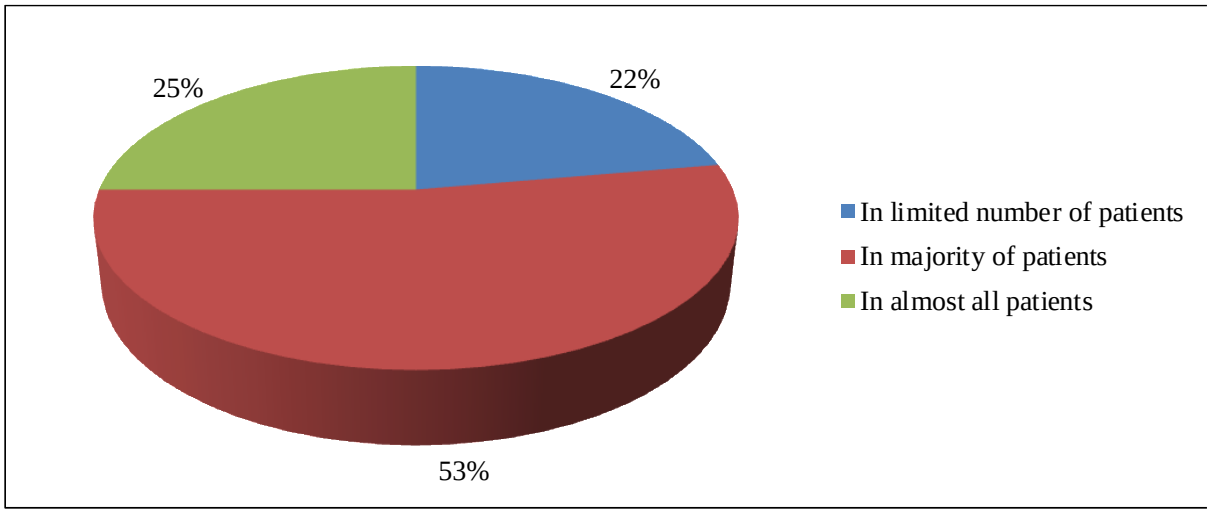
In clinical practice, improvement was observed in muscle strength, particularly in the lower limb, in the majority of patients after haemorrhagic stroke with the treatment of Citicoline.

2. In your clinical practice do you noted improvement in speech with citicoline treatment in patients with stroke?

A. In limited number of patients

B. In majority of patients

C. In almost all patients



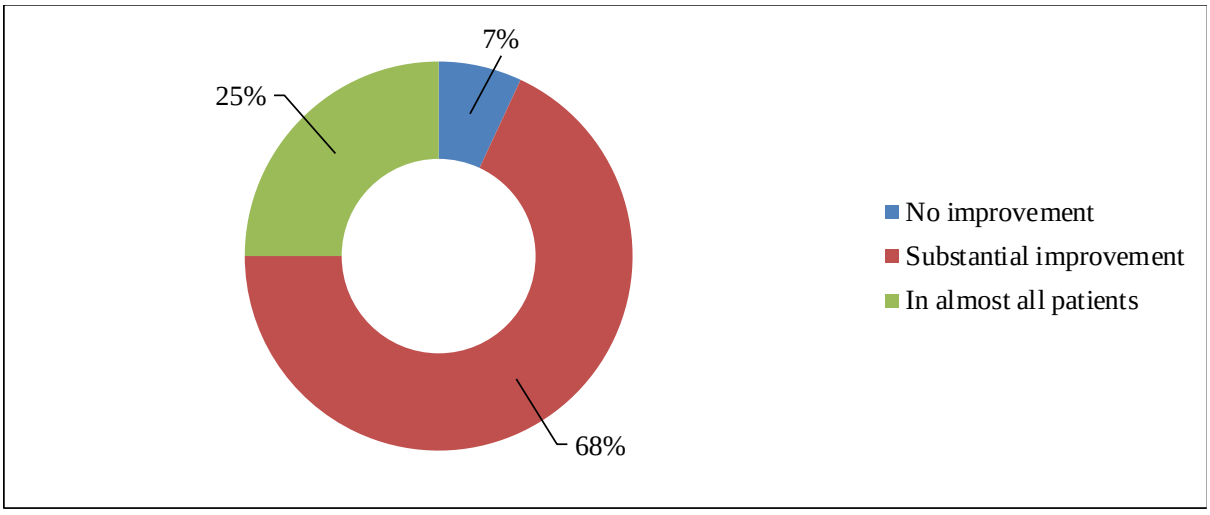
In clinical practice, improvement in speech with citicoline treatment is noted in the majority of patients with stroke. This suggests that citicoline may have a positive impact on speech recovery, although individual responses may vary.

