RESEARCH PAPER

Comparative Evaluation of Perindopril, Valsartan, and Valsartan–Sacubitril with Piracetam in Scopolamine-Induced Memory Impairment in Rats - An Experimental Study

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ABSTRACT

Introduction: ARBs and ACE inhibitors are widely used drugs for cardiovascular disorders, renal disease, and diabetes. Recently, they have been recognized for neuroprotective activity and are used in many brain disorders. Hence, the present study was done to explore effects of Perindopril, Valsartan, and Valsartan-Sacubitril combination on experimentally induced learning and memory impairment in Wistar rats.

Materials and Methods: 48 rats were divided into 6 groups, eight rats in each group, namely normal control, disease control, positive control (Piracetam 600mg/kg), test group I (Perindopril 4mg/kg), test group II (Valsartan 15mg/kg) and test group III (Valsartan-Sacubitril 30mg/kg). Except normal control group, all animals received intraperitoneal injection of Scopolamine 1mg/kg for 21 days to induce memory impairment. Piracetam and Test drugs were administered once daily orally for 21 consecutive days. On 0, 7th, 14th, and 21st day of the experiment, locomotor activity (Actophotometer), muscle strength (Wire hanging grip test) and memory functions (EPM, and MWM) of all animals were assessed. On 8th, 15th, and 22nd day of the experiment, retention memory functions (EPM, and MWM) were assessed.

Results: Animals treated with Scopolamine showed significant reduction in locomotor activity, grip strength and significant rise in TL and EL. Rats treated with Piracetam and test drugs showed significant increase in locomotor activity, grip strength and significant reduction in TL and EL when compared with disease control group. Similar results were seen in retention memory test.

Conclusion: Test drugs demonstrated neuroprotective effect in scopolamine-induced memory impairment in rats. Memory improvement by these test drugs was comparable with piracetam.

Keywords: Scopolamine, Perindopril, Valsartan, Valsartan-Sacubitril, Neuroprotection.

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INTRODUCTION

Dementia is a broad term for multiple brain disorders caused by neurodegenerative and vascular diseases. It is characterized by gradual, progressive impairment in the cognitive and behavioural functions such as learning skills, daily social or living activities, language, and memory.[1] Most of the neurodegenerative diseases are clinically presented as Dementia, Alzheimer's disease,

Parkinsonism, Motor Neuron Disease etc. Alzheimer disease (AD), being the main cause of dementia, is the biggest challenge for health care workers. WHO report of dementia 2021 describes that dementia is observed in almost 55 million people. It is predicted that this no. may increase upto 78 million in year 2030 and upto 139 million in year 2050. [2]

Currently, pharmacotherapy of prevention and treatment of dementia is aimed at protection from excitotoxicity N-Methyl-D-Aspartate antagonist (Mementamine) or supplementing neuronal transmission to activates central cholinergic system (Rivastigmine, Donepezil and Galantamine) or using miscellaneous drugs like nootropics (Piracetam, Pyritinol, Citicoline, Dihydroergotoxin, Piribedil) etc.[3] or some herbal preparations like Ginkgo biloba,[4]Shankhpushpi,[5]Aswagandha,[6] etc. However, these drugs are unable to arrest pathology of the disease process and also they produce significant adverse effects which has limited their use.[3] Therefore there is need to find more efficacious and safer drugs as alternative in learning and memory impairment.

Renin-Angiotensin System (RAS) regulates important functions of the body including control of blood volume and systemic vascular resistance. Apart from peripheral functions, it has been also documented to be found in the central nervous system (CNS) which plays an important role in various neurodegenerative diseases. RAS affects learning and cognitive functions by multiple mechanisms including deposition of amyloid ß (Aß), aggregation of tau protein, inflicting oxidative stress, neurotransmitters abnormalities, and neuroinflammation.[7]

