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Study Cerecetam on Aphasia in Patients with CVA

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Abstract

Cerebrovascular Attack is caused by decreased or no supply of blood to parts of brain due to clot formation in blood vessels (Ischemic stroke) or due to rupture of blood vessels (Hemorrhagic stroke) or due to Transient ischemic stroke which is the warning sign of stroke which leads to chief complaints of head ache, slurred speech/aphasia, weakness of limbs etc. Aphasia is an acquired neurogenic disorder caused by damage to cerebral cortex, bacterial infections or rarely due to neurogenerative disorder. There are 5 types of aphasia which is classified based on formation of infracts in regions of brain. Cerecetam is a neutrophil agent that show effect on speech improvement which is available in tablets(800mg), Ampoule(15ml), vial(60ml) each ml containing 200mg are available. The specific method followed was observational prospective study with time horizon of longitudinal study was conducted on 150 patients who are suffering with CVA and having c/o of Aphasia and slurred speech in Lalitha super specialty hospital with study period of 6 months and the data was analyzed quantitative and qualitative method. As for the method better results found by using assessment scale patients were assessed and a final report was prepared whether there is improvement in speech or no improvement of speech after administration of cerecetam with frequency of BD/TID for 2 weeks. The result x2 is 39.78 at Df 4 with significance level of 0.05, P value <0.05. The observed conclusion was Cerecetam plays a significant role in speech improvement in patients diagnosed with CVA and having c/o of slurred speech/aphasia. In Subcortical aphasia (66.6% cases), Broca's aphasia (24% cases), Global aphasia (4.1% cases), Cortical Aphasia (3.3% cases) there is speech improvement. Where as in Wernicke's Aphasia (1.6% cases) the drug cerecetam has less effect.

Keywords: Cerebrovascular Attack, Ischemic stroke.

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Introduction

Cerebrovascular Accident

CVA also called as brain attack or cerebrovascular accident or stroke which is caused due to decreased or no supply of blood flow and oxygen to parts of brain which leads to death or damage of brain cells that are deprived of oxygen and blood .The blood supply to brain is mainly by internal carotid artery supplies to anterior circulation of brain (cerebrum) and right vertebral and left vertebral artery that forms basilar artery supply blood to posterior circulation of brain (under side of cerebrum , brainstem and cerebellum)

Stroke is further classified into ischemic stroke, hemorrhagic stroke, transient ischemic attack based on formation of infarcts / lesions, rupture or leakage of blood in brain blood vessels such as basilar artery.

Ischemic Stroke

Ischemic stroke is caused due to formation of infarcts or lesions in parts of brain. It is further classified into:

1. **Thrombic ischemic stroke:** which is due to clot formation in blood vessels in that supply blood to brain.
2. **Embolic stroke:** formation of blood clots in other parts of body, rather than brain breakdown of clots take down due to hypertension and increased heart rate and clot travels to brain through those arteries that supply blood if the clot gets strucked in the artery leading to low blood and oxygen supply to brain cells.Both emboli and thrombic strokes results from atherosclerosis (Low HDL and high LDL)

- **Hemorrhagic Stroke:** which is caused due to rupture or leakage of blood vessels that supply blood to brain it is further classified into

1. **Intra cerebral hemorrhage (ICH):** Small blood vessels which supply blood to deeper tissues of brain get ruptured due to hypertension that causes leakage of blood to surrounding tissues of brain leading to formation of hematomas or blood clots as the ruptured artery is deprived of blood supply or oxygen to other brain tissues leading to stroke. Because of hematomas the blood cells die and toxins are released, which effects other tissues of brain

a) As blood supply to deeper areas of brain, deep hemorrhages can result to expand ventricles which contains CSF. Blockage of CSF causes ventricles to enlarge and leading to causes **HYDROCEPHALUS**.

2. **Sub arachnoid hemorrhage (SAH):** SAH, that results from the weaken blood vessel which forms the aneurysm called as cerebral aneurysm, intracerebral aneurysm and intracranial aneurysm. Rupture of these aneurysm causes leakage of the blood from that particular blood vessel causing deprived of surrounding brain tissues with blood and oxygen leading to stroke in the people, usually seen at the age of 40 years. Aneurysm takes long period of time to form, at that the patient is asymptomatic. After rupture of aneurysm symptoms such as eye pain, blurred vision, double vision, drooping of eyelids, severe headache, neck stiffness, dilated pupil. Hemorrhage in SA space where CSF fluid circulates may leads to paralysis and coma.