3. Do you observed improvement in level of consciousness in patients after hemorrhagic stroke with the treatment of Citicoline?

A. No improvement

B. Substantial improvement

C. In almost all patients



Improvement in the level of consciousness in patients after hemorrhagic stroke with citicoline treatment is observed to have substantial improvement according to 68% physicians.

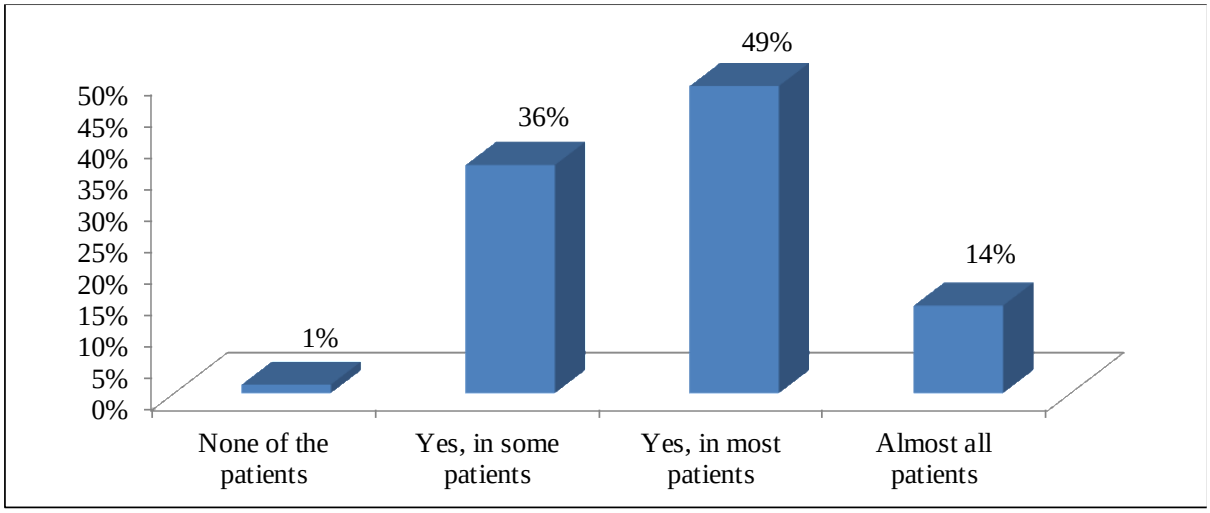
4. Do you observed improvement in gait (walk test) with the treatment of Citicoline after stroke in your clinical practice?

A. None of the patients

B. Yes, in some patients

C. Yes, in most patients

D. Almost all patients



Improvement in gait, as assessed by the walk test is observed in most patients with stroke after treatment with Citicoline in clinical practice.

