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The possible neurotherapeutic effects of mesenchymal stem cells on $AlCl_3$- induced Alzheimer's disease in adult albino rats

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Abstract: *Alzheimer disease (AD) is a progressive neurodegenerative disorder. The present study aimed to investigate the possible therapeutic effect of stem cells and rivastigmine drug as well as their combination on rat- model of $AlCl_3$ induced AD .*

Materials and methods: *80 adult male albino rats were enrolled in this study in 5 equal groups (16 rats each). Gr. I remained untreated and served as negative control. The remained rats were administered a daily oral dose of $AlCl_3$ (100mg/Kg b.w) allover the experimental period (12 weeks) .After the induction ofAD (28 days, Gr.2 served as positive control ,Gr.3 received a single dose of aqueous infusion of stem cells (10^6 cells/ rat) for 8 weeks,Gr.4 received a daily dose of rivastigmine (0.3 mg/kg b.w) ,Gr.5 received a combination of stem cells and rivastigmine for 8 weeks. The levels of antioxidants in serum and neurotransmitters in cortex and hippocampus regions of brain were studied after 4 and 8 weeks as well as the histopathological examination,*

conclusion: *our results revealed that the combined treatment of stem cells and rivastigmine showed a powerful magnification effect in the treatment of AD through their ability of reduce the most tested parameters in this investigation.*

Key words: *Alzheimer disease, stem cells, neurodegenerative, rivastigmine.*

I. Introduction

Alzheimer disease (AD) is a progressive, incurable**,** neurodegenerative and terminal disease**.** AD is characterized by abnormal clumps (amyloid plaques) and tangled bundles of fibers (neurofibrillary tangles) composed of misplaced proteins in the brain**.** .It is manifested by a progressive decline in cognitive abilities such as memory, comprehension**,** language**,** expression**,** learning**,** capacity**,** calculation**,** abstraction, judgment, spatial orientation and the recognition of familiar people or place **[1].** Patients with AD can categorized as either those with early-onset (familial) or more commonly**,** late-onset (non-familial).The early-onset AD is caused in the majority through mutations in the amyloid precursor protein and accounts for about 5% of cases while the late-onset AD is most often diagnosed in people older than 65 years of age. In 2000, the numbers of AD patients was accounted by 25 million worldwide and this number is expected to increase to 114 million by the year 2050 suggesting a dramatic increase in the burden of AD [2].

In animals, AD confirmed by Morris water maze technique [3] and also by the histological examination of brain tissues**.** Epidemiological studies suggest that environmental factors may be involved beside genetic risk factors. Min et al, 2003 [4] induced AD in rats by injection of Scopolamine (1mg-kg b.w) for 5 weeks. Exposure to high levels of aluminum leads to neurofibrillary degeneration and that Al conc.is increases in degenerating neurons in AD [5]. A new dimension is provided to show that Al –maltolate treated aged rabbits can be used as a suitable animal model for understanding the pathology of AD [6] **.** A major approach to the treatment of AD involves attempts to augment the cholinergic function of the brain **.**This involves the use of inhibitors of acetyl cholinesterase such as tacrine [7]**,** Donepezil [8], Rivastigmine [9]**,** Stem cells therapy is an intervention strategy that introduces new adult cells into damaged tissue in order to treat disease or injury [10] **,** AD is one of these diseases .Many invistigations show that transplantation of neural stem cells can improve cognition**,** reduce neuronal loss and enhance synaptic plasticity in animal models of AD. SC' s may offer a powerful new approach in the treatment of AD [11].

This study was conducted in a trial to reduce the possible common risk factors might progress the AD through a treatment by SC's and rivastigmine or their combination in Al Cl_3 – induced AD in adult albino rats.

II. Martials and methods

Matrials: $AlCl_3$ (MW 133.34) was purchased from Sigma- Aldrich Co. Rivastigmine (0.3mg) was purchased from Novartis Co. All the other chemicals used in this study were in a good and pure quality.

Methods: Induction of AD in rats was carried out by administration of daily oral dose of $AlCl_3$ equivalent to 100 mg/kg b.w. all over the experimental period [12].

