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PROTECTIVE EFFECT OF PENTOXIFYLLINE AND L- CARNITINE ON ELECTROCONVULSIVE THERAPY INDUCED AMNESIA

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ABSTRACT

The present study explores the protective effect of Pentoxifylline and L- carnitine on ECT induced retrograde amnesia. Adult male wistar rats received ECT once on alternate days for 2 weeks. Rats were administered pentoxifylline (50 mg/kg p.o) and L-Carnitine (60 mg/kg p.o) for 2 weeks. The spatial memory was assessed by Morris water maze, Passive avoidance test and the whole brain total acetylcholinesterase (AchE) was also estimated. The results of our study suggest that Pentoxifylline and L- carnitine significantly reversed the ECT induced spatial memory deficits and also inhibits the increase in AchE activity by ECT.

Key words: Pentoxifylline, L-carnitine, retrograde amnesia, Acetylcholinesterase, ECT.

INTRODUCTION

ECT is a successive therapy for all purpose of alleviating symptoms of specific mental disorders. ECT is considered as an effective treatment for patients who are risk to medications (e.g., during pregnancy or in elderly patients) (Sackeim and Devanand, 1995). But cognitive impairment with ECT, especially retrograde amnesia, is an important reason for its less utilization. The memory impairments are of two kinds: anterograde amnesia and retrograde amnesia. Anterograde amnesia refers to impairment in new learning, whereas retrograde amnesia describes the loss of previously acquired memories (Andrade, 2005).

Several studies have shown that retrograde amnesia (RA) occurs after ECT in the days after the course of treatment has finished (McCall *et al.*, 2006; Sackeim *et al.*, 2000), 2 and 4 weeks post-ECT (McCall *et al.*, 2004), 2 months post-ECT (Lisanby *et al.*, 2000; McElhiney *et al.*, 1995; Porter *et al.*, 2008; Sackeim *et al.*, 1993, 2000) but the effects are transient. The mechanism for ECT-induced RA is unclear since ECT stimulates large territories in the brain. Learning and memory dependent on normal cholinergic neurotransmission; the relationship of it may be dose-dependent (Weinberger *et al.*, 2006). Electroconvulsive shocks (ECS) down regulate muscarinic cholinergic receptors (Lerer *et al.*, 1984; Lerer, 1985). This explains the cognitive deficits associated with the treatment.

Immediately after ECT (Weizman *et al.*, 1987; Kronfol *et al.*, 1991) there was increase in cortisol levels which may over stimulate glucocorticoid receptors in the hippocampus; this leads to loss of dendritic spines and synapses (Sousa and Almeida, 2002) leading to retrograde amnesia. ECT also causes an excessive release of excitatory amino acids and, consequently, an excessive stimulation of their receptors; the end-result is excessive cation (particularly calcium) and water influx, and produces reversible oxidative stress (Chamberlin and Tsai, 1998).

Pentoxifylline (Ptx), a methylxanthine derivative and a phosphodiesterase inhibitor, has recently gained importance as a result of its anti-inflammatory properties. It has been used in cases of intermittent claudication. Other therapeutic indications ptx have been reported against experimental neurotoxicity (Bluthe, *et al.*, 2005), neuropathic pain (Liu, *et al.*, 2007) and nephrotoxicity (Da´ vila-Esqueda, *et al.*, 2005). It has inhibitory effects on various inflammatory mechanisms, including complement cascade, neutrophil adherence, and cytokine production (Bone, 1992; D'Hellencourt, *et al.*, 1996). Pentoxifylline has shown promising results in the survival of patients with traumatic brain edema as a free-radical scavenger and effective antioxidant (Abdul Rashid Bhat *et al.*, 2008).

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L-carnitine is a natural amino acid present in the body that plays an important role in fatty acid and carbohydrate metabolism. Its major function is the transport of long-chain fatty acids into mitochondria for oxidation, particularly in the heart and skeletal muscles. L-carnitine administration prevents age-related increment of DNA damage, thereby confirming the neuroprotective action of L-carnitine against aging (Packiasamy AR, 2005) and L-carnitine also protected rats from artificially induced oxidative stress in the brain. The protective effect was associated with decreased lipid peroxidation and increased superoxide dismutase activity in the brain (Sezen *et al.*, 2008).