Perindopril is an ACE inhibitor also been reported to exert anti apoptotic, anti-inflammatory, antioxidant, antithrombotic and profibrinolytic actions[8]. The inhibition of RAS by ARBs (valsartan, losartan, and candesartan) prevents the onset of AD by reducing amyloid β peptides and Angiotensin receptors 1 (AT1) initiated oxidative stress. ARBs improve cerebral blood flow and acetylcholine level and reduce acetyl cholinesterase activity and malondialdehyde (MDA) level.[9]

The salient feature of Alzheimer's disease is collection of abnormal aggregates of beta-amyloid resulting from an imbalance of Aβ production and its clearance. The clearance of Aβ mainly occurs by clearance through the blood-brain barrier and also by Aβ-degrading enzymes. Numerous in vitro and in vivo studies reported that neprilysin (NEP) is an important Aβ-degrading enzyme.[10] Inhibition of neprilysin increases the bioavailability of natriuretic peptides (NPs), bradykinin, and substance P. These substances are responsible for natriuresis, vasodilatation, and anti-proliferative effects. The classical example of angiotensin II-receptor-Neprilysin inhibitor group (ARNi) is valsartan/sacubitril.[11]

Recently, ACE-Is and ARBs reported promising results to target dementia as well as other neurodegenerative disorders. Improvement in learning and memory is observed by ACEI-perindopril and ARB-valsartan as shown in some studies.[9] However, there has been no study which directly compares effect of perindopril, valsartan and valsartan-sacubitril combination in experimental model of learning and memory impairment. Hence the present study was planned.

MATERIAL AND METHODS

After getting approval from institutional animal ethics committee the study was started. 48 healthy Wistar rats weighing 150-200 g, obtained from Central Animal House from our institute were housed and maintained in large, spacious polyacrylic cages at an ambient room temperature with 12-h light/12-h dark cycle, with free access to food and water. Animals were acclimatized for a week prior to the experiment.

48 rats were divided into six groups with eight animals in each group as follows:

Group I- Distilled Water

Group II– Scopolamine (1 mg/kg, i.p.)[12]

Group III- Scopolamine (1 mg/kg, i.p.) + Piracetam (600 mg/kg, po) [13]

Group IV- Scopolamine (1 mg/kg, i.p.) + Perindopril (4 mg/kg, po) [14]

Group V- Scopolamine (1 mg/kg, i.p.) + Valsartan (15 mg/kg, po) [15]

Group VI- Scopolamine (1 mg/kg, i.p.) + Valsartan-Sacubitril (30 mg/kg, po) [16]

Experimental design [12]

On day 0, 7, 14 and 21 of the study, behavioural activity (Actophotometer), muscular strength (Wire hanging grip test) and memory functions (EPM and

MWM) were evaluated. The retention of memory functions was evaluated on the next day i.e. on 1st, 8th, 15th, and 22nd day of the study.

Actophotometer[12]

The animal locomotor behaviour was monitored using actophotometer, equipped with acrylic cage, and surrounded by a stainless steel frame, with 8 beams of infrared light on both x and y horizontal axes. The number of beam crossovers, i.e., consecutive interruption of one beam followed immediately by interruption of the adjacent beam by the animal, was recorded by the instrument. The individual rat's activity was monitored at room temperature for 10 min. after treated with the respective drug and an activity score was recorded after 45 min. Reduction in activity score was taken as an index of central nervous system depression.

Wire hanging grip test [12]

Wire hanging grip test was conducted to assess the muscle strength of an animal. Two heavybased retort stands was kept at a distance of 55 cm, and 1mm thick thread is tied between the poles at a height of 35 cm. A layer of bedding material was placed to prevent injury to the animal when it falls down. During the test, the thread kept tightly attached to the frame to avoid vibration or unwanted displacement of the thread. Animal was placed at the centre of the wire, and latency time of fall was recorded in seconds. Reduction in latency of falling time was considered as central nervous system depression.