Experimental animals: This study was carried out using 80 adult male albino rats weighing 150-170g .They brought from the animal breeding of National Organization for Drug Control and Research (NODCAR)**,** Giza**,** Egypt. Rats were maintained in specific temperature and humidity all over the experiment and fed on a standard basal diet allowing free access of water and were subjected to 12**:** 12 h day light darkness .The ethical protocol for animals treatment were carried out.

Experimental design: Animals were randomly divided into equal 5 groups (16 rats each).G.1; remained untreated and served as negative control.G.2, served as positive control in which animals received a daily dose of $AlCl_3$ equivalent to 100 mg/ kg b.w till the end of the experiment (4wk's to the incidence of AD +8 wks of treatment).Gr.3, animals received a single i.v dose of MSC's equivalent to 10^6cells/rat in the rat tail vein [13] along with $AlCl_3$ for another 8 wks. Gr.4**:** animals received rivastigmine in a daily oral dose of 3mg⁄kg .bw for 8 wks after the incidence of AD [14].G.5, rats received MSC' s Plus rivastigmine at the same doses till the end of the experiment. Eight rats from each group were sacrificed after 4 and 8 weeks from the induction of AD in order to obtain blood samples and tissues to examine the brain tissues which were removed and homogenized from 2 different areas (hippocampus and cortex regions) in70% iced methanol.

Investigated parameters: In the blood the following techniques were carried out: Malondialdehyde**,** MDA [15] Nitric oxide**,** NO [16]. Reduced glutathione, GSH and oxidized glutathione, GSSG [17] In brain tissues: Dopamine (DA). Norepinephrine, Serotonin [18]. The excitatory and inhibitory amino acides [19]. Acetyl choline, ACh [20] and Acetyl choline esterase, AChE [21] were also determined.

Histopathological examination: Brain tissues were dissected and examined using hematoxylin and eosine stains [22].

Preparation of mesenchymal stem cells from rats: MSC' s was prepared according to the method described by Rochefort et al., [23].

Morris Water Maze Tank technique; It was done using the method of Guangqin et al., [24].
Statistical analysis: Data are expressed as mean ± SEM. One way variance analysis (ANOVA) test were applied to study the relationship between the different variables. T-.test was applied to compare the positive group with the negative group [25]**.** $P<0.05$ was considered significant. Statistical processor system support (SPSS) program was applied [26].

III. Results

The results of this study are shown in Tables (1-6) and Figs (1-3).These results revealed that $AlCl_3$ caused AD 4wks after treatment. MDA and GSSG were significantly increased after 4 wks of $AlCl_3$ treatment while NO and GSH were significantly decreased (Table1). Also, the neurotransmitters (DA, NE, 5HT) were significantly increased in brain cortex and hippocampus after induction of AD (Tables 2, 3). After $AlCl_3$ treatment, the excitatory amino acids were increased while the inhibitory amino acids were decreased in brain cortex and hippocampus. (Tables 4, 5). Also Table (6) proved that ACh was significantly decreased in both cortex and hippocampus while ChE activity was significantly increased. All the previous results are going parallel with the results shown in the Morris water maze tank technique (Fig,s 1, 2). Injection of stem cells ameliorated all test parameters under investigation**.** Also administration of rivastigmine caused a marked pronounced effect on different parameters under investigation. Administration of stem cells plus rivastigmine showed a marked synergistic effect of all parameters during this study .The histopathological studies (Fig, 3) confirm all the prementioned results.

Table (1): Effect of different treatments on serum MDA (nmol/ml), NO (µmol/ml), GSH (nmol/ml) and GSSG (nmol/ml) after 4 and 8 weeks from the induction of AD and % changes from the corresponding control.