MATERIALS AND METHODS

Experimental animals

Pathogen free adult male wistar rats weighing about 170-200g were used for the study. The study was carried on male animals to eliminate the sex related differences in the effects of the test compounds. Animals were kept in animal house at an ambient temperature of 25 ^{0}C at 45-55% relative humidity, with 12 hr each of the dark and light cycles. Animals were fed pellet diet and water *adlibitum.* CPCSEA guidelines for laboratory animal facilities (IJP-2003; 35:257-274) were followed.

Drugs

Pentoxifylline (Sun pharma), L-carnitine (Elder)

Treatments

Animals were divided into four groups, each consisting of six male wistar rats. Group I received normal saline (14 days), Group II received ECT, Group III received Ptx (50mg/kg) p.o + ECT, Group IV received Lcar (60mg/kg) p.o+ ECT.

INDUCTION OF AMNESIA

Rats were administered ECT once on alternate days for 2weeks **(**Dong Jun MSm et al; 2010). Maximal Electro convulsive shock (MES) stimulus consisted of 150 mA, 60HZ sine-waves delivered for 200 milli seconds (Abrams, 1992) were administered to the animals.

ASSESSMENT OF BEHAVIOURAL PARAMETERS:

Morris water maze task

The water maze task was run during four consecutive days after the first week of ECT treatment. It was done during the light period approximately between 08:00and15:00h. A circular tank was used as described by Morris (1984). The pool was 180cm in diameter and 60cm high, filled with 23 ± 1^{0}C water, and placed in a room that was rich in permanently located spatial cues including shelves, posters and illumination lights. The pool was divided into four quadrants designated northeast (NE), northwest (NW), southeast (SE) and southwest (SW). Position of the escape platform (9cmdiameter) was changed daily in the pseudo-random order (in the center of the NW,SW,NE or SE quadrants,1.5cm below the water surface, equidistant from the sidewall and the center of the pool). The platform provided the only escape from the water. Four different start points were equally spaced around perimeter of the pool at points NE, SE, SW and NW. On each training day, the three start points were used once each in a pseudo-random sequence (i.e. each trial was started from the different point).First, the rat was placed on the platform for15s for orientation. Then the rat was put in the water, facing wall of the pool, in one of the three quadrants that did not contain the platform, in a random sequence. The time of finding the escape platform was measured. If the rat did not find the platform within 60s, it was placed on it by the experimenter for 15s. The rat that failed to reach the platform was given a latency score 60s.The inter-trial interval was10min. At the end of session, all animals were towel and fan dried and returned to their home cages. The animals were trained during four consecutive days, each given one session of three trials daily. During each trial session, the time taken to find the hidden platform (latency) was recorded. Spatial working memory was assessed after the last training trial sessions, the platform was removed from the pool and rats were allowed to swim for 60 s to search for it. A record was kept of the number of crossing over the platform position in the pool quadrant where the platform had been previously placed (Walesiuk and Braszko, 2009; Kim *et al.*, 2003).

Step-Down Passive Avoidance

Passive shock avoidance paradigm

Passive avoidance behavior based on negative reinforcement was used to examine the long term memory. The apparatus consisted of a box (27x27x27cm) having three walls of wood and one wall of plexiglass featuring a grid floor (3mm stainless steel rods set 8mm apart), with a wooden platform (10x7x1.7cm) in the center of a grid floor. The box was illuminated with a 15W bulb during the experimental period; electric shock (20VAC) was delivered to the grid floor. Training was carried out in two similar sessions. Each mouse was gently placed in the wooden platform set in the center of the grid floor. When the mouse stepped down and placed on the wooden platform set in the center of the grid floor. When the mouse stopped down and placed all its paws on the grid floor, shocks were delivered for 15 sec and the step down latency (SDL) was recorded. SDL was define as the time taken by the mouse to step down from wooden platform to grid floor with its entire paw on the grid floor, animals showing SDL in the range (2- 15 sec) during the first test were used for the second session and the retention test. The second-session was carried out 90min after the first test. When the animals stepped down before 60sec, electric shocks were delivered for 15sec. During the second test, animals were removed from the shock free zone if they did not step down for a period of 60sec. Retention was tested after 24h in similar manner, except that the electric shocks were not applied to the grid floor. Each mouse was again placed on the platform, and the SDL was recorded, with an upper cut-off time of 300sec (Parle Milind and Dhingra, 2003).