- **Transient Ischemic Attack (TIA):** Also called as mini stroke.

A TIA occurs when blood supply to the brain is temporarily gets blocked due to a blood clot or reduced blood flow due to blockage in blood vessels that supply blood to the brain. Usually, the symptoms of TIA last about few seconds to minutes or minutes to hours and the symptoms are same as that of actual stroke. A mini stroke patient may have more chances to get stroke in the future and it is considered as a warning sign. Though it is not a serious, but needs emergency help and medical attention.

Etiology:

- Hypertension
- Atherosclerosis
- Diabetes mellitus
- Cardiovascular diseases

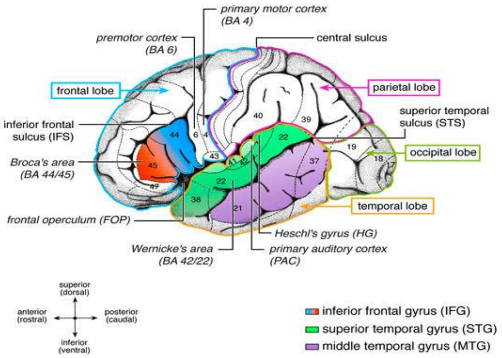
Risk Factors:

- Age
- Gender
- Smoking
- Alcohol
- Hormonal therapy

Symptoms:

- Headache
- Slurred speech
- Aphasia
- Weakness/numbness
- Reeling sensation
- Loss of balance
- Dizziness
- Confusion

APHASIA: - It a language and speech disorder which is acquired neurogenic disorder caused by damage to cerebral cortex(CVA), bacterial infections to brain, trauma (contusion, concussion), rarely neurodegenerative disorders(Alzheimer's disease, Parkinson's disease, bipolar disorder). complaints of CVA is aphasia, slurred speech along withhemiparesis/ The hemiplegia which is mainly due to left cerebral hemisphere damage as a result of occlusion of middle cerebral hemisphere causing lesions or infarcts, leading to right hemiparesis/hemiplegia.



Types Of Aphaisa:

Major aphasic syndrome – Broca's aphasia
Wernicke's aphasia
Other aphasic syndrome – Conduction aphasia
Global aphasia
Cortical aphasia ,
Sub cortical aphasia

Broca's Aphasia:

Broca's aphasia also called as non fluent/motor/expressive aphasia. Broca's aphasia which is named after French scientist Paul Broca in 1861 who stated that lesions or infarcts in frontal gyrus in left hemisphere leads to in proper speech production.

The Brodmann's area 44, 45 which consists of left hemisphere (posterior half of left inferior frontal gyrus) is responsible for motor functioning which means for speech production. The formation of infarcts/lesionsin these areas is due to decrease in blood supply from anterior cerebral artery (ACA) which is caused by occlusion leading to Broca's aphasia. Broca's aphasia observed in about 12% in acute stroke.

WERNICKE'S APHASIA

Also called as fluent/sensory/receptive aphasia. Wernicke's aphasia is named after German neurologist carl Wernicke who stated that lesions or infarcts in temporal lobe of brain extending to parietal lobe of left cerebral hemisphere leads to less grasping of words.

The Wernicke's area 22, 21, 37& BA39 responsible for sensory functioning (grasping of words). Area 22 consists of posterior temporal region of brain extending to parietal lobe. Formation of infarcts/lesions in these areas leads to Wernicke's aphasia. The etiology is that there is decreased blood flow to this area from inferior middle cerebral artery (MCA). Wernicke's aphasia is observed in about 16% in acute stroke.

CONDUCTION APHASIA

Also called asmotor afferent/central aphasia. Infarcts/lesions in other regions of brain that effect arcuate fasciculus (play role in language and speech production) that causes misinterpretation between Wernicke's area (superior temporal region of brain) to Broca's area (inferior frontal region of brain). It is observed in about 5 % in acute stroke.