Treatment	MDA (nmol/ml)				NO (□mol /ml)				GSH (nmol/ml)				GSSG (nmol/ml)			
	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change
- ve Control	71.4± 1.59	-	77.1± 2.83	-	3.32± 0.05	-	7.78± 0.27	-	171.1± 1.23	-	143.1± 4.47	-	81.1± 4.28	-	54.6± 1.15	-
+ve Control	154.8± 2.70***	116.8↑	169.5± 4.60***	119.8↑	1.42± 0.10***	57.2↓	4.50± 0.35***	42.2↓	76.5± 0.66***	55.3↓	122.6± 1.88***	14.3↓	255.5± 2.21***	215.0↑	77.8± 3.35***	42.5↑
St. Cells	109.6± 5.70•	29.2↓	100.1± 9.30•	40.9↓	2.32± 0.10•	63.4↑	6.38± 0.34•	41.8↑	124.9± 3.34•	63.3↑	124.7± 3.46	1.71↑	114.0± 6.33•	55.4↓	47.5± 0.43•	38.9↓
Rivast.	115.3± 3.10•	25.5↓	106.6± 4.2•	37.1↓	2.30± 0.11•	61.9↑	5.92± 0.22•	31.5↑	93.3± 1.45•	30.0↑	133.5± 1.88	8.89↑	137.3± 6.47•	46.3↓	35.6± 0.73•	54.2↓
St. Cells + Rivast.	80.1± 2.25•	48.2↓	96.0± 1.4•	43.4↓	3.21± 0.12•	126.1↑	9.99± 0.27•	122.0↑	101.7± 2.84•	32.9↑	137.2± 0.60	11.9↑	85.3± 8.60•	66.6↓	28.3± 0.43•	63.6↓

Mean values of 6 rats ± SE
•Gr. 2 compared with Gr. 1; Grs 3, 4, 5 compared with Gr.2.
Insignificant at p < 0.25, * very highly significant at p < 0.0005.**

Table (2): Effect of different treatments on neurotransmitters in brain cortex after 4 and 8 weeks from the induction of AD and % changes from the corresponding control.

Treatment	DA (□g/g tissue)				NE (□g/g tissue)				5HT (□g/g tissue)			
	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change
- ve Control	10.4±0.11		10.3±0.31		127.0±1.16		160.1±0.60		1.25±0.09		1.01±0.02	
+ve Control	11.8±0.05**	13.5↑	11.8±0.32**	4.42↑	175.3±2.95***	38.0↑	174.0±4.10**	8.86↑	2.57±0.13***	85.6↑	1.31±0.13*	29.7↑
St. Cells	9.44±0.11	20.0↓	11.3±0.31	4.24↓	155.7±0.64	11.2↓	153.5±0.76	11.8↓	1.02±0.05	60.3↓	1.10±0.06	16.0↓
Rivast.	8.83±0.17	25.2↓	8.50±0.22	28.0↓	152.5±0.87	13.10↓	168.6±2.02	3.10↓	1.40±0.08	45.5↓	1.65±0.04	25.9↑
St.Cells + Rivast.	8.07±0.13	31.6↓	9.36±0.46	20.7↓	136.3±1.68	22.2↓	150.6±0.23	13.4↓	0.58±0.04	77.4↓	1.88±0.05	43.5↑

Mean values of 6 rats ±SE
Gr.2 compared with Gr.1, GR, S 3, 4, 5 compared with Gr.2.
Insignificant at p<0.25*, significant at p<o.o5**, highly significant at p<0.01***, very highly significant at p<0.0005.

Table (3): Effect of different treatments on neurotransmiters in brain hippocampus after 4 and 8 weeks from the induction of AD and %changes from the corresponding control.

Treatment	DA (□g/g tissue)				NE (□g/g tissue)				5HT (□g/g tissue)			
	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change
- ve Control	10.3± 0.19	-	8.72± 0.07	-	172.6± 7.15	-	160.2± 6.84	-	1.86± 0.03	-	1.62± 0.03	-
+ve Control	11.8± 0.25***	14.6↑	10.8± 0.33***	23.99↑	334.1± 8.48***	93.6↑	190.8± 6.01**	19.1↑	2.48± 0.13***	33.3	1.85± 0.04***	14.2↑
St. Cells	9.40± 0.11•	20.3↓	5.05± 0.30•	53.2↓	160.3± 8.43•	52.0↓	150.7± 6.72	6.28↓	1.39± 0.06•	43.9	1.13± 0.06•	38.9↓
Rivast.	8.50± 0.12•	28.0↓	7.52± 0.08•	30.4↓	153.9± 1.03•	53.9↓	147.0± 1.07	8.58↓	1.56± 0.11•	37.1	1.17± 0.03•	36.8↓
St.Cells + Rivast.	7.50± 0.11•	36.4↓	5.58± 0.13•	48.3↓	144.1± 1.47•	56.9↓	139.2± 4.77	13.4↓	0.36± 0.03•	85.5	0.83± 0.03•	55.1↓

Mean values of 6 rats ± SE
•Gr. 2 compared with Gr. 1 ; Gr• s 3, 4, 5 compared with Gr. 2
Insignificant at p< 0.25 ., * significant at p <0.05 , ** highly significant at p<0.01
*** very highly significant at p < 0.0005.