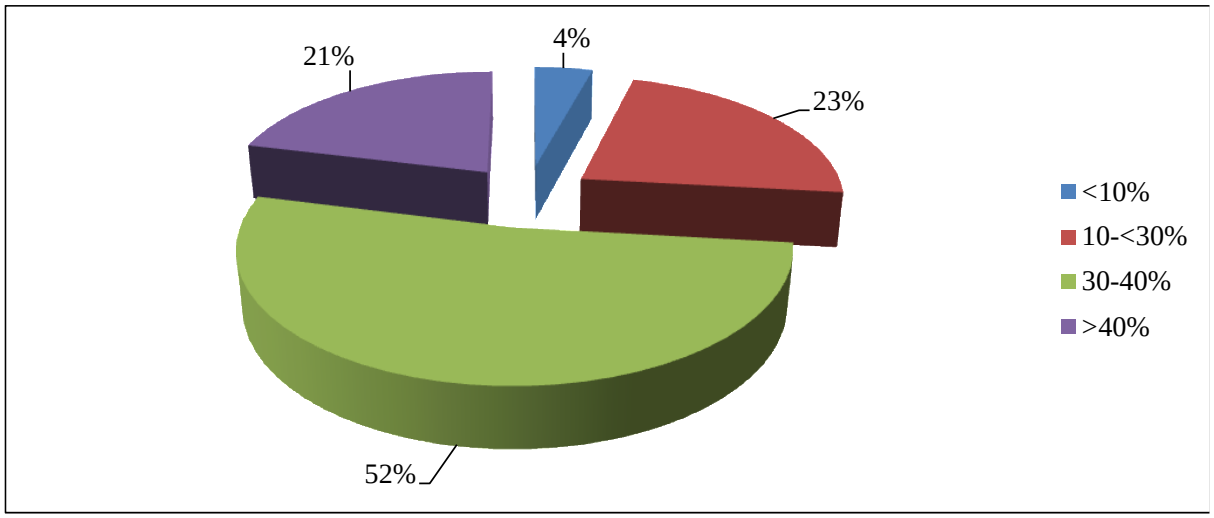
5. What percentage of patients receive Citicoline treatment in stroke management in your clinical practice?

A. <10%

B. 10-<30%

C. 30-40%

D. >40%



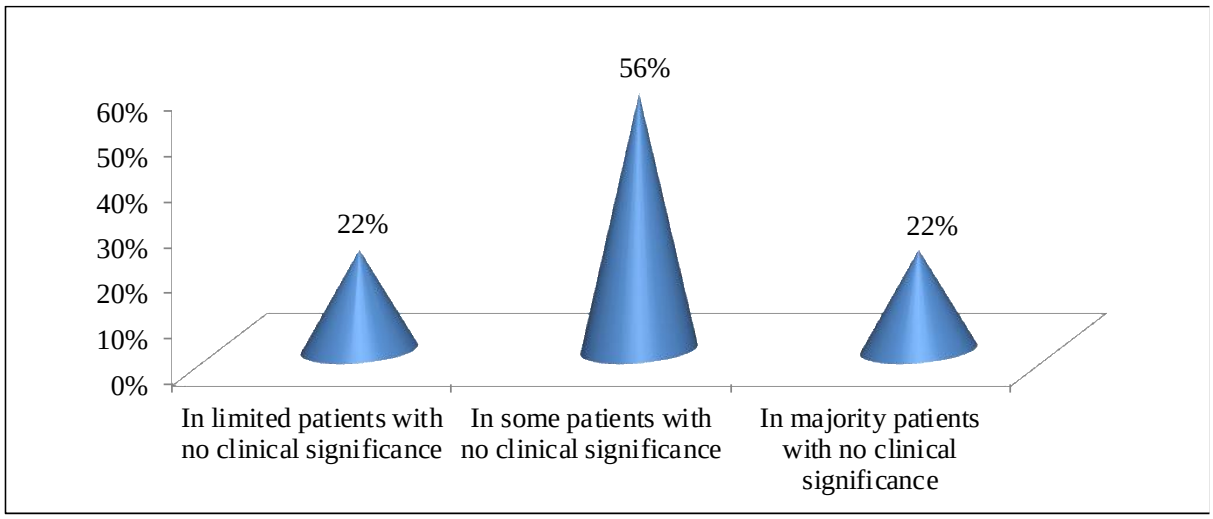
Approximately 30-40% of patients receive Citicoline treatment in stroke management in my clinical practice.