BIOCHEMICAL ESTIMATIONS

Estimation of brain acetylcholinesterase (AChE) activity

The whole brain AChE activity was measured using the (Ellman G L *et al*, 1961) method. This was measured on the basis of the formation of yellow colour due to the reaction of thiocholine with dithio bis nitro benzoate ions. The rate of formation of thiocholine from acetylcholine iodide in the presence of tissue cholinesterase was measured using a spectrophotometer. The sample was first treated with 5, 5'-dithionitrobenzoic acid (DTNB) and the optical density (OD) of the yellow colour compound formed during the reaction at 412 nm every minute for a period of three minutes was measured.

Statistical analysis

The statistical significance of the results of Morris water maze, passive shock avoidance tasks as well as AchE were analyzed using ANOVA, followed by Turkey- multiple comparison test, the P values <0.05 were considered as significance.

RESULTS

Effect of Ptx and LCAR on ECT induced changes in behavioral tasks

Effect on passive avoidance task

In the present study, ECT treated rats showed significant impairment of memory as indicated by decrease in the step down latency (SDL). The SDL was significantly decreased from ± in control rats to ± in ECT treated rats (P<). When Ptx + ECT and Lcar + ECT were administered, they significantly reversed the ECT induced impairment in spatial memory. Lcar along with ECT showed significant increase in SDL when compared to Ptx treated groups.

Effect on Morris water maze

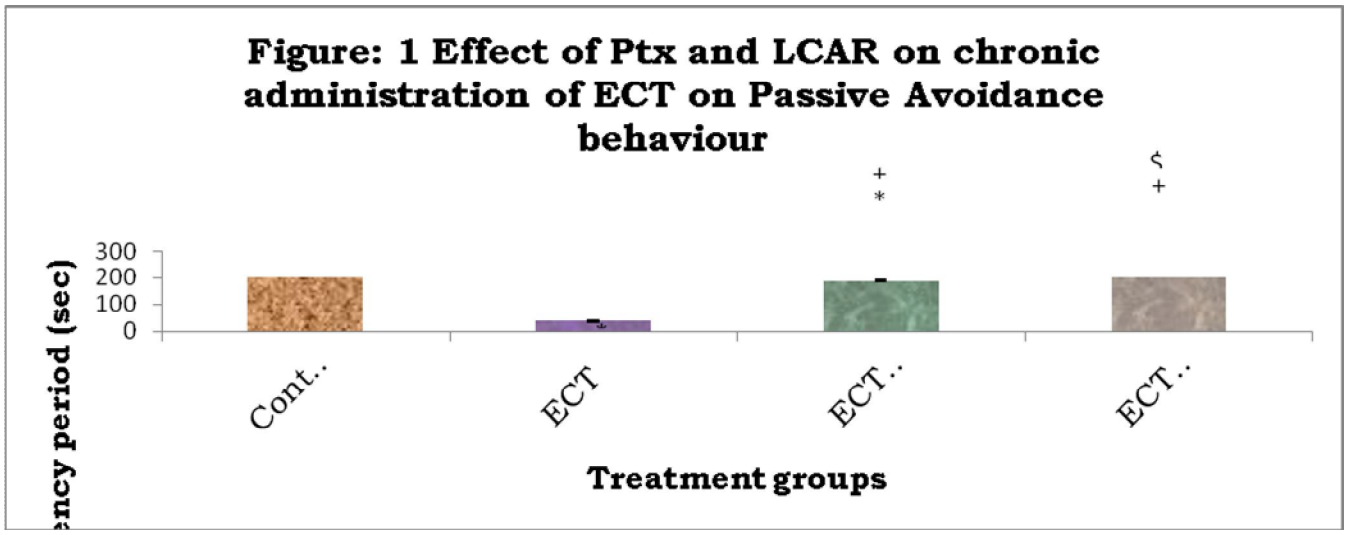
ECT treated rats showed increase in latency period and decrease in no. of crossings over the platform when compared to control. Ptx and Lcar administered along with ECT significantly improved spatial memory by decreasing the latency period and increase in the number of crossings over the platform. From the turkey's multiple comparison test it shows that Lcar significantly decreased the latency period and increased no. of crossings compared to Ptx group.