GLOBAL APHASIA:

Damage to perisylvian area of left hemisphere (inferior frontal, superior temporal region and often parietal region) lesions in these area is due to occlusion of left middle cerebral artery (MCA). It is observed in 32% in acute stroke.

CORTICAL APHASIA

In cortical aphasia no occlusion of cerebral arteries are seen in MRI or MRA. Most of 10% infarcts in brain are due to damage of watershed zones that leads to cortical aphasia.

*Watershed zones is the zone where there is dual blood supply from the branching ends of two large arteries of brain. Watershed zones are often due to hypotension, micro emboli, narrowing of arteries. In CT/MRI scan the watershed zones appear as ovoid/ wedge shape.

1. TRANSCORTICAL MOTOR APHASIA: Also called as dysexecutive aphasia as pre frontal cortex is effected due to damage to watershed zone between anterior cerebral artery (ACA) and middle ACA) and middle cerebral artery (MCA) because of occlusion in these arteries.
2. TRANSCORTICAL SENSORY APHASIA: Damage to watershed zone between middle cerebral artery (MCA) and posterior cerebral artery (PCA) because of occlusion in these arteries.
3. MIXED TRANSCORTICAL APHASIA: Area 44,45& 22 are normal (Wernicke's and Broca's area are normal) but surrounding areas are impaired due to watershed stroke.

SUB CORTICAL APHASIA:

Lesions in basal ganglia and thalamus due to occlusion in cerebral arteries causes subcortical aphasia

	Broca's aphasia	Wernicke's aphasia	Global aphasia
Repetition	Abnormal due to apraxia	Abnormal due to amnesia	Abnormal
Comprehension	Normal	Abnormal	Abnormal
Language	Normal but not fluent	Normal and fluent	Abnormal

*Usually lesions/infarcts in cortical and sub cortical regions result in dysarthria than aphasia.

CLINICAL MANIFESTATIONS

SIGNS:

- ✔ Transcortical motor and sensory aphasia – Repetition, comprehension and language is good
- ✔ Mixed transcortical aphasia – Repetition and comprehension is good and language is non fluent.

✔ Conduction aphasia – Repetition is abnormal, language and comprehension is normal.

ASSESSMENT OF APHASIA:

1. Boston diagnostic aphasia examination
2. Multilingual aphasia examination
3. Minnesota test for differential diagnosis of aphasia
4. Western aphasia battery
5. Bilingual aphasia test

DRUG INFORMATION OF CERECETAM

CERECETUM is a nootropic agent or also called as smart drug belongs to racetams group. It is a cyclic GABA derivatives but differ in mechanism of action from GABA drugs (barbiturates, benzodiazepines). This drug was approved in Europe and US as to improve brain functioning and dietary supplement. However this drug was not approved by USFDA as dietary supplement.

BRAND NAMES: CERECETAM, ULTACETAM, AMCETAM, ALCETAM, ZETAM, PIRAMAX, NOOTAJ, NOOTROPIL.

GENERIC NAME:piracetam

DOSE:

ORAL - 1.2g/1200mg oral for normal CNS functioning. 4.8g/day in divided doses. Up to 20g/day [nontoxic dose]

PARENTRAL - 1 to 2 g 3 times per day IV or IM

DOSAGE FORM:injection(vial, ampoule), tablet, capsules, syrup

MECHANISM OF ACTION:

- Cerecetam mechanism of action is unclear. Piracetam increases flexibility of cellular membrane which increases release of neurotransmitters leading to increase cellular metabolism in order to have sufficient oxygen supply to brain.
- Improve functioning of neurotransmitter such as Acetylcholine (memory process) which improve communication between nerve cells, protect brain and nervous system against shortness of breath
- Effect on NMDA receptors (involved in learning and memory processing)
- Increase oxygen supply to brain in conversion with ATP metabolism
- Inhibits calcium influx, if increase calcium levels in neuronal cells may cause death of cells leading to cognitive impairment, low muscle tone and weakness.