Morris water maze (MWM)[12]

Prior to training, animals were habituated for 2 days to the testing apparatus (circular tank. 150 cm diameter with a depth of 40 cm (water depth 30 cm)). The tank was kept in a room with spatial cues external to the maze, including coloured objects and posters hanging from the ceiling. On the first day, each animal was placed in the tank and allowed to explore it by swimming for 2 min, after which animal was towel dried and returned to its home cage. On the following day the rats were exposed for 2 min to the MWM which now contained an escape platform. Animals were exposed four times with 15 min inter-trial interval. For training trials, the tank water was made opaque by adding chalk powder5, and a stable Plexiglas escape platform (of height 28 cm) was submerged 2 cm below the water surface in the northwest (NW) quadrant of the maze. Training was given to all the animals which consist of four trials per day with 15 min inter-trial interval and continued for three consecutive days. For each trial, the animal was placed in the maze for 2 min, or until the escape platform was located. If after 2 min, the animal was unable to locate the escape platform, it was guided to it by the experimenter. Animals were kept on the platform for 15 sec, after which time they were towel dried and returned to their home cage. There were three start locations (NE, SW, and SE) and start location were randomized across groups/trials.

EL time to locate the hidden platform in the water maze was noted as an index of learning. Retention trial was carried out on next day after 24 hrs of administration of drug in which EL time was recorded. Significant improvement in memory function was indicated by reduction in EL time.

Elevated Plus Maze (EPM) [12]

All the animals were screened before inclusion into the study by using EPM. Each rat is placed at the end of an open arm, facing away from the central platform. Rat was allowed to move in one of the closest arm with all its four limb and this is called transfer latency (TL). Animals with TL less than 60 seconds on EPM were included for EPM test.

All rats in each group were treated with the respective drug doses orally for 21days. Transfer latency (TL) was recorded as the time (in seconds) taken by the animal to move from the open arm into one of the covered arms with all its four legs. The rats were allowed to explore the maze for 2 min. and returned to home cage. Retention of this learning task was examined 24 hrs after the first day trial. TL was recorded to assess learning ability of animals on the day 0, 7, 14 and 21, after 45 min of last dose of drug administration. TL was noted to assess animals learning retrieval i.e. memory in EPM, after 24 hrs of last drug dose administration, i.e. on 1st, 8th, 15th and 22nd day again. Significant improvement in memory function was indicated by reduction in TL.

Statistical Analysis:

All data were presented as the mean ± SEM. The Statistical package for social Science (SPSS), version 25 was used for analysis of results. Analysis of Variance (ANOVA) followed by Tukey's post hoc test was used for analysis of data and for comparisons between treated and control groups. The level of significance was set at $P<0.05$.

OBSERVATIONS AND RESULTS

On 14th and 21st day, significant reduction in time of escape latency was seen with piracetam, perindopril, valsartan and valsartan-sacubitril groups in comparison with scopolamine treated group. ($p \leq 0.05$ to $p \leq 0.001$). The results of test drugs were comparable with standard drug piracetam.

As seen in figure 1 Scopolamine treated animals produce significant increase in EL of retention task on 8th ($p \leq 0.05$), 15th ($p \leq 0.05$) and 22nd ($p \leq 0.01$) day when compared with normal control group. On 15th and 22nd day significant reduction in time of retention EL was seen with piracetam, and test groups in comparison with scopolamine treated group ($p \leq 0.05$ to $p \leq 0.001$). The results of test groups were comparable with piracetam.

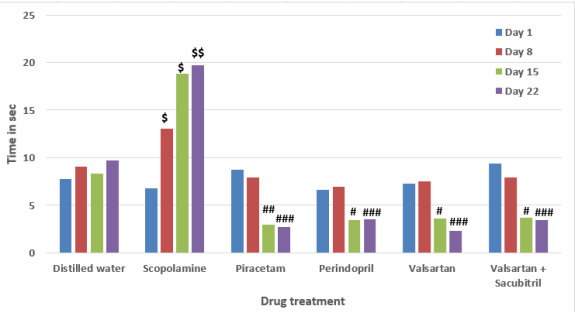

Figure 1 - Effect of piracetam, perindopril, valsartan and valsartan-sacubitril on escape latency time in scopolamine treated rats for retention memory

All values as Mean ± SEM (n=8), One way ANOVA followed by Tukey's post hoc test.