Table (4): Effect of different treatments on excitatory and inhibitory amino acids in cortex region of brain after 4 and 8 weeks from the induction of AD and % changes from the corresponding control.

Treatment	Excitatory Amino Acids								Inhibitory Amino Acid							
	Aspartic Acid (□g/g tissue)				Glutamic Acid (□g/g tissue)				Glycine (□g/g tissue)				GABA (□g/g tissue)			
	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change
- ve Control	4.22± 0.41	-	2.84± 0.25	-	0.89± 0.04	-	0.99± 0.08	-	2.72± 0.09	-	3.00± 0.20	-	4.15± 0.40	-	4.90± 0.40	
+ve Control	5.72± 0.50*	35.5↑	5.39± 0.51***	89.8↑	1.29± 0.11***	44.9↑	1.87± 0.14***	88.9↑	2.00± 0.24**	26.5↓	2.67± 0.08*	11.0↓	2.30± 0.20***	44.6↓	2.14± 0.11***	56.3↓
St. Cells	3.27± 0.23•	42.8↓	2.77± 0.16•	48.6↓	0.92± 0.04	28.7↓	0.95± 0.04•	49.2↓	2.15± 0.06	7.50↑	2.95± 0.06	10.5↑	2.43± 0.14	5.65↑	2.43± 0.21	13.6↑
Rivast.	3.88± 0.30	32.2↓	3.55± 0.23	34.1↓	1.09± 0.07	15.5↓	1.11± 0.05•	40.6↓	2.32± 0.11	16.0↑	2.83± 0.20	6.00↑	2.54± 0.14	10.4↑	2.83± 0.10	32.2↑
St. Cells + Rivast.	4.00± 0.38	30.1↓	2.36± 0.19•	56.2↓	0.95± 0.02	26.4↓	0.95± 0.02•	49.2↓	2.53± 0.08	26.5↓	2.93± 0.08	9.73↑	2.62± 0.08	13.9↑	2.64± 0.09	22.9↑

Mean values of 6 rats ± SE
Gr.2 compared with Gr.1;GR,S 3,4,5 compared withGr.2.
* significant at p<o.o5,**highly significant at p<0.01,*** very highly significant at p<0.0005 .

Table (5): Effect of different treatments on excitatory and inhibitory amino acids in hippocampus region of brain after 4 and 8 weeks from the induction of AD and % changes from the corresponding control.