Effect on AchE activity in the brain

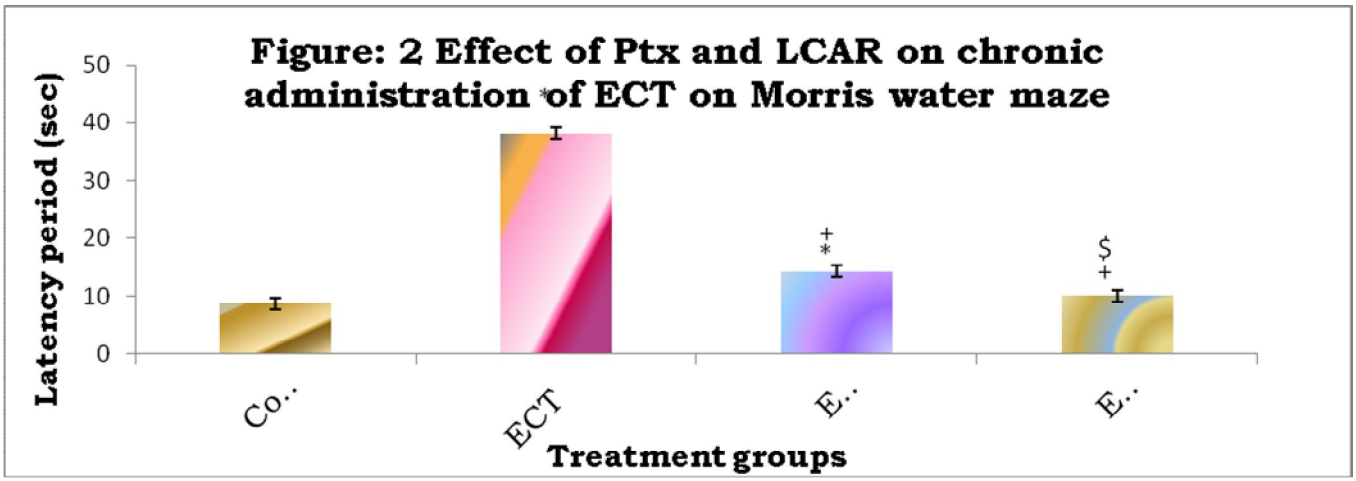
The AchE activity of the whole brain was markedly reduced (P<) after Ptx and Lcar (P<) treatment. Both the drugs significantly reversed the ECT induced increase in AchE activity in the brain which is considered as indicator of inhibition of AchE activity.

Histological analysis

A group of control, ECT, Ptx and Lcar treted animals were killed by decapitation and used for histological analyses. Brains were removed and fixed in 10% formalin solution. Thereafter, the brains were embedded in paraffin and 5 µm thick sections were caronally cut at the level of the dorsal hippocampus by a rotator microtome. Tissue sections were stained with hematoxylin and eosin. Histopathological observation of the tissue was carried out at the Sri Venkateswara University, Pathology Laboratory, Tirupati, Andhra Pradesh -517 502. (Maibritt B *et al.*, 1997).



Values expressed as mean ± standard error mean of 6 animals
***p<0.001, 0.01 Vs Control group,**
+p<0.001 Vs Corticosterone group,
$P<0.05 Corti + Ptx Vs Corti + Lcar
One way ANOVA followed by turkey's multiple comparision tests



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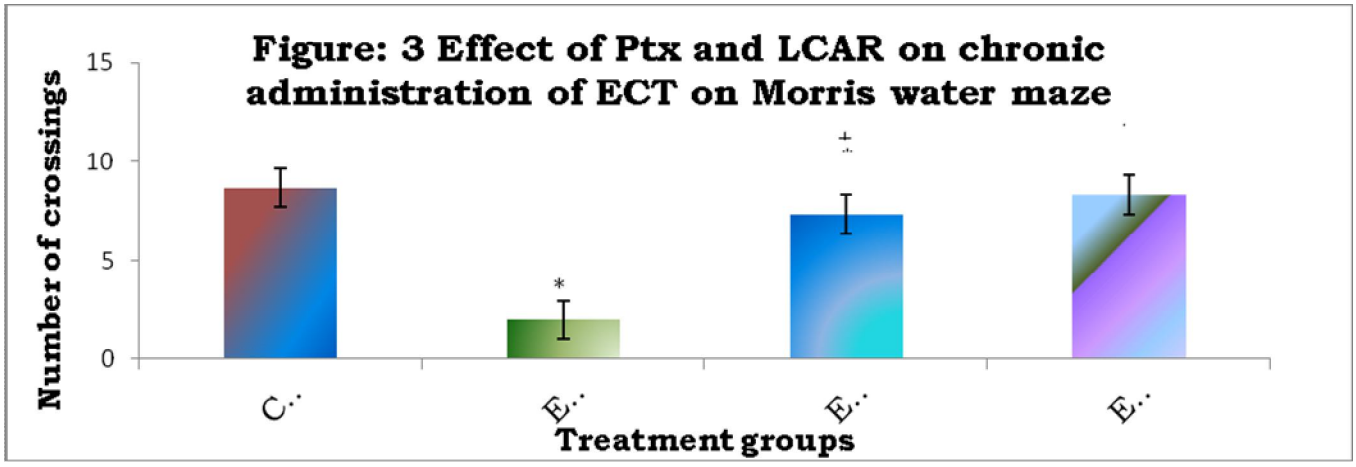