$ $p \leq 0.05$, $$ $p \leq 0.01$ compared with normal control,

$p \leq 0.05$, ## $p \leq 0.01$, ### $p \leq 0.001$ compared with disease control.

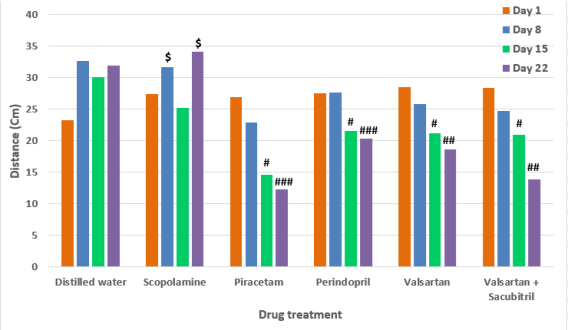

Figure 2- Effect of piracetam, perindopril, valsartan and valsartan-sacubitril on mean distance (MWM) travelled in scopolamine treated rats for retention memory

All values as Mean ± SEM (n=8), One way ANOVA followed by Tukey's post hoc test.

$ $p \leq 0.05$ compared with normal control,

$p \leq 0.05$, ## $p \leq 0.01$, ### $p \leq 0.001$ compared with disease control.

As seen in Fig 2 Scopolamine treated animals produced significant rise in mean distance travelled on 14th ($p \leq 0.05$) and 21st ($p \leq 0.01$) day when compared with normal control group. On 14th and 21st day, significant reduction in mean distance was seen with piracetam, perindopril, valsartan and valsartan-sacubitril groups in comparison with scopolamine treated group ($p \leq 0.05$ to $p \leq 0.01$). The results of perindopril, valsartan and valsartan-sacubitril groups were comparable with standard drug piracetam.

On 14th and 21st day, significant reduction in mean distance was seen with piracetam, perindopril, valsartan and valsartan-sacubitril groups in comparison with scopolamine treated group ($p \leq 0.05$ to $p \leq 0.001$). Same results was seen in retention memory.

As seen in table 1 scopolamine treated animals showed significant increase in number of entries into target zone on 7th ($p \leq 0.05$), 14th ($p \leq 0.01$) and 21st ($p \leq 0.001$) day in MWM in comparison with normal control group. On 7th day ($p \leq 0.05$), 14th day ($p \leq 0.05$) and 21st day ($p \leq 0.001$) significant reduction in number of entries in target zone were seen in piracetam group in comparison with scopolamine treated group. Animals in test groups showed significant improvement in number of entries in target zone on 14th and 21st day in comparison with scopolamine treated group ($p \leq 0.05$ to $p \leq 0.001$). The results of test group showed improvement in number of entries in target zone on 21st day in comparison with piracetam ($p \leq 0.05$ to $p \leq 0.01$).

Table 1 - Effect of piracetam, perindopril, valsartan and valsartan-sacubitril on number of entries into target quadrant in scopolamine treated rats for acquisition memory

Days → Drugs ↓	Day 0	Day 7	Day 14	Day 21
Distilled Water	5.85 ± 0.58	6.62 ± 0.49	7 ± 0.26	7.1 ± 0.39
Scopolamine	6 ±0.32	7.87 ±0.35$^{\$}$	9.87 ±0.29$^{\$\$}$	12.5 ±0.62$^{\$\$\$}$
Piracetam	6.37 ±0.59	5.25 ±0.36$^{\#}$	4.12 ±0.29$^{\#}$	3.12 ±0.29$^{\#\#\#}$

Perindopril	6.62 ±0.37	5.75 ±0.36	5.37 ±0.32$^{\#}$	5.12 ±0.39$^{\#\#\#,*}$
Valsartan	5.87 ±0.51	5.12 ±0.47	5 ±0.37$^{\#}$	4.5 ±0.32$^{\#\#\#,**}$
Valsartan + Sacubitril	6.12 ±0.29	5.25 ±0.31	4.62 ±0.18$^{\#\#}$	4.25 ±0.25$^{\#\#\#,*}$