ABSORPTION:

✔ Rapidly and completely absorbed, shows therapeutic action within 1.5 hours

✔ Bioavailability of oral formula is nearer to 100%

✔ Steady state concentration within 3 days of dosing

DISTRIBUTION: It cross blood brain barrier and placental barrier. Volume of distribution is 0.72/kg

METABOLISM: No metabolites are found as drug does not binds to plasma protein

EXCRETION: Excreted by urine &Half-life of Cerecetam is 4 – 5 hours

PHARMACODYNAMICS: It shows effects on RBC (in case of sickle cell anemia), platelets (antiplatelet action) and blood vessels (inhibits vasospasm)

INDICATIONS:

- Myoclonus
- Dyslexia
- Epilepsy
- Tardive dyskinesia (over use of antipsychotics)
- Dizziness
- Alzheimer's disease
- Schizophrenia
- Stroke

SIDE EFFECTS:

DRUG INTERACTIONS:

CERECETAM<>Antiplatelets, anticoagulants = increases bleeding.

CERECETAM<>Antithyroid agents = it causes confusion and irritability.

PRECAUTIONS: Caution is taken while patient is undergoing surgery and severe hemorrhage. Sudden withdrawal may cause reversal of symptoms such as slurred speech, jerking and twitching of muscles.

DOSE ADJUSTMENT: Dose adjustment is needed in case of patient with renal dysfunction

*If renal clearance is > 80ml/min, then normal dose/day with divided doses is given

CONTRAINDICATIONS:

- Renal impairment
- Hepatic impairment
- Cerebral hemorrhage
- Allergic reactions
- Huntington disease
- Surgery
- Nausea
- Vomiting
- Sleep changes
- Nervousness
- Weight gain

Pregnancy but no teratogenic effect as it crosses placental barrier.

❖The drug may excrete in breast milk hence avoided during lactation

❖Children under the age of 16 years.

AIM:

Study of cerecetam on aphasia in patients with CVA

OBJECTIVES:

- To know improvement of speech in patients with CVA who are having chief complaints of aphasia and slurred speech
- Improvement of speech in patients receiving cerecetam over a therapy of 2 weeks
- Assessment of speech after therapy with aphasia assessment scale (Boston Diagnostic Aphasia Examination)

METHODOLOGY:

Study philosophy: Mixed study containing both positivism(quantitative) and interpretivism(qualitative).

Study type: Inductive type(exploratory)

Study design/Study strategy: An observational prospective study

Study site: Lalitha super specialty hospital

Study period: Study will be carried out for a period of 6 months

Study criteria: The study will be carried out by considering following data.

Inclusion criteria –

✔ Patient with above age of 30 years, male and female.

✔ Patients with CVA of ischemic stroke with chief complaints of aphasia and dysarthria is included in the study

Exclusion criteria –

✔ Patients with other cognitive disorders such as Dementia, Schizophrenia, Parkinson's disease, Bipolar disorder.

✔ Patients with CVA of hemorrhagic stroke are excluded.

Time horizon: Longitudinal

Sampling strategy: Probability (random, representative)

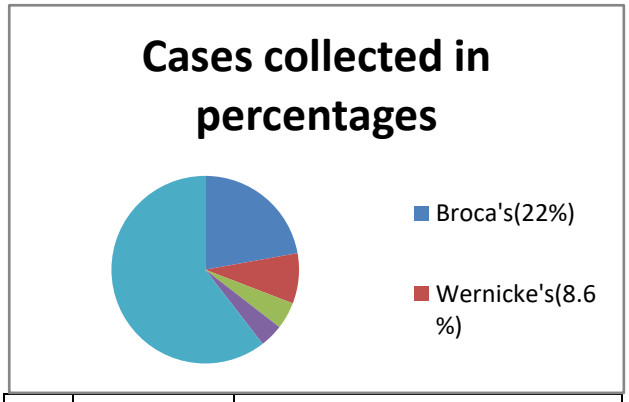
Data collection: Qualitative collection method where subject was interviewed and observation of subject takes place.