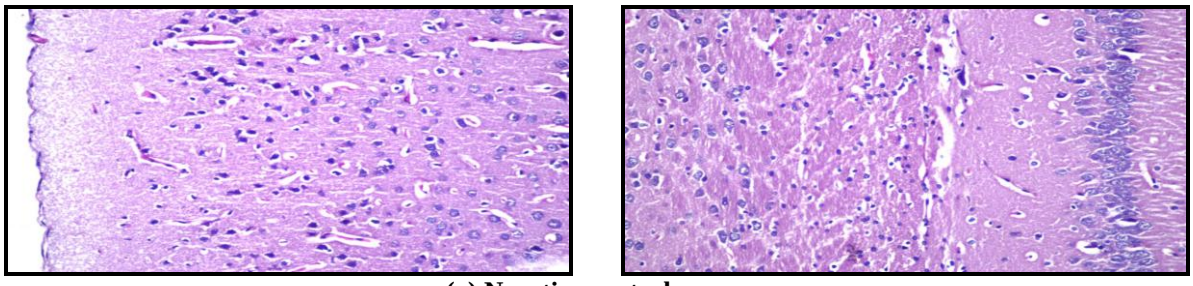
Treatment	Excitatory Amino Acids								Inhibitory Amino Acid							
	Aspartic Acid (□g/g tissue)				Glutamic Acid (□g/g tissue)				Glycine (□g/g tissue)				GABA (□g/g tissue)			
	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change
- ve Control	1.55± 0.08	-	2.88± 0.09	-	0.99± 0.09	-	0.93± 0.01	-	1.70± 0.06	-	2.02± 0.20	-	1.57± 0.01	-	2.95± 0.07	-
+ve Control	4.39± 0.21***	183↑	3.99± 0.12***	38.5↑	2.03± 0.20***	105.0↑	1.55± 0.14**	66.7↑	1.58± 0.02*	7.06↓	1.05± 0.03**	48.0↓	1.82± 0.10*	15.9	1.40± 0.11***	52.5↓
St.Cells	2.48± 0.18•	43.5↓	2.13± 0.19•	46.6↓	0.95± 0.04•	53.2↓	0.90± 0.03•	41.9↓	1.95± 0.06	23.4↑	1.05± 0.06	42.9↑	1.95± 0.01	7.14	2.20± 0.09	57.1↑
Rivast.	3.25± 0.11	26.0↓	2.93± 0.11	26.6↓	1.11± 0.06•	45.8↓	1.32± 0.02	14.8↓	1.60± 0.01	1.27↑	1.67± 0.13•	59.0↑	1.90± 0.02	4.40	1.83± 0.06	30.7↑
St.Cells + Rivast.	2.48± 0.19•	43.5↓	1.78± 0.02•	55.4↓	0.92± 0.02•	54.7↓	0.92± 0.01•	40.6↓	1.55± 0.02	1.90↓	1.55± 0.13•	47.6↑	1.64± 0.09	9.89	2.19± 0.06•	56.4↑

Mean values of 6 rats ± SE
•Gr. 2 compared with Gr. 1; Gr,s 3,4,5 compared withG.2.
*significant at p< 0.05,**highly significant at p<0.01 *** very highly significant at p<0.0005.

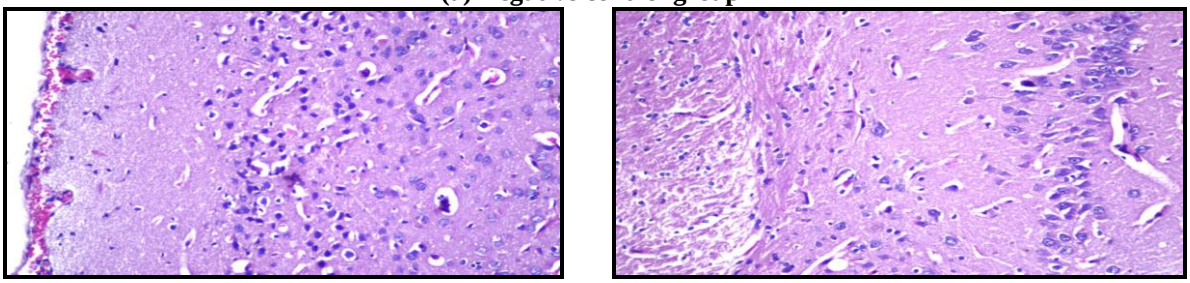
Table (6): Effect of different treatments on acetyl choline (ACh) and Choline Esterase (ChE) in cortex and hippocampus regions of brain after 4And 8 weeks from the induction of AD and % changes from the corresponding control.

Treat.	Cortex region								Hippocampus region							
	ACh (□g/g tissue)				ChE (□g/g tissue)				ACh(□g/g tissue)				ChE(□g/g tissue)			
	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change	4 weeks	% change	8 weeks	% change
- ve Control	1.60± 0.01	-	1.55± 0.01	-	4040± 88.2	-	4236± 94.4	-	1.82± 0.04	-	1.88± 0.02	-	4442± 54.0	-	3960± 16.1	-
+ve Control	0.71± 0.01***	55.6↓	0.78± 0.01***	49.7↓	5885± 12.1***	45.7↑	4862± 126.9***	14.8↑	0.98± 0.03***	46.1↓	1.22± 0.06***	35.1↓	6101± 15.1***	37.3↑	4203± 56.0***	6.14↑
St. Cells	3.31± 0.07•	366.2↑	2.78± 0.07•	267.9↑	2943± 16.5•	50.0↓	2579± 52.5•	47.0↓	3.65± 0.05•	272.4↑	3.75± 0.04•	192.6↑	3237± 34.9•	46.9↓	3588± 37.3	14.6↓
Rivast.	2.24± 0.01•	215.5↑	2.19± 0.02•	180.8↑	3904± 28.6	33.7↓	3424± 137.0	29.6↓	2.62± 0.06•	167.3↑	2.74± 0.04•	124.6↑	4154± 61.9	31.9↓	3754± 34.9	10.7↓
St. Cells + Rivast.	3.79± 0.06•	433.8↑	3.06± 0.03•	292.3↑	2773± 50.9•	52.9↓	2546± 46.0•	47.6↓	4.07± 0.06•	315.3↑	3.00± 0.07•	145.9↑	2977± 11.4•	51.2↓	3366± 11.3	19.9↓

