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A STUDY OF POSSIBLE PROTECTION BY NEFIRACETAM ON ESLICARBAZEPINE INDUCED MEMORY IMPAIRMENT IN TEMPORAL LOBE EPILEPSY

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Keywords:

Memory, Eslicarbazepine, Temporal lobe epilepsy, Lithium-pilocarpine, Nefiracetam, Radial Arm Maze

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ABSTRACT: Memory impairment (MI) is commonly seen in epilepsy and is at times aggravated by antiepileptic therapy. Recent studies reported that co-administration of nootropic agent with an antiepileptic drug (AED) might decrease the MI. This study was designed to evaluate MI activity of Eslicarbazepine (ESL) in temporal lobe epilepsy (TLE) and to assess the protective effect of Nefiracetam (NEF) which is a racetam group nootropic. MI activity was evaluated by radial arm maze (RAM) on lithium-pilocarpine induced TLE in Wistar Albino Rats. Antiepileptic activity of ESL was also assessed in the absence and presence of NEF. ESL treated a group of animals had increased errors in RAM, compared to the control group which indicated the presence of MI. The extent of MI was decreased when given a half dose of ESL. ESL aggravated the MI in epileptic rats which was very much similar to phenytoin, a standard more than the control group. Co-administration of NEF reversed the MI induced by ESL significantly. It was also observed that NEF treated animals have shown activity as that of the normal group of animals, demonstrating that NEF ameliorates MI in TLE. The anticonvulsant activity was found to be synergized due to the co-administration of NEF when compared to control, and ESL alone treated animals. The combination of a reduced dose of ESL and Nefiracetam was very potent compared to ESL and Phenytoin alone. The reduced dose of ESL and NEF showed a very synergistic effect as nootropic without altering the Anti-epileptic activity.

INTRODUCTION: Epilepsy is a neurological disorder where the recurrent seizure occurs due to the abnormal electrical firing [1, 2]. These seizures occur as episodes which can vary from brief and almost undetectable to a long period of vigorous shaking. The main cause of epilepsy is not cleared although some may develop epilepsy due to brain injury, stroke, tumor, drugs, genetic mutations, *etc*. Memory impairment is one of the major problems associated with epilepsy. Moreover, temporal lobe deals with memory storage and encoding.

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The abnormal functions of the neurotransmitter of the brain lead to the stress, tiredness in the brain which causes a lapse in memory. Moreover, antiepileptic therapy induces memory impairment especially in the case of TLE [3, 4]. When AEDs are administered like all the other drugs, AEDs do have adverse effects. At high dose sedation, unsteadiness, slurring, of speech has been observed. Other side effects include nausea, rash, dysplasia, memory impairment. The side effects occur at the starting of treatment and may become less troublesome in most of the cases, but there is offset in the improvement of patient's cognition.

MATERIALS AND METHODS:

Animals: Wistar rats of either sex (200-250 g) procured from Biogen Laboratory Animal Facility, was used for the study which was carried out during the year 2016-17.

The animals were housed in polypropylene cages at 23-27 °C with a natural light-dark cycle. The rats were fed on a standard pellet diet and water *ad libitum.*

The animals were allowed to acclimatize to laboratory conditions for a week before the start of the experiment. Groups of 8 rats were used in all sets of experiments except the normal group (6 rats). All the experiments were by the approval number 201/2016 of Institutional Animal Ethics Committee (IAEC) of JSS College of Pharmacy, Mysuru.

Drugs Procurement: Eslicarbazepine (ESL) and Diazepam injections were procured from JSS Hospital, Mysuru, and Pilocarpine, Lithium chloride, Nefiracetam were procured from Sigma Aldrich.