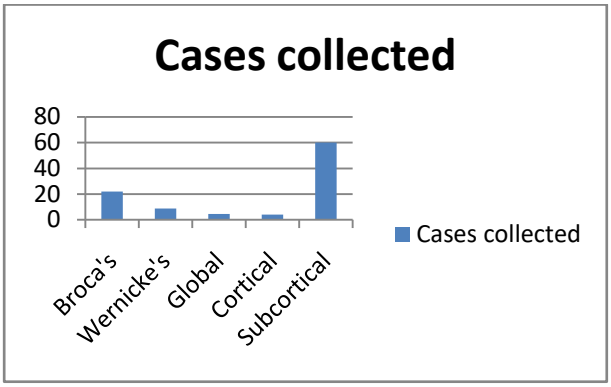
Data analysis: Both qualitative (content analysis) and quantitative (chi-square test).

Results

Total number of CVA cases in which patients who are having the chief complaints of slurred speech and aphasia, the cases collected are 150. Out of 150 collected cases the type of aphasia the CVA patients had developed are as follows –

S. NO	TYPES OF APHASIA	TOTAL NO. OF CASES COLLECTED
1	Broca's aphasia	34
2	Wernicke's aphasia	13
3	Global aphasia	7
4	Cortical aphasia	6
5	Subcortical aphasia	90





The quantitative analysis used for this prospective observational study is Chisquare test

CATEGORY	BROCA'S	WERNICKE'S	GLOBAL	CORTICAL	SUB CORTICAL	TOTAL
Speech	29	2	5	4	80	120
No Speech	5	11	2	2	10	30
Total	34	13	7	6	90	150

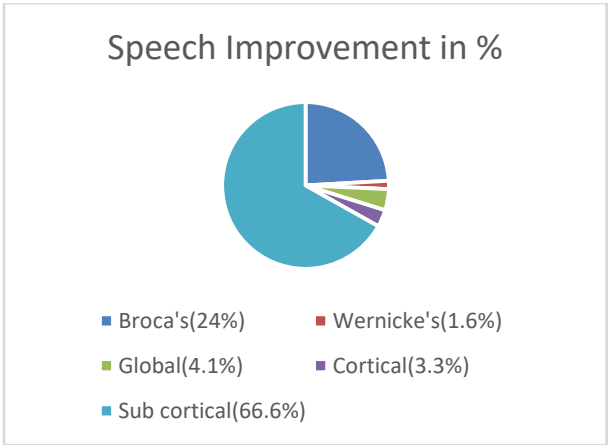
O	E	O-E	(O-E)2	(O-E)2/E
29	27.2	1.8	3.24	0.11
2	10.4	-8.4	70.56	6.7
5	5.6	-0.6	0.36	0.06
4	4.8	-0.8	0.64	0.13
80	72	8	64	0.88
5	6.8	-1.8	3.24	0.47
11	2.6	8.4	70.56	27.1
2	1.4	0.6	0.36	0.25
2	1.2	0.8	0.64	0.53
10	18	-8	64	3.55

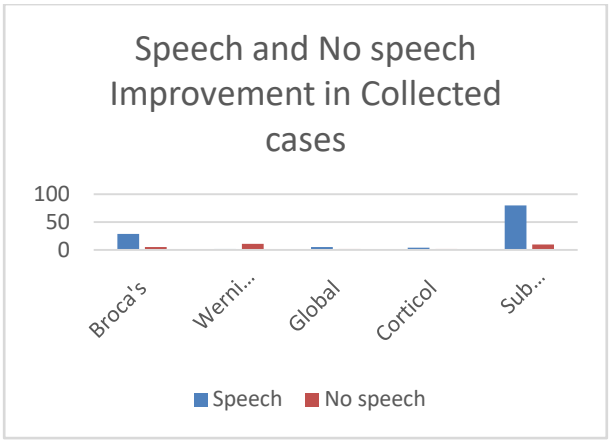
X2 = 0.1+6.7+0.06+0.13+0.88+0.47+27.1+0.25+0.53+3.55

X2 = 39.78

TYPE OF APHASIA	SPEECH IMPROVED
Broca's	29
Wernicke's	2
Global	5
Cortical	4
Subcortical	80