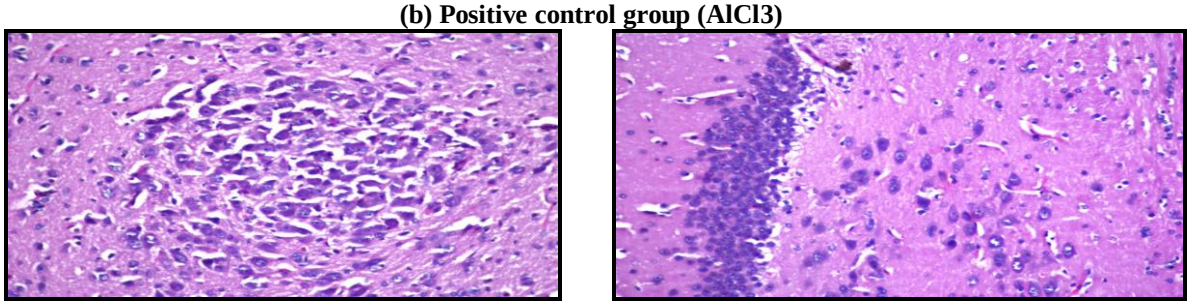
Mean values of 6 rats ± SE
Gr. 2 compared with Gr; 1,Gr s, 3 ,4 ,5 compared with Gr .2
*** very highly significant at p < 0.0005.



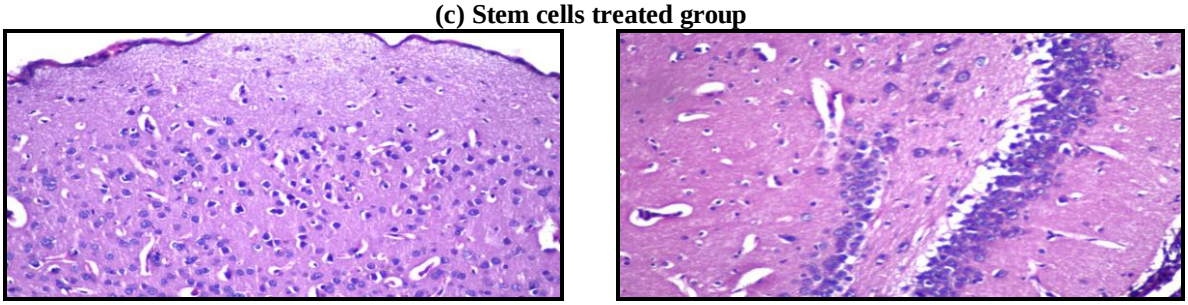
(a) Negative control group



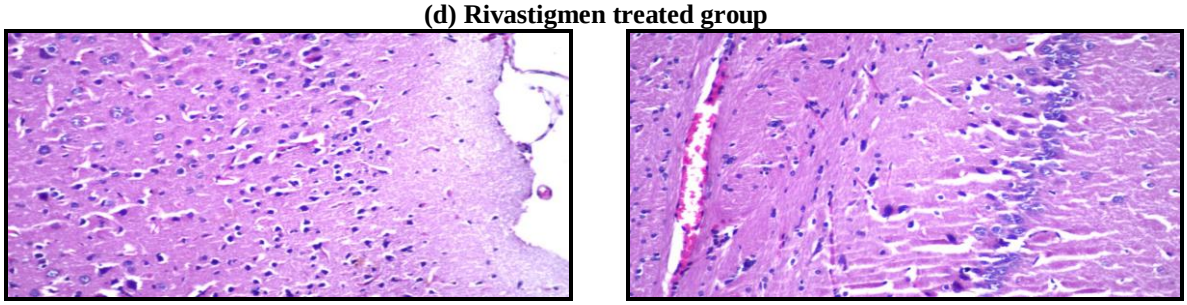
(b) Positive control group (AlCl3)