All values as Mean ± SEM (n=8), One way ANOVA followed by Tukey's post hoc test.
$^{\$}$ $p \leq 0.05$, $^{\$\$}$ $p \leq 0.01$, $^{\$\$\$}$ $p \leq 0.001$ compared with normal control,
$^{\#}$ $p \leq 0.05$, $^{\#\#}$ $p \leq 0.01$, $^{\#\#\#}$ $p \leq 0.001$ compared with disease control,
* $p \leq 0.05$, ** $p \leq 0.01$ compared with standard control.

Scopolamine treated animals showed significant increase in number of entries into target zone on 15th ($p \leq 0.05$) and 22st ($p \leq 0.01$) day in MWM in comparison with normal control group. On 8th ($p \leq 0.05$), 15th ($p \leq 0.01$) and 22st ($P \leq 0.01$) day significant decrease in number of entries in target zone were seen in standard control piracetam group compared to scopolamine group. Animals in test groups showed significant decrease in number of entries in target zone on 8th, 15th and 22nd day as compared to scopolamine treated group ($p \leq 0.05$ to $p \leq 0.01$). The results of test groups showed significant difference compared piracetam mainly on day 22 ($p \leq 0.05$ to $p \leq 0.01$).

Effect of piracetam, perindopril, valsartan and valsartan-sacubitril on transfer latency time (EPM) in scopolamine treated rats for acquisition memory

Scopolamine treated animals showed significant increase in TL time on 14th ($p \leq 0.05$) and 21st ($p \leq 0.01$) day in EPM in comparison with normal control group. On 14th and 21st day significant reduction in TL was noted in test groups compared to scopolamine treated group ($p \leq 0.05$ to $p \leq 0.001$). The test drugs produced comparable results with piracetam.

As seen in figure 3 Scopolamine treated group showed significant rise in retention TL time on 15th ($p \leq 0.05$) and 22nd ($p \leq 0.01$) day compared to normal control group. Significant reduction in retention TL was noted in piracetam group on day 8 ($p \leq 0.05$), 15 ($p \leq 0.05$) and 22 ($p \leq 0.01$) in comparison with Scopolamine treated group. Also significant reduction of retention TL was noted on 15th and 22nd day in test groups.

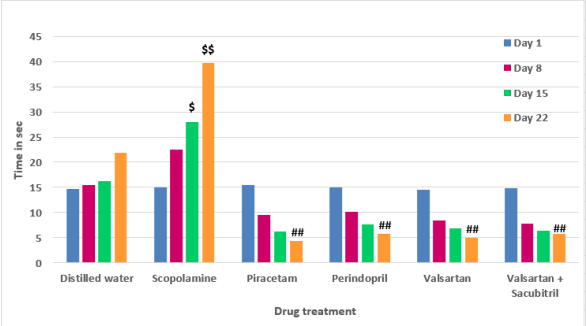

Figure 3 - Effect of piracetam, perindopril, valsartan and valsartan-sacubitril on TL time in scopolamine treated rats for retention memory
All values as Mean ± SEM (n=8), One way ANOVA followed by Tukey's post hoc test.
$ $p \leq 0.05$, $$ $p \leq 0.01$ compared with normal control,
# $p \leq 0.05$, ## $p \leq 0.01$ compared with disease control.