6. In your clinical practice, do you observe occasional digestive intolerance with the oral treatment of Citicoline?

A. In limited patients with no clinical significance

B. In some patients with no clinical significance

C. In majority patients with no clinical significance

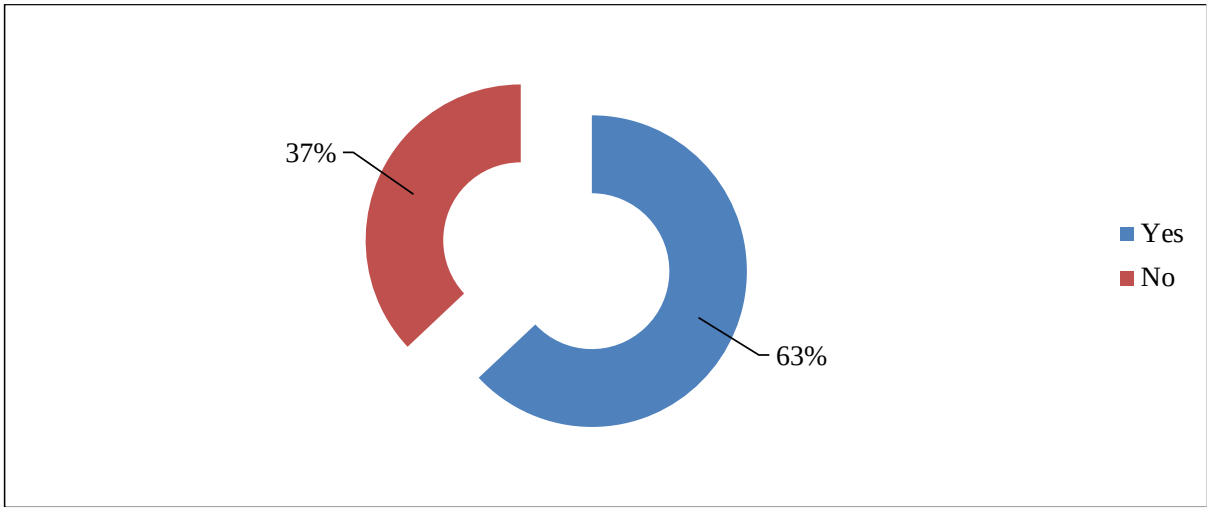


Occasional digestive intolerance with oral Citicoline treatment is observed in some patients with no clinical significance in my clinical practice.

7. In your clinical practice, do you observe occasional excitability or restlessness with the treatment of parenteral Citicoline?

A. Yes

B. No



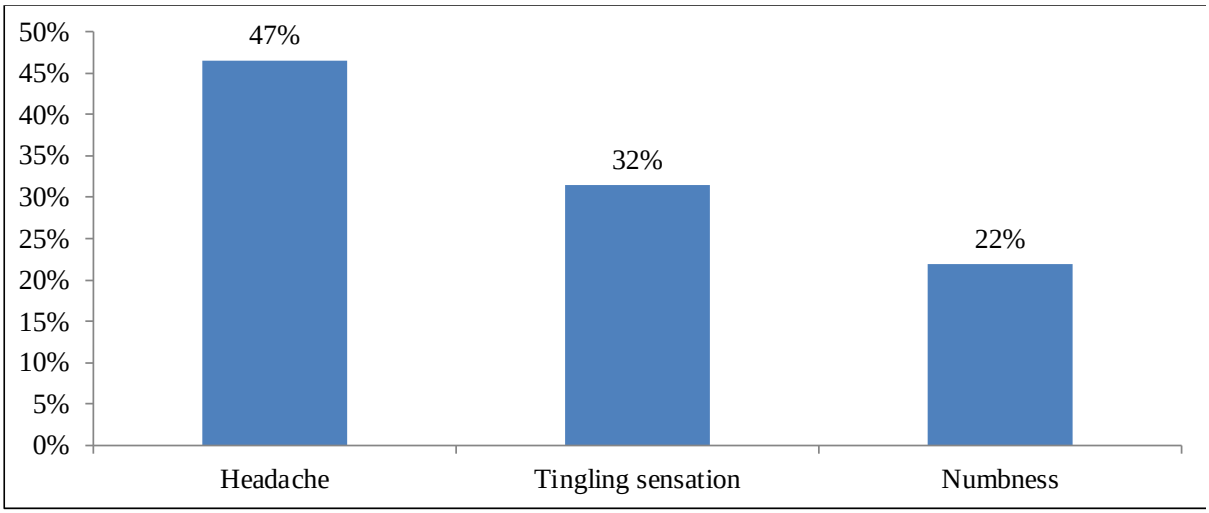
In clinical practice, occasional excitability or restlessness is observed with the treatment of parenteral Citicoline in 63% of cases.