(c) Stem cells treated group



(d) Rivastigmen treated group



(e) Stem cells + Rivastigmen treated group

Figure 3: Histopathological study of different groups after 8 weeks of treatment in cortex (left figure) and hippocampus (right figure) regions of brain.

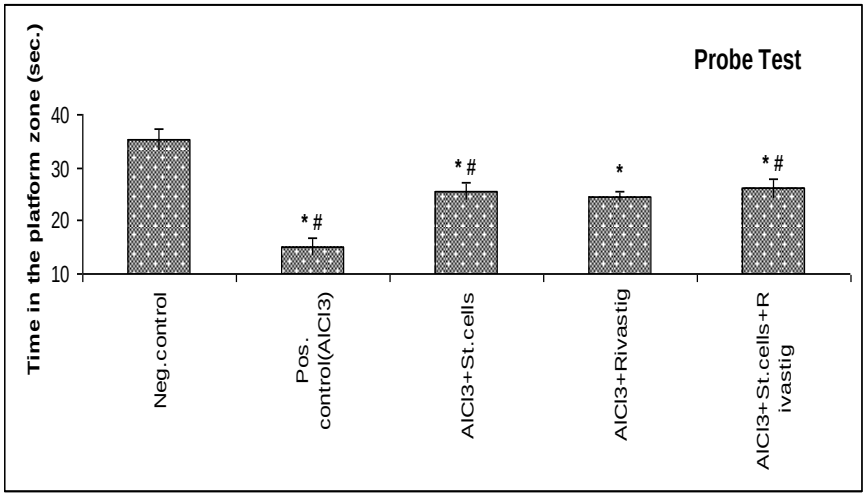


Fig. (1): Effect of stem cells, Rivastigmen and their combined treatment on memory impairment in $AlCl_3$ induced AD.

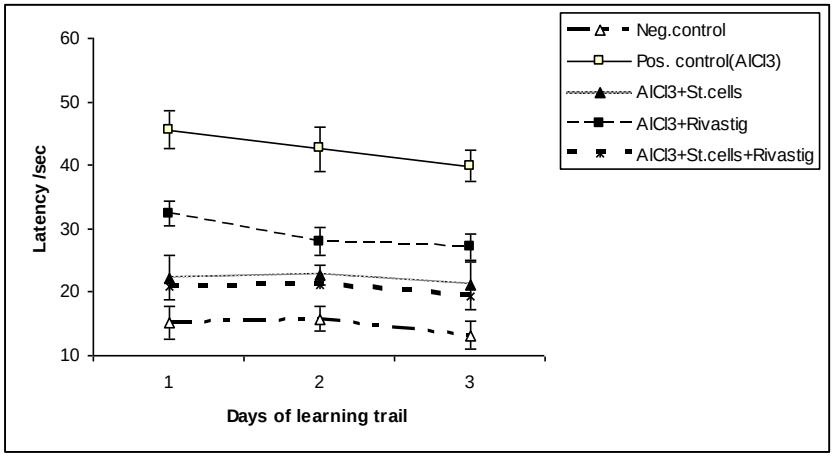


Fig. (2): Effect of stem cells, Rivastigmen and their combined treatment on learning impairment in $AlCl_3$ induced AD.