Effect of piracetam, perindopril, valsartan and valsartan-sacubitril on time spend on open arm (EPM) in scopolamine treated rats for acquisition memory

The scopolamine treated group showed significant increase in time spent on open arm on 21st ($p \leq 0.05$) day in EPM in comparison with normal control group. On 14th and 21st day significant decrease in time spent on open arm was seen in piracetam and test groups ($p \leq 0.05$ to $p \leq 0.001$) when compared to scopolamine treated group. But the results of perindopril, valsartan and valsartan-sacubitril groups were comparable with standard drug Piracetam.
As seen in figure 4 Scopolamine treated animals produced significant reduction in locomotor activity on 7th ($p \leq 0.01$), 14th ($p \leq 0.01$) and 21st ($p \leq 0.001$) day compared to normal control group. On 7th, 14th and 21st day, significant increase in locomotor activity was seen with piracetam, and test groups in comparison with scopolamine treated group ($p \leq 0.05$ to $p \leq 0.001$).The test groups produced significant change in locomotor activity ($p \leq 0.05$ to $p \leq 0.001$) on day 14 and day 21 when compared with piracetam.

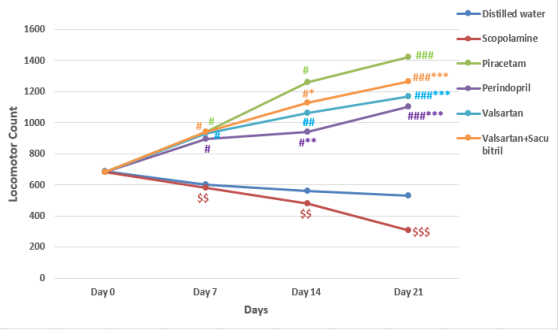

Figure 4- Effect of piracetam, perindopril, valsartan and valsartan-sacubitril on locomotor activity in scopolamine treated rats

All values as Mean ± SEM (n=8), One-way ANOVA followed by Tukey's post hoc test.

$$ p ≤ 0.01, $$$ p ≤ 0.001 compared with normal control,

#P ≤ 0.05, ##P ≤ 0.01, ###P ≤ 0.001 compared with disease control,

*P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001 compared with standard control.

Table 2 - Effect of piracetam, perindopril, valsartan and valsartan-sacubitril on time of fall in wire hanging test in scopolamine treated rats

Days → Drugs ↓	Day 0	Day 7	Day 14	Day 21
Distilled Water	25±0.75	22±1.01	28±1.35	20±0.82
Scopolamine	10±0.62	8±0.55	6±0.41$	2±0.32$$$
Piracetam	21±0.86	31±0.66#	42±0.49##	47±0.59###
Perindopril	22±0.88	26±1.10#,*	32±1.04#,*	36±0.75###,**
Valsartan	21±0.71	26±2.39#	32±0.99#	37±0.52###
Valsartan + Sacubitril	21±0.46	28±1.02#	35±0.83##,*	39±0.80###,**

All values as Mean ± SEM (n=8), One way ANOVA followed by Tukey's post hoc test.

$ p ≤ 0.05, $$$ p ≤ 0.001 compared with normal control,

p ≤ 0.05, ## p ≤ 0.01, ### p ≤ 0.001 compared with disease control,

* p ≤ 0.05, ** p ≤ 0.01 compared with standard control.

As seen in table 2 Scopolamine treated animals showed significant reduction in time of fall from the wire on 14th (p ≤ 0.05) and 21st (p ≤ 0.001) day in comparison with normal control group. On 7th, 14th and 21st day, significant rise in time of fall was noted with piracetam, and test groups in comparison with scopolamine treated group (p ≤ 0.05 to p ≤ 0.001).The test drugs treated groups produced significantly different change in time of fall from the wire (P ≤ 0.05 to P ≤ 0.01) on day 7,14 and 21 when compared with piracetam.

DISCUSSION

Neurotoxins are used since ages for development of animal models of neurological disorders such as AD, PD, temporal lobe epilepsy etc. It includes scopolamine, diazepam, glucocorticoids, Streptozotocin, alcohol, colchicine, and cisplatin etc.[17] Scopolamine induced memory impairment is the commonly used experimental model for evaluation of neurodegenerative disorders. In this study also scopolamine was used to induce memory impairment.