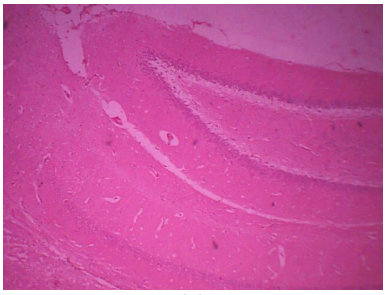
Values expressed as mean ± standard error mean of 6 animals
***p<0.001, 0.05 Vs Control group,**
+p<0.001 Vs Corticosterone group,
One way ANOVA followed by turkey's multiple comparision test

BIOCHEMICAL ESTIMATIONS – BRAIN ACETYLCHOLINESTERASE LEVELS IN ECT TREATED GROUPS

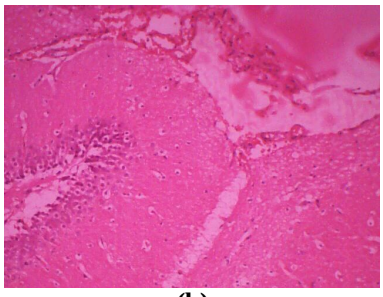
S.No	Groups	AChE µmoles (10^{-5})
1.	Control	148.9 ± 0.565
2.	ECT	175 ± 1.495 [a]
3.	ECT + Ptx	119.6 ± 1.973 [a b]
4.	ECT + Lcar	114.3 ± 1.725 [a b]

Values are expressed as Mean ± SEM.
One way ANOVA followed by Turkey's Multiple Comparison Test.
[a] p<0.001 Vs Control group,
[b] p<0.001 Vs ECT group.

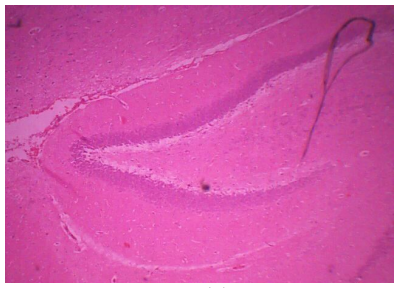
HISTOPATHOLOGICAL STUDIES



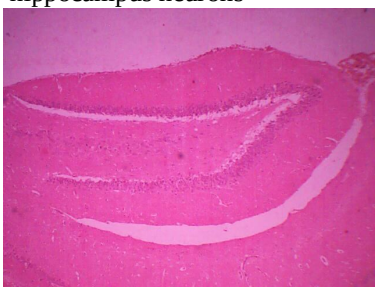
(a)
Control (Saline) – Normal hippocampus neurons



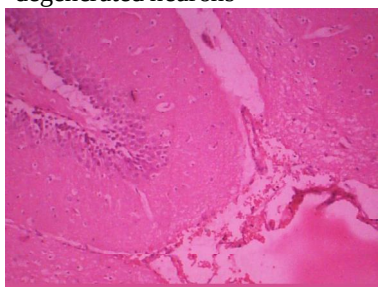
(b)
ECT–Damaged, dispersed degenerated neurons



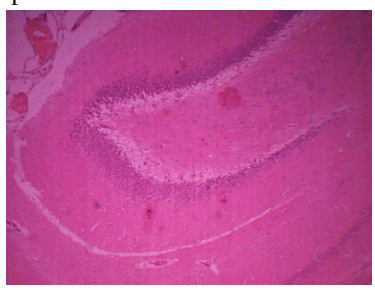
(c)
ECT + Ptx - moderately preserved neurons