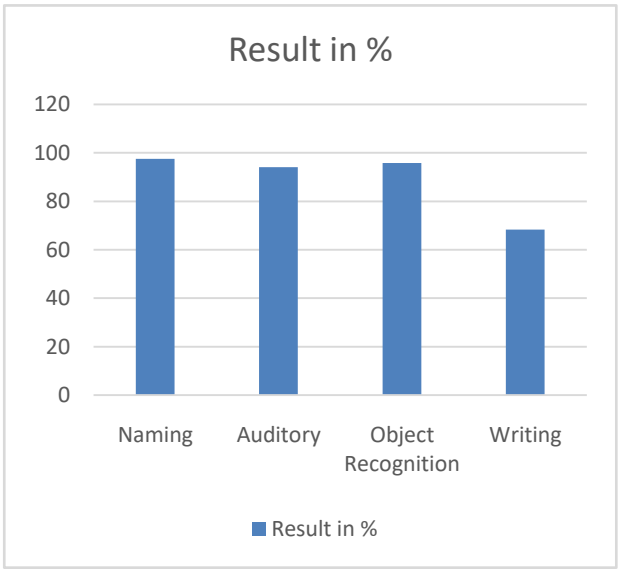
The result of chisquare is 39.78 with Df 4 at 0.05 level of significance , the P valve is > 0.05. The results of speech improvement after administration of piracetam are as follows which is assessed by using aphasia assessment scale –





Aphasia Assessment Scale results are as follows:

Assessment Scale	Result in numbers
Naming	117
Auditory	113
Object Recognition	115
Writing	82



Discussion

✔ Study of cerecetam on aphasia in patients with CVA is a Observational Prospective Study where data is collected in Lalitha super specality hospital with random, representative sampling statergy explaining the qualitative and quantitative analysis.

✔ Taking into consideration, research work of AMO Bakheit (2009), Kessler (2010), Zhangjie (2016)

who stated that there is less effect of cerecetam on speech improvement in CVA patients and is having less side effects and is a neuroprotectiveagent . We conducted the research work (Study of Cerecetam on Aphasia in patients with CVA) to know whether the drug show effect on speech improvement or not .

✔ We collected total cases of 150 patients who are suffering with Ischemic stroke and Transient ischemic attack who are having cheif complaints of Aphasia or Slurred speech along with head ache and other comorbidities such as HTN, DM, Thyroid disorders and excluded hemorrhagic stroke because according to AH Gouliav.et.al(1994) Cerecetam is having an additive effect which shows Anti platelet and Anticoagulant activity there by increases bleeding hence in our study we excluded the patients who are suffering with hemorrhagic stroke.

✔ Type of Aphasia the subject had developed after CVA can be known by CT, MRI, MR Angiogram. If there is Infracts in Frontal and parietal lobe it is considered as Broca's Aphasia (34 cases), Infracts in Parietal and Temporal lobe as Wernicke's Aphasia(13cases) and infracts in frontal, parietal and temporal lobe as Global Aphasia (7 cases) and Water shed territories as Cortical Aphasia (6 cases) and infracts or lesions in Basal ganglia and thalamus as Subcorticol Aphasia (90 cases).

✔ All 150 patients have administrated Cerecetam with dose of 800mg i.e; 33.6g/2week with a frequency of BD/TID and after 2 Weeks of time period the patient was assessed by using Aphasia Assessment Scale the results are as follows Naming (117 cases), Auditory (113 cases), Object Recognition (115 cases), Writing (82 cases)

✔ A quantitative analysis was done by using chi square test the result of X2 value is 39.78 with Df 4 at Level of significance 0.05, the P value is <0.05.

Conclusion

Cerecetam is a Neuroprotective, nootropil agent which is have shown effect on speech improvement. Most of CVA collected cases there is infracts in sub corticol region which leads to slurring of speech in patients. Out of 150 collected cases, 120 patients have improved speech after having treated with cerecetam with a dose of 800mg. In Sub corticol Aphasia, Broca's Aphasia, Global Aphasia, Cortical Aphasia there is Speech Improvement where as in Wernicke's Aphasia there is less effect of cerecetam in speech improvement.

In few cases where the drug cerecetam is withheld due to surgery for 3-5 days these patients had developed which become normal after treatment with cerecetam, hence the drug cerecetam should not be withheld.

Cerecetam is having less side effects and there is beneficial effect on speech improvement and is a cognitive enhancer.

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