8. Which of the following side effects of Citicoline mostly come across in your clinical practice?

A. Headache

B. Tingling sensation

C. Numbness

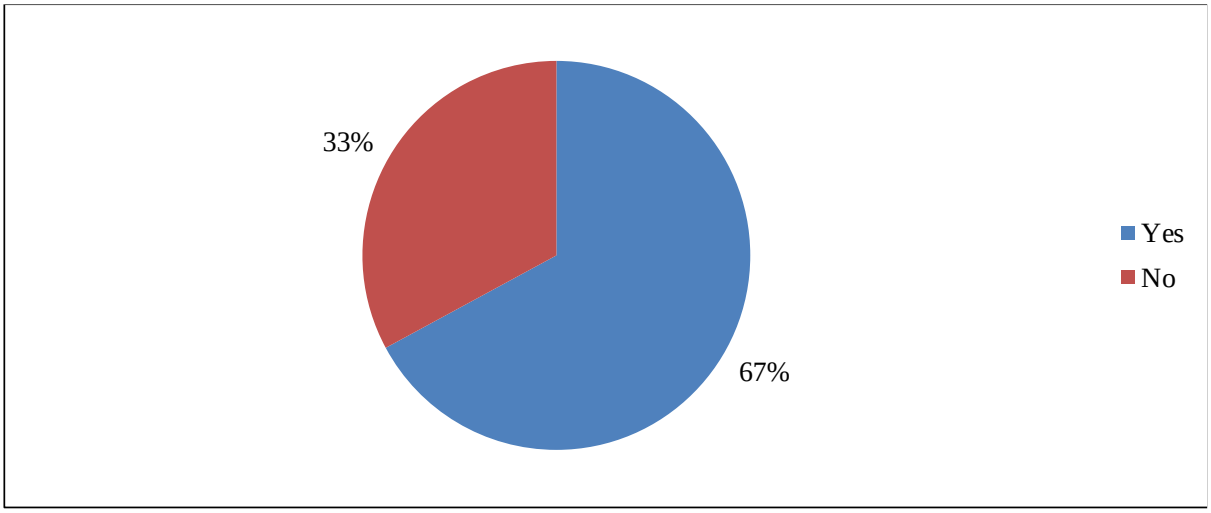


In clinical practice, headache is the most encountered side effect of Citicoline, occurring in 47% of cases.

9. In your clinical practice, do you observe clinically significant ECG and EEG abnormalities with the treatment of Citicoline?

A. Yes

B. No



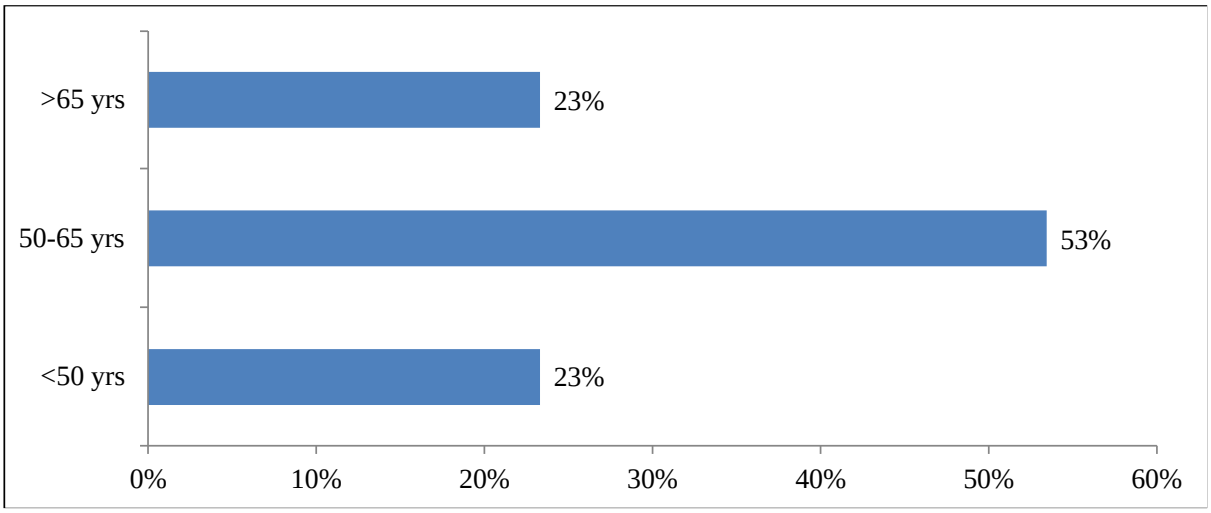
In clinical practice, clinically significant ECG and EEG abnormalities are observed with the treatment of Citicoline in 67% of cases.