For induction of cognitive impairment in animals, scopolamine, an anticholinergic drug, plays a vital role. It non-selectively blocks acetylcholine muscarinic receptors in the cerebral cortex in animal and leads to reduced release of Ach.[18] According to El-Sherbiny et al., scopolamine can induce increased oxidative stress within rat brain. [19] In the present study, scopolamine had induced transient but significant memory impairment as shown by increased time of EL, mean distance travelled and no. of entries into target quadrant in MWM. It had also increased time of TL in EPM. The reduction in locomotor activity and time of fall in wire hanging test was also noted with scopolamine (Figure 4, Table 2). It also affected retention memory significantly (Figure 2,3). Some animal studies also observed consistent findings and they concluded that scopolamine produced these effects by blocking muscarinic receptors/increasing acetyl cholinesterase activity. [20]

Piracetam is a GABA (gamma amino butyric acid)[21] derivative which acts as nootropic agent. Nootropic represent a new class of psychotropic agents with selective facilitatory effect on integrative functions of the central nervous system, particularly on intellectual performances, learning capability and memory. [22]

Piracetam is commonly used for management of cognitive impairment.It has agonist effect on 5-HT serotonin receptors and antagonist effect on glutamate receptors.[23] It reverses scopolamine induced amnesia. .[24] In the present study, piracetam was

used as standard positive control. Piracetam had resulted into reduction of time of EL, mean distance travelled and no. of entries into target quadrant of MWM. It had also reduced time of TL in EPM. The rise in locomotor activity and time of fall in wire hanging test was also noted with piracetam (Figure 4, Table 2). These results showed that it had prevented scopolamine-induced behavioral and memory impairment in rats. This memory enhancing activity is mainly due to its facilitatory effect on the retention of spatial memory in scopolamine-induced memory impairment (Figure 2,3).

The drugs acting on RAAS are now evaluated as a new target for various neurodegenerative disorders. AT2 receptor activation has beneficial role in neurogenesis, cerebral blood flow[25] and learning and memory.[26] They also attenuate inflammation, oxidative stress.[27] and abnormal neuronal firing.[28] which is seen with AT1 receptor stimulation.

In addition to AT1 and AT2 receptors, central nervous system also shows some other receptors including AT4 and Mas receptors which are involved in the process of learning and memory. The accumulation of beta-amyloid peptide in the brain lead to neuronal membrane damage, oxidative stress and Cholinergic neuronal damage in the brain.[29]Pathological phosphorylated tau proteins are increased because of Beta-amyloid peptides which leads to formation of neurofibrillary tangles. These abnormal aggregates of beta-amyloid will form plaques which is pathological hallmark of AD. [30] These Aβ plaques are degraded by the enzymes like Neprilysin, insulin degrading enzyme (IDE), endothelin converting enzyme (ECE) etc. [31] There also occurs non-enzymatic degradation of amyloid-β. In 1980s (Thiorphan) and later in 1990s (Sacubitril) new class of drugs, Neprilysin inhibitors were developed. These drugs leads to amyloid-β accumulation in the brain on which subsequently leads to age-related macular degeneration, cerebral amyloid angiopathy, and AD. [32] They also cause a rise in natriuretic peptide levels and natriuriesis, as shown in some animal studies, but effect on blood pressure and systemic vascular resistance is inconsistent. [33] Beneficial effects on natriuriesis, diuresis, and hemodynamic was observed when these drugs were used for short term in humans. [33] However long term use showed vasoconstriction mainly due to more circulating concentration of the vasopressors angiotensin II and endothelin. [34]

Angiotensin receptor-neprilysin inhibitor (ARNi) is a dual acting novel drug formulation. This drug is combination of Ang II receptor blocker valsartan and the NEP inhibitor sacubitril has multiple effects on different systems of the body. [35] Neprilysin activity is increased and at the same time detrimental effects of the RAAS are inhibited by this drug combination. This combination received US FDA approval with the serious risks of cognitive dysfunction.[36] One ongoing multicentric clinical trial , PERSPECTIVE trial, is assessing long-term neurocognitive safety of sacubitril/valsartan results.[37]