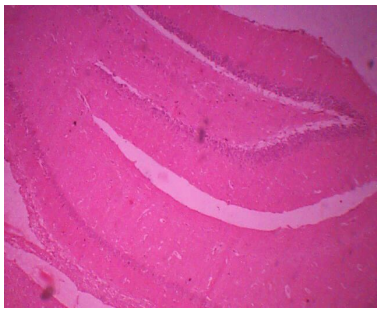
(d
ECT + Lcar – Preserved neural cells in hippocampus



(e)
Corticosterone – damaged, dispersed and degenerated neurons



(f)
Corti+ptx – moderately preserved neural cells



(g)
Corti + Lcar – preserved cells in hippocampus

DISCUSSION

The results of the present study indicate that ECT induced significant impairment in learning and memory and also showed increase in AchE activity in brain. ECT is considered as an effective treatment for patients who are risk to medications (e.g., during pregnancy or in elderly patients) (Sackeim and Devanand, 1995). It is the most effective treatment for severe depression and other psychiatric disorders. It is also associated with several side effects. Most of these side effects are temporary, such as acute confusion and temporary anterograde amnesia (AA) and retrograde amnesia (RA) (Calev *et al.*, 1991; McCall *et al.*, 2002, 2004; Ng *et al.*, 2000; Sackeim *et al.*, 1993). The mechanism for ECT-induced RA is unclear. Several hypotheses have been proposed for the induction of amnesia by ECT, including direct effects of applied electrical current to the medial temporal lobe areas associated with memory, massive release of excitatory neurotransmitters and activation of their receptors, decreased cholinergic transmission, and disruption of long term potentiation (LTP) (Pigot *et al.*, 2008).

In the present study ECT treated rats showed significant increase in latency period and decrease in no. of crossings over the platform in Morris water maze when compared to control confirming the memory impairment. Ptx (50mg/kg) p.o + ECT and Lcar (60mg/kg) p.o+ ECT significantly reversed the ECT induced RA. On Passive avoidance task ECT treated group showed decrease in SDL which was significantly reversed by Ptx and Lcar administration.

Glucocorticoid levels are increased soon after ECT which alters brain glucose metabolism, potentiating the toxic effect of excitatory amino acids such as glutamate, and impairing neurotrophic factors that may be crucial for neuronal recovery from injury (Sapolsky, 1996).

In the present study AchE activity in the brain was increased in ECT treated group when compared to control group. Administration of Ptx and Lcar significantly decreased the levels of AchE in the brain. This explains the protective role of Ptx and Lcar on brain.

Pentoxifylline is a competitive nonselective phosphodiesterase inhibitor which raises intracellular cAMP, activates PKA, inhibits TNF-alpha and leukotriene synthesis, and reduces inflammation and innate immunity. After ECT administration it has been reported that there is generation of free radicals ( ). The protective effect Ptx may be due their antioxidant properties on brain. It also improves the decreased cholinergic transmission induced by ECT.

L-carnitine has been reported to be an endogenous amine that reduce the synthesis of reactive oxygen metabolites and increase NO production causing endothelium-dependent relaxations in hypertensive rats (Koeck and Kremser, 2003). L-Carnitine treatment improves not only the total L-carnitine serum concentrations but also acetylcarnitine serum concentrations. Moreover, the action of L-carnitine on the central nervous system can slow cognitive deterioration that occurs as a result of the normal physiologic aging of nervous cells (Malaguarnera *et al.*, 2006; Brevetti *et al.*, 1991). The increased acetylcarnitine levels in brain might be responsible for reversal ECT induced cognitive impairment.

The results of this study confirmed that Ptx and Lcar protect rats from ECT induced retrograde amnesia. This protection was evident from, the significant improvement in Morris water maze task, Passive avoidance task and reversal increased AchE activity in brain. Lcar showed significant improvement when compared to Ptx. This might be due their major involvement in cholinergic transmission in brain. If the risk factors for ECT-related cognitive side effects were better understood it would be easy to protect the patients and implement prophylactic interventions. In conclusion our study suggests that prophylactic treatment with these drugs may protect the patients from retrograde amnesia induced by ECT.

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