Methods: *In-vivo* Activities:

Lithium-Pilocarpine Model: [5, 6] In this model, the cholinomimetic convulsing pilocarpine is used to induce a status epilepticus, which is followed by hippocampal damage and development of spontaneous recurrent seizure. Pilocarpine (30mg/ kg i.p.) was administered in combination with lithium chloride (3 mmol s.c.), which reduces the Pilocarpine dose and mortality. Temporal lobe Epilepsy (TLE) was induced by administration of Pilocarpine 30 mg/kg intra-peritoneal on every 7th Day of treatment and Lithium chloride was given 24 h before pilocarpine administration to minimize the mortality rate. The memory impairment activity was assessed on 8th, 15th, 22nd and 29th day by radial arm maze and the Anti-epileptic activity was assessed on every 7th day for the entire treatment period.

TABLE 1: GROUPING, TREATMENT, AND EVALUATION

Group	No. of Animals	Treatment	Evaluation
Normal	6	Vehicle (0.5% Na-CMC p.o.) was administered for 29 days	Antiepileptic activity on every 7th day followed by memory impairment on every 8th day
Control	8	Vehicle (0.5% Na CMC) p.o. daily as suspension in vehicle for 29 days + Pilocarpine on every 7th day	--do--
Phenytoin	8	Phenytoin (25mg/kg) p.o. daily as a suspension in the vehicle for 29 days + Pilocarpine on every 7th day	--do--
ESL ND	8	ESL (40mg/kg) p.o. daily as suspension in vehicle for 29 days + Pilocarpine on every 7th day	--do--
ESL RD	8	ESL (20mg/kg p.o.) daily as a suspension in the vehicle for 29 days. + Pilocarpine on every 7th day	--do--
ESL ND + NEF	8	ESL (40 mg/kg p.o.) and NEF administration for 29 days + Pilocarpine on every 7th day	--do--
ESL RD + NEF	8	ESL 20 mg/kg p.o. and NEF administration for 29 days + Pilocarpine on every 7th day	--do--
NEF	8	10 mg/kg p.o. administration for 29 days + Pilocarpine on every 7th day	--do--
Total	54		

ESL- Eslicarbazepine, NEF- Nefiracetam, ND-Normal Dose, RD-Reduced dose

TABLE 2: TREATMENT SCHEDULE AND EVALUATION

	RAM Model
Day 1-5	Animals were trained for RAM test
Day 6-34	Animals were treated with regular treatment as shown in Table 1. TLE will be induced by Pilocarpine; Memory impairment activity was measured on every 8th day and antiepileptic activity on every 7th Day.

Racine Scale to Measure Temporal Lobe Epilepsy: [7-9]

0. No response
1. Hypoactivity
2. Myoclonic jerks of the head and head bobbing.
3. Bilateral activity of the whole body.
4. Rearing of limbs.
5. Generalized tonic-clonic activity and loss of posture.

The control group was given Diazepam 10 mg/kg i.p. to stop the TLE at stage 4 of the Racine scale to save the life of the animal as they were not treated by any drug.

Radial Arm Maze: [10, 11] 8-Arm radial maze. For rats, the central platform has to be ≥45 cm in diameter to accommodate the animal and allow it to turn easily between arms. A wall, 25 cm high, surrounds the central platform. The arms are 87 cm long and 10 cm wide, radiating from the central platform at equal angles. Each arm has a 5-mm-deep hole 1 cm from the end, which is used as a food cup, and each arm is separated from the center. A LED light was used to create aversion. The first entry to any arm is counted as exploration, and the repeated entry to the baited arm is working, and non-baited arm is Reference error.

RESULTS AND DISCUSSION:

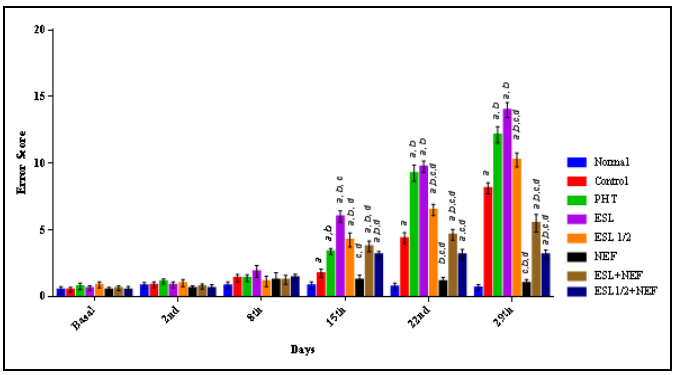

FIG. 1: WORKING MEMORY

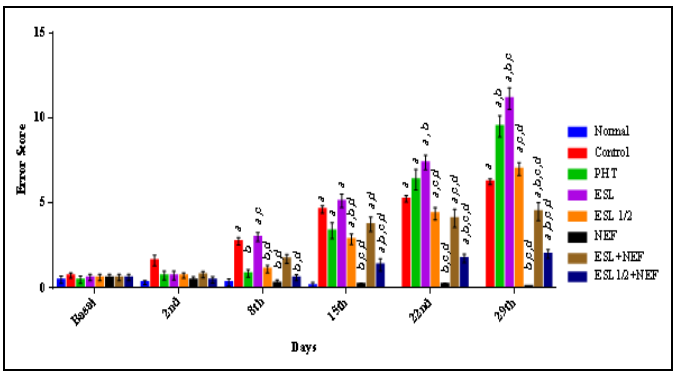

FIG. 2: REFERENCE MEMORY

MEAN ± SEM, n = 8, p≤0.05, a-significant when compared to Normal, b-significant when compared to control, c-significant when compared to phenytoin (PHT), d-significant when compared to Eslicarbazepine (ESL)

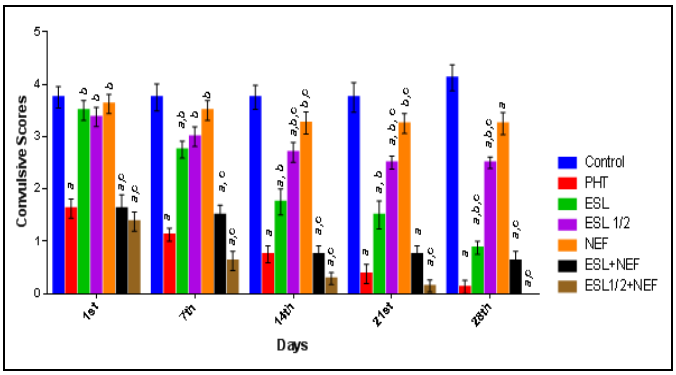

FIG. 3: ANTI-EPILEPTIC ACTIVITY

MEAN ± SEM, n = 8, p≤0.05, a-significant when compared to Control, b-significant when compared to phenytoin(PHT), c-significant when compared to Eslicarbazepine (ESL)

DISCUSSION: Working memory & Reference memory was assessed in radial arm maze as per **Table 1**, the ESL induced groups showed more memory impairment than the control group, and the ESL reduced dose group was seen to have less memory impairment, but it has less anti-epileptic activity than ESL normal dose. The combination of ESL & Nefiracetam which reduces the memory impairment significantly than ESL but not as compared to ESL reduce dose & NEF combination.

ESL Reduced dose & NEF combination was seen to have a synergistic effect of reducing memory impairment without altering its anti-epileptic activity.

CONCLUSION: In major drawback of anti-epileptic treatment is memory impairment especially in temporal lobe epilepsy because temporal lobe is the major part which deals with the memory encoding and storage. The study aimed to treat epilepsy and reduce the memory impairment induced by ESL. The memory impairment was seen more in ESL treated group compared to control as AEDs aggravates more memory impairment. The ESL half doses also reduce memory impairment but not as compared to the control group. The combination of Nefiracetam, which is a nootropic with ESL reduces memory impairment but not as compared ESL reduced dose & Nefiracetam combination.

The combination of ESL reduced the dose and NEF was seen to have a synergistic effect of reducing the memory impairment without altering the anti-epileptic effect in lithium-pilocarpine induced TLE in rats model.

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CONFLICT OF INTEREST: The authors declared no conflict of interest.

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