- **Data expressed as mean values of 6 rats ± SE.M.**
- *** Significant difference vs. Control P <0.05.**
- **• Significant difference vs. $AlCl_3$ P <0.05.**

IV. Discussion

Neurodegenerative diseases such as Alzheimer's disease (AD) are characterized by neurodegenerative changes and apoptosis of neurons involved in network leading to loss of sensation and decline in cognitive abilities i.e memory**,** comprehension**,** language**,** expression**,** learning capacity**, judgment** and recognition of people or place [1]. $AlCl_3$ is one tool which induce AD model in the experimental animals. In this study, $AlCl_3$ induce AD after 28 days of treatment .It is proved by the Morris water maze tank experiment , different biochemical methods and the histopathological examination of the brain tissue. Our results are going parallel with those of [27]. Administration of aluminium resulted in a significant increase in plasma and tissue aluminium concentration. However the relationship between tissue aluminium levels and Al toxicity is highly complicated because elevated tissue Al levels does not necessarily produced detrimental effects [28]. Al in low concentration acts as antioxidant, but in high concentration acts as provident [29]. Kanwall et al, [30] reported that memory impairment in the $AlCl_3$ – induced animal model of AD is associated with the increased oxidative stress in blood brain tissues which is going in accordance with our results. $AlCl_3$ induced a significant increase in the levels of monoamines in cortex and hippocampus regions of brain .These monoamines are the most familiar neurotransmitters which are play a role in mood and thought processes, control the ability to focus, concentrate and remember things, regulate sleep and control the appetite center of the brain. $AlCl_3$ destroys the microtubule integrity of the neurons thereby causing degeneration in the brain cells and this can be associated with a significant alteration of various neurotransmitters levels in different regions DA, NE and serotonin are released from locus ceruleus in the brain and are responsible for various, functions like attention and motor

process [31]. The increasing levels of excitatory amino acids (aspartate, glutamate) and decreasing levels of inhibitory amino acids (glycine, GABA) are involved in the neurological disorders e.g AD. Glutamate**,** the major excitatory neurotransmitters in the CNS and its over stimulation through its receptors has been clearly implicated in the neuronal injury observed in several neurodegenerative disorders [32]. Possible involvement of GABA receptor systems in scop- induced memory deficits was investigated by different authors [33] They extended support to the cholinergic concept in cognitive performance and provided an evidence for the influence of GABA and glycine (inhibitory amino acids) modulation in scope- induced learning and memory loss in mice. Aluminium can react with glutmate to form an aluminium L-glutmate complex which is neurotoxic [34] and may increase neuronal oxidative stress. $AlCl_3$ may reversibly binds to some allosteric sites in ChE molecule causing a change in its secondary structure leading to increase catalytic activity and decrease ACh content. $AlCl_3$ induces oxidative stress possibly by impairing mitochondrial function and / or AChE activation and subsequent ACh depletion [20]. Neural stem cells release diffusible factors that may improve the survival of aged and degenerating neurons in the brain [35]. Our results proved that stem cells caused a significant ameliorative effect in different parameters under investigation. Bone marrow derived stem cells contribute to cell turnover and repair in various tissue types including brain [36]. It was hypothesized that MSC's transplantation may have beneficial effects in AD patients through playing a specific and a general role in AD .

This role is via microglial activation, which are resident in the central nervous system (CNS) that regulate innate immunity and participate in adaptive immune response in CNS tissues. Microglia has neuroprotective agents [37]. In general MSC' s promotes endogenous neurogenesis in the hippocampus and finally through secreting neurotropic factors of nutritional value as brain derived neurotrophic factor.

Rivastigmine displayed a pronounced ameliorative effect on AD induced rats during the course of treatment. Rivastigmine is one of agents that prevent the progression of AD disease and its pathological changes. AD involves cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are known to be involved in attention , learning**,** memory and other cognitive processes .Rivastigmine ,a brain-selective acetyl and butyryl-cholinesterase inhibitor of the carbamate type , is though to facilitate cholinergice neurotransmission by slowing the degeneration of ACh released by functionally intact cholinergic neurons .Data from animal studies indicate that rivastigmine selectively increases the availability of ACh in the cortex and hippocampus regions of brain [38]**.** Administrations of rivastigmine along with stem cells cause a synergistic effect during the course of treatment. There was no histological alteration in the regions of brain during the course of experiment in the control animals. $AlCl_3$ causes congestion in the blood vessels of the menings associated with oedema as well as diffuse gliosis in the cerebrum and neuronal cells of the hippocampus showed apoptosis. Treatment with stem cells ,,rivastigmine or their combination ameliorated these altrations to a measurable degree.

V. Conclusion

All the prementioned results hopeful to use stem cells in a large scale in the near future to treat many diseases including AD as a single tool of treatment or with the aid of other treatment**.**

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