10. In your clinical practice, which of the following age group of patients predominantly experience side effects with the treatment of Citicoline, mostly digestive intolerance?

A. <50 yrs

B. 50-65 yrs

C. >65 yrs



In clinical practice, patients aged 50-65 years predominantly experience side effects, mostly digestive intolerance, with the treatment of Citicoline.

SUMMARY

1. In clinical practice, improvement was observed in muscle strength, particularly in the lower limb, in the majority of patients after haemorrhagic stroke with the treatment of Citicoline.

2. In clinical practice, improvement in speech with citicoline treatment is noted in the majority of patients with stroke. This suggests that citicoline may have a positive impact on speech recovery, although individual responses may vary.

3. Improvement in the level of consciousness in patients after hemorrhagic stroke with citicoline treatment is observed to have substantial improvement according to 68% physicians.

4. Improvement in gait, as assessed by the walk test is observed in most patients with stroke after treatment with Citicoline in clinical practice.

5. Approximately 30-40% of patients receive Citicoline treatment in stroke management in my clinical practice.

6. Occasional digestive intolerance with oral Citicoline treatment is observed in some patients with no clinical significance in my clinical practice.

7. In clinical practice, occasional excitability or restlessness is observed with the treatment of parenteral Citicoline in 63% of cases.

8. In clinical practice, headache is the most encountered side effect of Citicoline, occurring in 47% of cases.

9. In clinical practice, clinically significant ECG and EEG abnormalities are observed with the treatment of Citicoline in 67% of cases.

10. In clinical practice, patients aged 50-65 years predominantly experience side effects, mostly digestive intolerance, with the treatment of Citicoline.

CONSULTING OPINION

Market Opportunities:

Understanding the perception of Indian physicians regarding the role of Citicoline in stroke management presents significant opportunities to enhance treatment protocols and patient outcomes. By analyzing current practices and identifying potential gaps, healthcare stakeholders can develop tailored strategies to improve the efficacy and adoption of Citicoline in the Indian context.

Value for Healthcare Professionals:

Indian physicians can derive substantial value from the effective use of Citicoline in stroke management. Citicoline offers a promising adjunct therapy that enhances recovery outcomes, such as muscle strength, speech, and cognitive function, particularly after hemorrhagic strokes. Aligning clinical practice with evidence-based guidelines and leveraging the benefits of Citicoline can lead to improved patient outcomes and professional satisfaction.

Adverse Effect Management:

Effectively managing adverse effects associated with Citicoline is crucial for ensuring patient safety and treatment adherence. Physicians must be vigilant in monitoring for potential side effects such as headaches, excitability, restlessness, and digestive intolerance. Establishing robust protocols for adverse event management and educating patients about possible side effects can mitigate risks and enhance the overall treatment experience.

Effective Management:

Optimizing the management of stroke with Citicoline involves a comprehensive approach that addresses various aspects of patient recovery. Citicoline has been observed to improve muscle strength, speech, and level of consciousness, contributing to better rehabilitation outcomes. Physicians should integrate Citicoline into a holistic stroke management plan that includes physical therapy, speech therapy, and other supportive measures.

Market Positioning:

Positioning Citicoline in the Indian healthcare market requires a strategic understanding of local epidemiology, healthcare practices, and patient preferences. Highlighting the clinical benefits, safety profile, and potential for improved stroke recovery can enhance the adoption of Citicoline among healthcare providers. Collaborative efforts between pharmaceutical companies and healthcare professionals can drive market penetration and acceptance.

Personalized Treatment Decisions:

Tailoring the use of Citicoline based on individual patient characteristics is key to optimizing stroke management. Factors such as the type and severity of stroke, patient age, comorbidities, and response to initial therapy should guide the decision-making process. Personalized treatment strategies can enhance patient adherence, satisfaction, and overall outcomes.

Improving Patient Outcomes:

The ultimate goal of incorporating Citicoline into stroke management practices is to improve patient outcomes and quality of life. By adopting evidence-based practices, fostering interdisciplinary collaboration, and prioritizing patient-centered care, physicians can achieve better recovery rates, reduced disability, and improved long-term prognosis for stroke patients in India.

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