The test drugs perindopril, valsartan and valsartan-sacubitril combination improved acquisition and retention memory in rats as seen by reduction in time of EL, mean distance travelled and no. of entries into target quadrant of MWM model. The reduction in time of EL was found to be comparable with standard control piracetam (Figure 2). As seen in observations, the mean distance travelled upto escape platform in MWM by all test group animals was comparable with piracetam on 14th and 21st day. No. of entries in target quadrants were significantly more with perindopril and valsartan-sacubitril animals ($p \leq 0.05$) and valsartan animals ($p \leq 0.01$) on 21st day but the no. of entries in target quadrants were comparable with piracetam on day 7 and 14

The time of TL and retention TL in EPM model by perindopril, valsartan and valsartan-sacubitril was comparable on day 14 and 21 with piracetam.

Scopolamine-induced hyperactivity was observed in some studies. [38] However, some studies also reported reduced locomotor activity and muscular strength by scopolamine. [39] The present study found that scopolamine induced significant reduction in locomotor activity on day 7, 14 ($p \leq 0.01$) and day 21($p \leq 0.001$). The standard drug piracetam had produced significant hyperactivity ($p \leq 0.001$). The test drugs improved the locomotor activity on day 21 but improvement was significantly less as compared to piracetam. (Figure 4).

For measurement of muscle strength and endurance in rats, wire hanging grip test is commonly used. In the present study, scopolamine showed significant reduction in time of fall on wire hanging grip test on 14th ($P \leq 0.05$) and 21st ($P \leq 0.001$) day in comparison with normal group. The muscle strength of animals treated with valsartan do not produce significant difference in comparison with piracetam. Though the time of fall of animals treated

with perindopril and valsartan-sacubitril was improved, it was significantly less when compared with piracetam. (Table 2)

After oral administration of test drugs for 21 days, significant improvement was observed in cognitive functions, grip strength and body coordination of rats. It is seen as diminished EL, improved TL, improved activity and muscle strength as compared to control animals. These findings suggested the possible cognitive enhancement or neuroprotective role of perindopril, valsartan and valsartan-sacubitril.

ACEI and ARBs exert a protective effect against oxidative damage induced by scopolamine. Nade et al [40] also reported cognitive enhancing activity by inhibition of AChE activity and by regulation of the antioxidant system or increase formation of Ang IV. Raghavendra et al. [41], compared the effect of captopril and losartan and suggested that both drugs were equally effective in enhancing retention of memory when administered prior to training.[41]

In the present study, one of the ACEIs perindopril, one of the ARBs valsartan and one of the ARNi , valsartan-sacubitril, improved the memory impairment induced by scopolamine and resulted in cognitive enhancement transiently proving their role in neuroprotection. Thus, ACEI or ARBs or ARNi might offer a useful therapeutic choice in prevention of dementia or other cognitive disorders. The neuroprotection offered by all these test drugs was comparable with the standard control piracetam. Drugs that reduce oxidative processes, inhibit apoptosis and reduce inflammation may add benefit in the treatment neurodegenerative disorders. The test drugs perindopril,[40]valsartan[40] and valsartan-sacubitril[42] have anti-oxidant as well as anti-apoptotic activity. However, only anti-oxidant and anti-apoptotic role of these drugs imparts neuroprotective activity or any other mechanism is involved needs further investigations before their clinical use as prophylactic drugs in neurodegenerative disorders. Hence, repurposing ACEI or ARBs or ARNi for the treatment of brain disorders, currently without effective therapy, may be of immediate and major translational value. However, long term adverse effects of ARNi should be taken into consideration.

CONCLUSION

Scopolamine, in the dose of 1mg/kg for 21 days, produces significant change in learning and memory activities, locomotor activity and Muscle coordination indicating impairment in learning and memory.

Perindopril, Valsartan and Valsartan-Sacubitril combination have neuroprotective activity.

Neuroprotective action of all these test drugs are comparable with standard positive control drug Piracetam.

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